# The fat mass and obesity-associated protein (*Fto*) regulates activity of the dopaminergic circuitry

# Inaugural-Dissertation

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A learning experience is one of those things that say, "You know that thing you just did? Don't do that." - Douglas Adams -

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# Abbreviations

2-OG	2-oxoglutarate
α-MSH	$\alpha$ -melanocyte stimulating hormone
ABH	AlkB homolog
AC	adenylyl cyclase
ADHD	attention-deficit/hyperactivity disorder
AlkB	$\alpha$ -ketoglutarate-dependent dioxygenases
ALKBH	alkB alkylation repair homolog
AgRP	agouti-related peptide
APOE	apolipoprotein
ARC	arcuate nucleus
BDNF	brain-derived neurotrophic factor
BMI	body mass index
BOLD	blood oxygen dependent
BW	body weight
cAMP	cyclic adenosine monophosphate
CART	cocaine and amphetamine regulated transcript
CARTPT	CART prepropeptide
cDNA	complementary DNA
CDS	coding sequence
CPu	caudate putamen
CUTL1	cut-like homeobox 1
DA	dopamine
DAT	dopamine transporter
DAPI	4-,6-Diamidin-2-phenylindol

DNA	deoxyribonucleic acid
DMH	dorsomedial hypothalamus
DRD2	type-2 dopamine receptor
DRD <sub>3</sub>	type-3 dopamine receptor
ES cells	embryonic stem cells
EUCOMM	European Conditional Mouse Mutagenesis Program
FC	fold change
FDR	false discovery rate
FLP	flippase (recombination enzyme)
Ft	fused toes
FTO	fat mass and obesity associated protein
GABA	$\gamma$ -aminobutyric acid
GIRK	G protein-coupled inwardly rectifying potassium channel
GO	gene ontology
GRIN1	glutamate receptor, ionotropic, N-methyl-D-aspartate 1
GTT	glucose tolerance test
GWAS	genome wide association studies
ICV	intracerebroventricular
IGF-1	insulin-like growth factor
I.P.	intraperitoneal
IRS	insulin receptor substrate
ITT	insulin tolerance test
kD	kilo Dalton
КО	knock out
LH	lateral hypothalamus
m <sup>3</sup> T	3-methylthymine
m <sup>3</sup> U	3-methyluracil
m <sup>5</sup> C	5-methylcytosine

m <sup>6</sup> A <sub>m</sub>	N6 methyl-2'-O-methyladenosine
m <sup>7</sup> G	N7-methylguanosine
MC4R	melanocortin 4 receptor
MCH	melanocyte concentrating hormone
MEF	mouse embryonic fibroblast
meRIP-Seq	methylated RNA immunoprecipitation with next-generation se-
	quencing
mRNA	messenger ribonucleic acid
miRNA	micro RNA
MSC	multi-synthetase complex
mTORC1	mammalian target of rapamycin complex 1
N <sub>m</sub>	2'-O-methylnucleotide
NA	noradrenaline
NAc	nucleus accumbens
NMDAR1	N-methyl-D-aspartate receptor subunit 1
NPY	neuropeptide Y
PBS	phosphate buffered saline
PCR	polymerase chain reaction
PFA	paraformaldehyde
РКА	protein kinase A
POMC	pro-opiomelanocortin
PVN	paraventricular nucleus
РҮҮ	peptide YY
qPCR	quantitative polymerase chain reaction
RNA	ribonucleic acid
rRNA	ribosomal RNA
RMA	robust multiarray average
RPKM	reads per kilobase per million reads
RPGRIP1L	retinitis pigmentosa GTPase regulator-interacting protein-1 like

RT	room temperature
ssDNA/RNA	single stranded DNA/RNA
SDS	sodium dodecyl sulfate
SEM	standard error of the mean
siRNA	small-interfering RNA
snRNA	small nuclear RNA
SNP	single nucleotide polymorphism
SN	substantia nigra
SNpc	substantia nigra pars compacta
STAT <sub>3</sub>	signal transducer and activator of transcription 3
TBS	tris buffered saline
TE	Tris/HCl EDTA
TG	transgene
TH	tyrosine hydroxylase
tRNA	transfer RNA
UCP-1	uncoupling protein 1
UPLC	ultra performance liquid chromatography
UTR	untranslated region
UV	ultraviolet
VMH	ventromedial hypothalamus
VTA	ventral tegmental area
WAT	white adipose tissue
WHO	World Health Organization
WT	wildtype

### Abstract

In 2007 genome wide sequencing led to the identification of common genetic variations within intronic regions of the human *FTO* gene that are associated with obesity related traits. To date, neither the consequence of these variations for *FTO* expression, nor the exact molecular function of the FTO protein are known.

This study shows that inactivation of the murine *Fto* gene alters the function of the midbrain dopaminergic circuitry. Loss of FTO impairs the dopamine neuron autoreceptor feedback inhibition that depends on dopamine receptors type 2 (DRD2), type 3 (DRD3) and G protein coupled inwardly rectifying potassium channels (GIRKs). This attenuation of the autoinhibitory feedback loop was observed for both whole body *Fto*-deficient and dopamine neuron restricted *Fto* knock out (*Fto*<sup> $\Delta$ DAT</sup>) mice. While *Fto*-deficient mice exhibited deficits in their responses to stimulation with cocaine, *Fto*<sup> $\Delta$ DAT</sup> mice displayed a hypersensitivity to the locomotor and reward stimulating effects of cocaine and resembled DRD2 autoreceptor-deficient mice.

On the molecular level, FTO encodes a nucleic acid demethylase that is able to remove N6-methyladenosine (m<sup>6</sup>A) from messenger RNA. Analysis of m<sup>6</sup>A in mRNA of *Fto*-deficient midbrain and striatum showed that FTO acts as a m<sup>6</sup>A demethylase *in vivo*. Increased methylation, however, was only demonstrated for a subset of all m<sup>6</sup>A methylated transcripts. This subset included many transcripts important for cell-cell and neuronal signaling. Furthermore, many of these hypermethylated transcripts are components of dopaminergic signaling and some of these displayed a deregulation on the protein level in *Fto*-deficient mice, such as DRD<sub>3</sub>, GIRK<sub>2</sub> and NMDAR<sub>1</sub>.

Taken together, FTO, via acting as a m<sup>6</sup>A demethylase, plays an important role

in regulating the dopamine autoinhibitory feedback loop and hence impinges on dopamine circuit function. Malfunction of dopamine signaling has been implicated in a variety of diseases such as depression, schizophrenia or ADHD and therefore poses the question whether *FTO* genomic variation is associated with diseases other than obesity and whether association with obesity related traits is partly due to alterations in dopamine circuit function.

### Zusammenfassung

Genomweite Sequenzierung führte in 2007 zur Entdeckung weit verbreiteter genetischer Variationen in nicht-kodierenden Regionen des humanen *FTO* Gens, welche mit verschiedenen Merkmalen krankhaften Übergewichts assoziiert sind. Bis heute sind sowohl die Auswirkungen dieser Variationen auf die Expression von *FTO*, als auch die exakte molekulare Funktion des FTO Proteins unbekannt.

In dieser Studie konnte gezeigt werden, dass die Inaktivierung von murinem *Fto* die Funktion des dopaminergen Systems des Mittelhirns beeinflusst. Verlust von FTO führte zu einer Beeinträchtigung der autoinhibitorischen Rückkopplungsschleife dopaminerger Neurone, welche von Dopaminrezeptoren des Typs 2 (DRD2), Typs 3 (DRD3) und G Protein gekoppelten einwärts gleichrichtenden Kalium Kanälen (GIRKs) abhängig ist. Diese Fehlfunktion der autoinhibitorischen Rückkopplung konnte sowohl bei ganzkörper-*Fto*-defizienten, als auch bei spezifischem Verlust der *Fto* Expression in dopaminergen Neuronen (*Fto*<sup>ΔDAT</sup>) beobachtet werden. Während dies in ganzkörper-*Fto*-defizienten Mäusen zu verminderten Antworten auf Kokain Stimulation führte, erfuhren *Fto*<sup>ΔDAT</sup> Mäuse eine erhöhte Sensitivität für die bewegungs- und belohnungsstimulierende Wirkung von Kokain.

Auf molekularer Ebene kodiert das FTO Protein für eine Nukleinsäure Demethylase, die *N*6-Methyladenosin (m<sup>6</sup>A) von Boten-RNA (mRNA) entfernen kann. Die Analyse von m<sup>6</sup>A Modifizierungen in mRNA *Fto* defizienter Mäuse zeigte, dass FTO *in vivo* als m<sup>6</sup>A Demethylase agiert. Erhöhte Methylierungsmuster konnten allerdings nur in einem Teil aller prinzipiell m<sup>6</sup>A modifizierten Transkripte nachgewiesen werden. Diese Teilmenge hypermethylierter Transkripte beinhaltete zum großen Teil wichtige Komponenten der Zell-Zell und neuronalen Kommunikation. Darüber hinaus befanden sich unter den hypermethylierten Transkripten wichtige Bestandteile der dopaminergen Signalweiterleitung. Für einige dieser Komponenten (z.B. DRD<sub>3</sub>, GIRK<sub>2</sub> und NMDAR<sub>1</sub>) wurde eine verminderte Proteinexpression nachgewiesen.

Zusammengefasst erfüllt FTO als m<sup>6</sup>A Demethylase eine wichtige Rolle in der Kontrolle der autoinhibitorischen Rückkopplungsschleife in dopaminergen Neuronen und beeinflusst die Funktion des dopaminergen Systems sowohl auf Netzwerk-, als auch auf Einzelzellebene. Fehlfunktionen des dopaminergen Systems treten bei verschiedensten Krankheitsbildern auf, wie z.B. Depression, Schizophrenie oder Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung. Daher stellt sich die Frage, ob genomische Variabilität im *FTO* Locus auch mit anderen Erkrankungen als Übergewicht assoziiert ist, beziehungsweise ob den Assoziationen mit verschiedenen Merkmalen krankhaften Übergewichts zum Teil eine Veränderung des dopaminergen Systems zu Grunde liegt.

### 1 Introduction

#### 1.1 Obesity and obesity associated diseases

Over the last decades the prevalence of obesity has dramatically increased, prompting the World Health Organisation (WHO) to classify obesity as an epidemic of global proportion. Recent estimations suggest that about 1.4 billion people are overweight of which one third is considered obese (source: WHO). This increase in obesity is not only observed in western society, but is also identified as a threat to developing countries [Malik et al., 2013]. Overweight (body mass index (BMI)  $\geq$  25 kg/m<sup>2</sup>) and obesity (BMI  $\geq$  30 kg/m<sup>2</sup>) are known risk factors for type 2 diabetes mellitus (T2DM), cardiovascular disease and certain forms of cancer, all of which contribute to the increased mortality that is observed for obese patients [Katzmarzyk et al., 2003]. Moreover, even neurodegenerative diseases such as Alzheimer's disease have been associated with obesity [Hildreth et al., 2012]. These comorbidities render obesity one of the biggest challenges to modern society. Obesity not only decreases the individual quality of life, but is also becoming a far reaching socio-economic problem, placing a massive burden on our health systems [Cawley & Meyerhoefer, 2012; Finkelstein et al., 2009]. Thus, a necessity emerged to understand the genetics and molecular mechanisms of body weight regulation and to develop strategies to tackle the progressing obesity epidemic.

#### 1.1.1 Monogenic obesity

Since obesity has moved into focus, the study of severely obese patients has led to the identification of several loss-of-function mutations within the human genome [Farooqi & O'Rahilly, 2006]. These rare cases of monogenic obesity include e.g. mutations of leptin [Montague *et al.*, 1997], the leptin receptor [Clément *et al.*, 1998], proopiomelanocortin (POMC)[Krude *et al.*, 1998] and melanocortin 4 receptor (MC4R) [Yeo *et al.*, 1998; Farooqi *et al.*, 2003]. Individuals suffering from one of these mutations inevitably face obesity, regardless of environmental factors. Many of these studies have helped to identify critical components of the mechanisms governing energy homeostasis. Some of these patients have even benefited from treatment made available through their diagnosis. Leptin deficient patients, for example, are treated with recombinant leptin, leading to body weight loss and enabling them to lead a normal life [Farooqi *et al.*, 1999].

Monogenic forms of obesity are rare within the population and the frequency of these genomic variations has not changed since the prevalence of obesity is rising [Caballero, 2007]. Hence, rare loss-of-function mutations are not the underlying reason for the steady increase in overweight people observed since the middle of the 20<sup>th</sup> century.

#### 1.1.2 Polygenic obesity

Current research on the increasing prevalence of obesity in the general population, hence termed common obesity, investigates the influence of environmental factors on energy homeostasis. Our sedentary lifestyle, lack of physical activity and unlimited access to energy rich, highly palatable nutrition promote a misbalance between energy intake and energy expenditure, ultimately leading to weight gain [Swinburn *et al.*, 2011]. Still, considerable variation of BMI is observed in a given population that in general faces the same environmental changes and temptations. Common variations in the human genome are believed to shape the individual susceptibility to environmental factors, thus leading to the apparent divergence of BMI within a population [Maes *et al.*, 1997]. The sum of the variations carried by an individual may therefore define how environmental factors impact on certain features, such as body weight regulation.

In former years, identification of obesity related traits in the human genome

was a laborious task that had to rely on the candidate approach. Genes that were functionally related to body weight regulation were investigated for variations and subsequently tested for associations with body weight [Loos, 2012]. Due to the hypothesis driven approach, however, this method lacked the power to identify yet unknown players in body weight regulation.

Since whole genome sequencing has become affordable, genome wide association studies (GWAS) represent the means to perform hypothesis generating studies. Increasing sample sizes over the years has increased the discovery rate tremendously. In recent years, GWAS helped to identify several common genetic variations that are associated with obesity related traits, regardless of any known or unknown function for these genes [Loos, 2012; Willer *et al.*, 2009; Speliotes *et al.*, 2010]. To date, 52 loci have been associated with BMI, body fat percentage, waist circumference, waist-to-hip ratio and early onset obesity. Some of those were already known to take part in the regulation of energy homeostasis, such as variants near the insulin receptor substrate (IRS) 1 [Kilpeläinen *et al.*, 2011], near MC4R [Loos *et al.*, 2008] or within the brain-derived neurotrophic factor (BDNF) locus [Thorleifsson *et al.*, 2009]. Many of the identified loci, however, have not been known for any association with obesity related traits before [Loos, 2012].

The effect size of each individual genomic variant is relatively small, increasing the body weight per allele by as little as 200 grams [Loos, 2012]. Rather the effect of all variants present in the genome will define each individual's susceptibility to obesity. Thus, not only identifying predisposing loci and their respective molecular function, but also understanding the network of the entirety of genomic variation is important.

### 1.2 Regulation of body weight

#### 1.2.1 Energy homeostasis

In order to ensure a steady body weight, a process called energy homeostasis ensures that both energy intake and energy expenditure are balanced. Usually, times of excessive binge eating or undernutrition are compensated over the following course of days or weeks to maintain body weight [Schwartz *et al.*, 2000; Schwartz & Porte, 2005]. Malfunction of these regulatory mechanisms favoring increased energy intake and reduced energy expenditure lead to increased body weight and obesity [Schwartz *et al.*, 2000; Schwartz & Porte, 2005].

Over the past decades, several peripheral hormones have been identified that convey the current energy status of the human organism. The anorectic hormone leptin, produced by white adipocytes relative to their lipid content and released into the blood stream, is a measure for the current energy storage of the body [Friedman, 2011, 2010]. While initially administration of recombinant leptin was thought to be a potential treatment for obesity, studies showed that obese patients have high levels of circulating leptin and the body lost its ability to process the signal [Könner & Brüning, 2012; Myers et al., 2008]. The second hormone insulin is released by pancreatic  $\beta$ -cells in response to increasing blood glucose levels after food intake and ensures the uptake of glucose in peripheral organs such as the liver, muscle and adipose tissue [Kahn, 1994; Könner et al., 2009]. Moreover, insulin, like leptin, was found to signal to specific neuronal populations and regulate food intake [Könner et al., 2009; Könner & Brüning, 2012; Belgardt & Brüning, 2010]. A third hormone, the orexigenic ghrelin, is secreted by the stomach and intestine, with levels decreasing after food intake and increasing with food deprivation [Cummings & Overduin, 2007]. Leptin, insulin and ghrelin, are only three examples of hormones involved in energy homeostasis. Jointly, these hormones are the signal infrastructure conveying information about the peripheral energy status to the central nervous system, the master regulator of energy homeostasis

[Schwartz *et al.*, 2000; Könner *et al.*, 2009]. The evaluation of these hormonal signals within the brain then leads to the behavioral outcome. Further investigations showed, that failure of brain circuits to interpret the circulating signals, e.g. insulin and/or leptin resistance, has major impacts on energy homeostasis [Könner & Brüning, 2012].

#### 1.2.2 CNS in regulation of energy homeostasis

Already more than 70 years ago, lesion experiments in rats demonstrated that the hypothalamic area of the brain plays a critical role in the regulation of body weight [Hetherington & Ranson, 1940]. Since then, further refinement of methodology led to the dissection of different nuclei within the hypothalamus in the control of energy homeostasis [Könner *et al.*, 2009; Belgardt & Brüning, 2010; Kleinridders *et al.*, 2009].

The first order neurons of the homeostatic system reside within the mediobasal hypothalamus [Könner et al., 2009; Belgardt & Brüning, 2010]. The close proximity to the blood-brain barrier render the anorexigenic POMC/CART (pro-opiomelanocortin/cocaine and amphetamine regulated transcript) and the orexigenic AgRP/NPY (agouti-related peptide/neuropeptide Y) neurons of the arcuate nucleus (ARC) sensitive to the hormones circulating in the blood stream. Consistently, activity of these neurons is regulated by insulin, leptin, ghrelin and even circulating levels of glucose [Könner et al., 2009; Belgardt & Brüning, 2010]. POMC/CART neurons release  $\alpha$ -MSH ( $\alpha$ -melanocyte stimulating hormone), a cleavage product of pro-opiomelanocortin, which in turn activates MC4 receptors on the second order neurons that reside e.g. within the paraventricular nucleus of the hypothalamus (PVN) [Könner et al., 2009]. Activation of those second order neurons in the PVN leads to a decrease in food intake [Balthasar et al., 2005]. Activation of AgRP/NPY neurons on the other hand silences the POMC/CART neurons through  $\gamma$ -aminobutyric acid (GABA) released from AgRP/NPY neuron synapses [Atasoy et al., 2012; Könner et al., 2009; Belgardt & Brüning, 2010]. Moreover, these neurons

release AgRP, which is an inverse agonist of MC4 receptors, blocking those receptors and thereby preventing *α*-MSH mediated activation of second order neurons [Könner *et al.*, 2009; Belgardt & Brüning, 2010]. As a result, food intake is increased, while energy expenditure is reduced [Könner *et al.*, 2009; Belgardt & Brüning, 2010].

Additionally, other hypothalamic nuclei feed into the homeostatic control of body weight, such as the ventromedial (VMH), dorsomedial (DMH) and lateral hypothalamic (LH) areas [Belgardt & Brüning, 2010; Könner et al., 2009]. The LH is of special notion, as it represents one possible link of the homeostatic system to other brain areas, such as the dopaminergic midbrain neurons which control the hedonic and reward related behaviours [Sternson, 2013; Berthoud, 2011; Simerly, 2006; Saper et al., 2002]. Orexin, secreted from orexinergic neurons within the LH, has been demonstrated to be a potent mediator of wakefulness in control of sleep/wake cycles in mammals [Sakurai et al., 1998; Harris & Aston-Jones, 2006; Adamantidis et al., 2007; Tsunematsu et al., 2011]. Consistently, leptin inhibits orexinergic neurons, thus allowing periods of rest and sleep in the satiated state [Yamanaka et al., 2003]. Neurons of the LH project onto midbrain dopaminergic neurons and release orexin, which subsequently alters dopaminergic neuron function via orexin receptors [Sharf et al., 2010; Borgland et al., 2006]. Hence, the LH represents one possible interface of homeostatic and hedonic regulation of food intake. Further evidence points towards projections from the hypothalamus (AgRP/NPY neurons) directly to DA neurons [Palmiter, 2012]. Conceptually, the ventral striatum (nucleus accumbens, NAc), may represent the integrative center, processing information from the energy sensing hypothalamic nuclei, from the midbrain that conveys rewarding aspects of food intake and from higher brain centers that feed experience and decision making into the equation. Consolidation of all inputs will then lead to a subsequent behavioural outcome that may lead to food intake [Simerly, 2006].

### 1.3 The dopaminergic system

#### 1.3.1 Dopamine and dopaminergic neurons

Dopamine (DA) belongs to the family of catecholamine neurotransmitters and as such is a precursor of norepinephrine and epinephrine [Björklund, 2007]. Initially not regarded as such, dopamine is an independent neurotransmitter involved in important physiological processes [Carlsson *et al.*, 1958]. The total number of dopaminergic neurons (DA neurons) increases in mammals according to the growth of cortical and striatal regions, with mice having approximately 20,000 to 30,000 DA neurons, monkeys 160,000 to 320,000 and humans 400,000 to 600,000 [Björklund, 2007]. About 70 to 75 % of these neurons reside within the midbrain in the ventral tegmental area (VTA), substantia nigra (SN) and retrorubral field, while the remaining dopamine neurons are found, for example, within the hypothalamus and olfactory bulbs [Björklund, 2007; Bentivoglio & Morelli, 2005]. Opposing the relatively low number of dopamine neurons is the fact that each dopaminergic neuron may have synaptic contact to 300-400 neurons, placing the dopaminergic pathways among the most prominent innervating circuits in the brain [Schultz, 1998].

Classically, midbrain dopaminergic neurons have been categorized into three different pathways. First, the nigrostriatal pathway of SN dopamine neurons projecting to the dorsal striatum (caudate putamen, CPu). Second, the mesolimbic pathway of VTA dopamine neurons projecting to the ventral striatum (nucleus accumbens, NAc), the amygdala and olfactory tubercle. Third and finally, the meso-cortical pathway of dopamine neurons projecting to cortical areas [Björklund, 2007]. Novel tracing methods, however, question this view of dopaminergic projections and suggest a more complex projection pattern and cross-projections along these classical pathways [Björklund, 2007].

Dopamine has been implicated in a variety of processes including voluntary movement, reward, attention, motivation, sleep, memory and learning [Iversen &

Iversen, 2007; Beaulieu & Gainetdinov, 2011; Björklund, 2007; Di Chiara, 2005; Dunnett, 2005]. Loss of striatal dopamine neuron inervation represents the hallmark of Parkinson's disease, moving dopaminergic function into the focus of Parkinson's treatment [Iversen & Iversen, 2007; Sulzer, 2007].

#### 1.3.2 Dopamine receptors and dopamine signaling

Five different dopamine receptors belonging to two different classes are known. The D1-like dopamine receptors, including dopamine receptors D1 (DRD1) and D<sub>5</sub> (DRD<sub>5</sub>), and the D<sub>2</sub>-like receptors, including dopamine receptors D<sub>2</sub> (DRD<sub>2</sub>), D<sub>3</sub> (DRD<sub>3</sub>) and D<sub>4</sub> (DRD<sub>4</sub>) [Beaulieu & Gainetdinov, 2011]. Dopamine receptors are widely expressed within the brain, but also in peripheral tissues, such as the adrenal glands and sympathetic ganglia. DRD1 is mainly expressed within the ventral and dorsal striatum, the substantia nigra, amygdala and olfactory bulb and represents the major receptor of the direct basal ganglia pathway [Beaulieu & Gainetdinov, 2011]. DRD2s are the main receptors involved in the indirect basal ganglia pathway and are highly expressed in dorsal and ventral striatum, as well as the olfactory tubercle [Beaulieu & Gainetdinov, 2011]. DRD3s are mainly found within the ventral striatum (NAc) and the olfactory tubercle. DRD2 and DRD3, however, are the only receptors that are also expressed presynaptically in the SN and VTA [Beaulieu & Gainetdinov, 2011]. D4 and D5 receptors exhibit the lowest expression of all dopamine receptors and are found within a variety of areas, including cortical areas, hippocampus, hypothalamus and midbrain [Beaulieu & Gainetdinov, 2011].

Genes of the DRD1 and DRD5 do not have introns and thus these receptors are not expressed in different splice isoforms [Beaulieu & Gainetdinov, 2011]. DRD2, DRD3 and DRD4, however, have intronic regions in their respective genes and several isoforms have been described, the most prominent ones being the DRD2S (short isoform), that shows preferentially presynaptic expression, and the DRD2L (long isoform), that is predominantly found postsynpatically [De Mei *et al.*, 2009]. Dopamine receptors belong to the family of G protein-coupled receptors and as such their main target is the regulation of the adenylyl cyclase (AC) and cAMP production [Hyman *et al.*, 2006; Beaulieu & Gainetdinov, 2011]. Whereas D2-like receptors inhibit the AC via  $G\alpha_{i/o}$ , D1-like receptors increase the activity of AC via  $G\alpha_{s/olf}$  and thus increase cAMP levels. As a result of G protein signaling, dopamine receptors modulate activity of important signaling mediators, such as protein kinase A (PKA), phospholipase C (PKC) and protein kinase B (AKT) (see Figure 1.1) [Hyman *et al.*, 2006; Beaulieu & Gainetdinov, 2011].

Despite modulation of AC activity, several other signaling modalities have been reported for dopamine receptors. Both DRD5 and DRD1 have been implicated in regulation of phospholipase C (PLC) via  $G\alpha_q$ , potentially linking dopamine signaling to intracellular calcium mobilization [Beaulieu & Gainetdinov, 2011]. Whether this connection is mainly through DRD5 or DRD1 (or DRD1:DRD2 heterodimers), however, remains to be elucidated. D2-like receptors, on the other hand, have been demonstrated to activate PLC via  $G\beta_{\gamma}$ , while inhibiting L- and N-type calcium channels through the same G protein cascade [Beaulieu & Gainetdinov, 2011]. Moreover, D2-like receptors regulate neuronal activity through  $G\beta_{\gamma}$  mediated activation of G protein-coupled inwardly rectifying potassium channels (GIRKs), which hyperpolarize and hence inhibit neurons (Figure 1.1) [Lüscher & Slesinger, 2010]. Following activation by dopamine, dopamine receptor signaling may be terminated through phosphorylation by G protein-coupled receptor kinases (GRKs) and subsequent internalization. Phosphorylation, however, may also promote a late signaling event in D2-like receptors that inhibits protein kinase B (AKT/PKB) in a  $\beta$ -arrestin 2 and protein phosphatase 2A (PP2A) dependent manner (Figure 1.1) [Beaulieu & Gainetdinov, 2011].

#### 1.3.3 Dopamine and reward related behaviors

One of the primary functions of the dopaminergic system is the modulation of behavioral responses [Pandit *et al.*, 2011; Volkow *et al.*, 2013; Wise, 2013]. A major



#### Figure 1.1: Pre- and postsynaptic dopamine receptor signaling.

Dopamine is synthesized from tyrosine via the tyrosine hydroxylase and subsequent decarboxylation via the DOPA decarboxylase. Dopamine receptors are divided into two groups, the D1-like receptors (DRD1 and DRD5) and the D2-like receptors (DRD2, DRD3 and DRD4). While D1-like receptors are only present postsynaptically on dopamine target neurons, DRD2 and DRD3 receptors are also found presynaptically on dopamine neurons. Dopamine receptors are G protein-coupled receptors, that are able to trigger several responses. DRD1-like receptors positively regulate the adenylyl cyclase (AC) via  $G\alpha_{s/olf}$  leading to increasing levels of cAMP and protein kinase A (PKA) activity. Moreover, D1-like receptors phospholipase C (PLC) activity is increased via  $G\alpha_{a}$ .

D2-like receptors, on the other hand, negatively regulate AC activity (via  $G\alpha_{i/o}$ ) and AKT (in a  $\beta$ -arrestin 2 ( $\beta$ Arr2) and protein phosphatase 2A (PP2A) dependent manner). Furthermore, coupling to  $G\beta_{\gamma}$  positively regulates PLC and may lead to opening of G protein-coupled inwardly rectifying potassium channels (GIRK), while inhibiting L- and N-type calcium channels. Presynaptic coupling of D2-like receptors to GIRKs has been found to play an important role in the dopamine autoreceptor feedback loop. Termination of dopaminergic signaling is finally achieved through reuptake of dopamine via the dopamine transporter expressed on dopamine neurons.

aspect of this function is encoding the motivational value, being rewarding or aversive, of substances, such as drugs and food, or behaviors like sexual reproduction [Kenny, 2011; Kelley & Berridge, 2002]. As a consequence, dopamine signaling adjusts the probability for a repetition of a certain behavior, being it e.g. drug abuse or highly palatable food intake [Schultz, 2010; Volkow *et al.*, 2013; Schultz, 2007]. Hence, underlying these alterations is a learning process that depends on reinforcing experiences that describe the 'liking' of the performed behaviors [Iversen & Iversen, 2007; Schultz, 2007].

First evidence for the involvement of dopaminergic pathways in reward related motivation stem from self stimulation studies. Electrical stimulation of dopaminergic afferents along the medial forebrain bundle, the LH that is connecting to the midbrain dopamine neurons or dopamine neurons themselves (VTA) causes a favorable sensation that subsequently leads to increasing self stimulation in both rodents and humans [Wise, 2013; Volkow *et al.*, 2013]. Subsequent studies established the role of the dopaminergic system in a complex system of neuronal circuits shaping motivation and reinforcement of behaviors [Schultz, 2007; Pandit *et al.*, 2011].

To encode the motivational value, dopamine neurons exhibit episodes of burst firing that subsequently lead to increased dopamine levels in the synaptic cleft [Schultz, 2010; Overton & Clark, 1997]. These burst firing events were observed in response to motivating stimuli, such as ingestion of sweet liquid in monkeys [Schultz, 2010, 1998]. Moreover, these rewarding stimuli have been successfully coupled to visual or auditory stimuli that, when preceding the actual reward, elicit anticipatory dopamine neuron burst firing [Schultz, 1998]. Absence of the rewarding stimuli following the conditioned stimulus, however, leads to a paucity in dopamine neuron firing, hence encoding the prediction error of the missing motivational stimulus and adjusting behavior [Schultz, 1998]. The very same mechanism is furthermore hypothesized to underly the drug taking response and subsequent craving and seeking for drugs, hallmarks of drug addiction [Pandit *et al.*, 2011;

Volkow *et al.*, 2013]. Moreover, many addictive drugs directly influence the dopaminergic system. Cocaine, for example, blocks the dopamine transporter (DAT) expressed on dopaminergic neurons and prevents re-uptake of dopamine from the synaptic cleft and thus attenuates DA signaling shut down [Hyman *et al.*, 2006]. Similarly, amphetamine potentiates dopamine signaling through increasing DA release from dopaminergic synapses [Hyman *et al.*, 2006]. Despite drug abuse and addiction, malfunction of the dopaminergic circuitry has been implicated in conditions such as attention deficit/hyperactivity syndrome (ADHD) [Swanson *et al.*, 2007], Tourette's syndrome [McNaught & Mink, 2011], schizophrenia [Beaulieu & Gainetdinov, 2011; Iversen & Iversen, 2007], bipolar disorder and major depression [Beaulieu & Gainetdinov, 2011].

Dopamine signaling is not causing a fast postsynaptic response, but rather modulates the properties of postsynaptic neurons [Kauer & Malenka, 2007; Hyman *et al.*, 2006]. Thus, dopamine is instrumental in synaptic plasticity and adaptations of synaptic transmission, thought to be the underlying mechanism of learning processes [Kauer & Malenka, 2007].

#### 1.3.4 Dopamine and obesity

The dopaminergic system is "the brain's natural reinforcement system" [Salamone & Correa, 2002]. As such, it is believed that the motivational value of natural rewarding stimuli, such as food and the behavior leading to the consumption of food, are encoded in the dopaminergic system [Pandit *et al.*, 2011; Volkow *et al.*, 2013]. From an evolutionary perspective, reinforcing food intake was ensuring the ability to overeat in times of plenty to prepare for times of need [Pandit *et al.*, 2011; Schwartz *et al.*, 2003]. In fact, food has been demonstrated in some cases to be preferred over drugs [Lenoir *et al.*, 2007]. Several studies suggest common alterations of the dopaminergic circuitry in addiction and obesity [Volkow *et al.*, 2013; Wise, 2013; Bello & Hajnal, 2010; Kenny, 2011].

Drugs of abuse increase extra synaptic levels of dopamine [Kauer & Malenka,

2007; Di Chiara & Imperato, 1988]. In the same manner, eating and drinking cause elevated levels of dopamine in the ventral and dorsal striatum [Yoshida et al., 1992; Small *et al.*, 2003]. Both pharmacological dopamine depletion, as well as genetically engineered DA-deficiency in mice causes hypophagia [Salamone et al., 1993; Zhou & Palmiter, 1995]. Moreover, obesity and chronic drug abuse reduce dopamine type 2 receptor (DRD2) availability in human striatum [Volkow et al., 2002; Wang et al., 2001]. Consistently, DRD2 levels are reduced in obese rats [Hamdi et al., 1992; Johnson & Kenny, 2010]. Knock-down of striatal DRD2s, on the other hand, caused obsessive food seeking in rats [Johnson & Kenny, 2010]. Chronic exposure to a high fat diet in rats increases the threshold for electric self stimulation in the LH [Johnson & Kenny, 2010]. The very same is observed in rats after prolonged cocaine treatment [Ahmed *et al.*, 2002]. Moreover, high fat diet exposure dampens the preference for amphetamine cues and lowers the operant response to sucrose [Davis et al., 2008]. Consistently, human obesity has been shown to decrease the lifetime risk for drug abuse [Simon et al., 2006]. Vice versa, food restriction was demonstrated to increase the sensitivity for drugs and to reduce the threshold for lateral hypothalamic self administration [Carroll *et al.*, 1979; Carroll & Meisch, 1981; Davis *et al.*, 2010; Abrahamsen *et al.*, 1995].

During food restriction, levels of endocrine hormones change. In case of leptin and insulin, food deprivation decreases circulating levels [Könner *et al.*, 2009]. Food restriction has been demonstrated to decrease *Dat* mRNA and activity in the striatum, whereas centrally applied insulin increases *Dat* mRNA levels in the midbrain [Patterson *et al.*, 1998; Figlewicz *et al.*, 1994]. Both leptin and insulin receptors are expressed on dopaminergic neurons and both insulin and leptin potently modulate dopamine neuron activity [Figlewicz *et al.*, 2003; Fulton *et al.*, 2006; Könner *et al.*, 2011]. Intracerebroventricular (ICV) injection of leptin inhibited dopamine neuron firing, reducing food intake and dopamine levels in the ventral striatum. Knock down of midbrain leptin receptors, on the other hand, increases food intake and the sensitivity to sucrose and highly palatable food [Hommel *et al.*, 2006; Krügel *et al.*, 2003]. Consistently, ICV leptin administration is able to modulate LH self stimulation [Fulton *et al.*, 2000] and both insulin and leptin decrease sucrose self stimulation [Figlewicz *et al.*, 2006].

In humans, obesity causes increased brain activity in response to feeding associated cues [Volkow *et al.*, 2008]. The same is observed in leptin deficient patients, however, leptin treatment is able to reduce the increased brain activity, as well as food liking and caloric intake [Farooqi *et al.*, 2007]. Despite insulin and leptin, several other hormones an neuropeptides have been linked to drug abuse and reward related behavior, including orexin, oxytocin, galanin, melanocortin, neuropeptide Y (NPY) and peptide YY (PYY), further supporting the connections of homeostatic and hedonic feeding control [Volkow *et al.*, 2013].

#### 1.3.5 DRD2/DRD3 autoreceptor feedback loop

To regulate dopaminergic synaptic transmission, DA neurons feature an autoinhibitory feedback loop that terminates dopamine release [Beaulieu & Gainetdinov, 2011; De Mei *et al.*, 2009; Joseph *et al.*, 2002; Sibley, 1999; Missale *et al.*, 1998]. Both DRD2 and DRD3, but not D1-like receptors, are presynaptically expressed and were shown to couple to GIRKs (Figure 1.1) [De Mei *et al.*, 2009; Beaulieu & Gainetdinov, 2011; Sibley, 1999; Mercuri *et al.*, 1997]. Upon dopamine release opening of these channels leads to an inhibition of firing and thus termination of dopamine release from DA neurons [Paladini *et al.*, 2003]. Findings for presynaptic D3 receptors, however, are in part controversial, showing potent inhibition for VTA, but not SN dopamine neurons [Davila *et al.*, 2003; Lejeune & Millan, 1995; Kuzhikandathil *et al.*, 1998; Gainetdinov *et al.*, 1996; Joseph *et al.*, 2002]. In addition to the regulation of dopamine neuron firing, presynaptic dopamine receptors are implicated in the direct regulation of dopamine synthesis [Wolf & Roth, 1990; Anzalone *et al.*, 2012; Joseph *et al.*, 2002].

In mice, loss of DRD2 autoreceptors causes cocaine supersensitivity and increases motivation for reward, while body weight and food intake remain unaltered [Bello *et al.*, 2011]. In humans, reduced dopamine autoreceptor availability is associated with increased impulsivity [Buckholtz *et al.*, 2010]. Taken together, dopamine autoreceptor function is likely to play a critical role in the proper function of the dopaminergic system and may lead to elevated DA neuron excitability and aberrant DA release. Hence, malfunction of the autoinhibitory feedback loop may impinge on complex human behavior, such as impulsivity, reinforcement or drug abuse [Bello *et al.*, 2011; Buckholtz *et al.*, 2010].

#### 1.4 The fat mass and obesity-associated protein (FTO)

#### 1.4.1 Genome wide association studies

#### Associations with obesity-related traits

First identified as one of the genes deleted in the *fused toes* (*Ft*) mouse mutant [Peters *et al.*, 1999; van der Hoeven *et al.*, 1994], general interest in FTO (fat mass and obesity-associated protein) was triggered through the robust association of a single nucleotide polymorphism (SNP, rs9939609) within the *FTO* gene with obesity-related traits (Figure 1.2 a) [Frayling *et al.*, 2007; Dina *et al.*, 2007; Scuteri *et al.*, 2007]. These findings, to date, have been replicated in both adults and children in independent populations of various, though not all, ethnicities [den Hoed *et al.*, 2009; Cecil *et al.*, 2008; Fang *et al.*, 2010; Grant *et al.*, 2008; Bollepalli *et al.*, 2010; Liu *et al.*, 2010; Adeyemo *et al.*, 2010; Chang *et al.*, 2008; Tan *et al.*, 2008; Croteau-Chonka *et al.*, 2011; Yajnik *et al.*, 2009]. While initially FTO was associated with changes in BMI, subsequent studies with increased sample size confirmed the associations not only for BMI, but additionally for e.g. body fat percentage, waist circumference and obesity risk [Loos, 2012].

To date, the majority of *FTO* single nucleotide polymorphisms associated with obesity are situated in the first intron of the human gene, forming a cluster of SNPs that predisposes to obesity (Figure 1.2 a) [Willer *et al.*, 2009; Jacobsson *et al.*, 2012]. The overall effect size for the human *FTO* obesity-associated risk alleles,



Figure 1.2: Genome wide association studies link *FTO* to obesity (a) A cluster of single nucleotide polymorphisms (SNPs) within the first intron of the human *FTO* gene is significantly associated with increased BMI. Upstream and in opposite orientation of the *FTO* gene, the ciliary gene *RPGRIP1L* is situated (Figure adapted from Willer *et al.* [2009]). (b) Before adiposity rebound at the age of 5.5 years in children, an inverse association between *FTO* genetic variation and BMI is detected. After the adiposity rebound, the correlation reverses and *FTO* SNPs are associated with increased BMI (A = obesity risk allele, T = non-obesity risk allele; Figure adapted from Sovio *et al.* [2011]).

however, is relatively small. One copy of the risk allele may account for as much as 1.5 kg increased body mass or approximately  $0.4 \text{ kg/m}^2$  higher body mass index [Frayling *et al.*, 2007]. This, however, renders the *FTO* SNPs not only the genomic variants with the strongest obesity association, but also the variant with the biggest effect size [Loos, 2012].

Interestingly, the positive association of *FTO* genomic variation develops at the age of 5.5 years and is detectable in adults and elderly (Figure 1.2 b) [Sovio *et al.*, 2011; Frayling *et al.*, 2007; Dina *et al.*, 2007; Scuteri *et al.*, 2007]. Before the age of 2.5 years, however, an inverse association of *FTO* genotype and BMI is detected [Sovio *et al.*, 2011]. The reversal of the relationship seems to coincide with the adiposity rebound, the time point at which the BMI of children starts to steadily increase after a period of decline from 2 to 5 years of age. Interestingly, each copy of the rs9939609 risk-allele accelerates development by 2.4 %, resulting in a shift of adiposity rebound in children.

#### Influence on energy intake

Additional assessment of eating behaviour revealed an increased energy intake for FTO risk-allele carriers in comparison to controls [Cecil et al., 2008; Timpson et al., 2008; Speakman et al., 2008; Wardle et al., 2009; Haupt et al., 2009], possibly due to an increase in fat consumption [Timpson et al., 2008; Tanofsky-Kraff et al., 2009]. At the point of adiposity rebound (age 4-5) that coincides with the beginning of the positive correlation of *FTO* variants with BMI, children with the obesity risk-alleles already show increased consumption of highly palatable food [Wardle et al., 2009]. Hence, this shift in food preference may represent, at least partly, the underlying mechanism leading to increased BMIs observed later in life. Further studies assessing the eating behaviour of children support this notion, reporting increased food responsiveness (ages 3-4, questionnaire example: "Even if my child is full, he/she finds room to eat his/her favourite food")[Velders et al., 2012], impaired satiety response (age 8-11 years; questionnaire example: "My child cannot eat a meal if he/she has had a snack just before.") [Wardle et al., 2008], loss of control over eating (ages 6-19)[Tanofsky-Kraff et al., 2009] and lower postprandial responses in hungry or satiated state [den Hoed et al., 2009; Karra et al., 2013].

Further attempts to link *FTO* variants to changes in energy expenditure have been inconclusive so far. Both decreased, as well as increased energy expenditure have been reported [Keller *et al.*, 2011; Jonsson & Franks, 2009]. The majority of studies, however, failed to find any association between *FTO* genotypes and energy expenditure [Speakman *et al.*, 2008; Goossens *et al.*, 2009; Hakanen *et al.*, 2009; Haupt *et al.*, 2009; Berentzen *et al.*, 2008]. On the contrary, physical activity attenuates the impact of *FTO* genotypes on BMI [Vimaleswaran *et al.*, 2009; Kilpelaeinen *et al.*, 2011].

#### Non obesity-related associations

Despite the robust association with obesity-related traits, *FTO* SNPs have recently been associated with non obesity-related conditions. Some of these associations, however, may indirectly impinge on energy intake. Decreased total consumption of

alcohol (beer and spirits) independently of BMI is observed for rs9939609 risk-allele carriers, with the consumption of larger amounts distributed over fewer occasions as compared to controls [Sobczyk-Kopciol *et al.*, 2011]. Correspondingly, the obesity risk-allele was inversely correlated with alcohol dependency. Moreover, smokers amongst obesity risk-allele carriers started tobacco consumption later in life and smoke less cigarettes during times of heavy smoking [Sobczyk-Kopciol *et al.*, 2011].

Both rs9930609 and rs8050136 *FTO* SNPs are linked to attention-deficit/ hyperactivity syndrome (ADHD) [Velders *et al.*, 2012; Choudhry *et al.*, 2013]. Despite the fact that unmedicated ADHD is associated with increasing risk of childhood obesity [Waring *et al.*, 2008], these *FTO* variants are inversely correlated with ADHD independent of BMI. Independent of the assessed ADHD symptoms, rs9930609 carriers furthermore exhibited improved emotional control and increased food responsiveness [Velders *et al.*, 2012].

First associations between several *FTO* genomic variations and major depressive disorder described the modifying effects of this psychiatric disease on the *FTO* dependent differences in BMI [Rivera *et al.*, 2012]. Subsequently, the inverse relation between depression and the rs9930609 *FTO* SNP was demonstrated [Samaan *et al.*, 2012]. Since depression is known to correlate positively with obesity [Pine *et al.*, 2001; Dockray *et al.*, 2009], this inverse association is surprising. These findings suggest a protective effect of the *FTO* obesity risk-alleles for major depressive disorder, with each copy of the allele decreasing the risk to develop depression by approximately 8% [Samaan *et al.*, 2012].

Despite psychiatric disorders that manifest early in life, *FTO* genomic variation was furthermore linked to aging-associated cognitive decline. Reduced verbal fluency is observed for obese male homozygous carriers of the obesity associated rs9939609 'A' allele [Benedict *et al.*, 2011]. Normal weight SNP carriers, as well as normal and overweight non-carriers, however, retain their verbal capabilities. Correspondingly, elderly subjects in treatment for cardiovascular disease and positive for the rs8050136 risk-allele perform worse in a memory performance test (Califor-
nia Verbal Learning Test) [Alosco *et al.*, 2013]. Cognitive decline for *FTO* genotypes was further confirmed, independent of age, gender, BMI or diabetes [Bressler *et al.*, 2013].

Dementia and Alzheimer's disease are additional aging-associated diseases that are linked to genotypic variation of the *FTO* gene. Carrying two copies of the rs9930609 obesity risk-allele increases the risk to develop dementia and Alzheimer's, with no influence of physical activity, cardiovascular disease, BMI or diabetes on this association [Keller *et al.*, 2011]. Strikingly, the risk for dementia and Alzheimer's is almost triplicated by an interaction of *FTO* and apolipoprotein E (APOE)  $\epsilon_4$  risk alleles. In line with these findings, healthy elderly rs3751812 SNP carriers exhibit structural brain changes with an average reduction in brain volume of 8% (frontal lobes) to 12% (occipital lobes) [Ho *et al.*, 2010].

Finally, the mortality rate was shown to be increased for rs9939609 SNP carriers, independent of obesity [Zimmermann *et al.*, 2009]. Non carriers exhibit a 42% reduced mortality rate, when compared to risk-allele carriers. Of note, diseases of the nervous system were only found in risk-allele carriers as a cause of death. These fatalities are, however, not the underlying reason for the overall elevated mortality rate of risk-allele carriers.

#### Functional aspects of FTO single nucleotide polymorphisms

To date, the functional outcome of the genetic variation found within human *FTO* is unknown. In fact, it still remains elusive, whether *FTO* is affected by these variations at all. So far, only few studies tried to address the outcome of single nucleotide polymorphism in the first intron of the *FTO* gene on its expression and found increased *FTO* expression in peripheral blood cells and fibroblasts of rs9939609 risk allele carriers [Karra *et al.*, 2013; Berulava & Horsthemke, 2010]. Due to the small sample size of these studies and the questionable functional relevance of *FTO* expression in peripheral blood cells and fibroblasts, however, these results are not compelling with respect to the biological function of FTO.

Orientated in the opposite direction and close to the first exon of FTO, lies

the transcriptional start site of the RPGRIP1L gene (retinitis pigmentosa GTPase regulator-interacting protein-1 like), that may as well be affected by the SNPs situated within this chromosomal area [Jacobsson et al., 2012; Stratigopoulos et al., 2008]. Two putative CUX1 (CUTL1; cut-like homeobox 1) binding sites were found within the SNP cluster, potentially leading to a transcriptional co-regulation of FTO and RPGRIP1L [Frayling et al., 2007; Stratigopoulos et al., 2008, 2011]. Binding of the p110 CUX1 isoform was further demonstrated to increase the activity of human FTO and RPGRIP1L minimal promotors, whereas the p200 isoform decreased the activity [Stratigopoulos et al., 2011]. Additional evidence gathered in rodent cell culture experiments points to a role of FTO and RPGRIP1L in leptin receptor clustering at the ciliary pole. Thus, through increasing *Fto* and *Rpgrip1l* expression, Cux1 may increase leptin receptor trafficking to the ciliary pole and increase leptin sensitivity [Stratigopoulos et al., 2011]. As a result, FTO and RPGRIP1L may alter food intake by affecting leptin sensitivity. Interestingly, the binding affinity of the promoter activity increasing p110 isoform was found to be decreased in carriers of the obesity-associated rs8050136 SNP. The potential decrease in FTO and RPGRIP1L expression may in turn lead to a decreased leptin sensitivity, which could be the underlying reason for the increased energy intake observed in obesity risk-allele carriers [Stratigopoulos et al., 2011]. How FTO and/or RPGRIP1L would affect leptin receptor clustering is not known in detail. RPGRIP1L, however, is part of the basal cilium [Vierkotten et al., 2007; Delous et al., 2007] and is thus a potential link to ciliopathies, some of which are known to be related to obesity, such as the Alström and Bardet Biedl syndromes [Berbari et al., 2013; Heydet et al., 2013; Girard & Petrovsky, 2011; Ansley et al., 2003; Davenport et al., 2007]. Conversely, though, Ftm-deficient mice (the ortholog of RPGRIP1L) have renal, hepatic and brain abnormalities and no body weight phenotype [Delous et al., 2007]. Moreover, patients with the Joubert and Meckel syndromes, both caused by loss-of-function mutations in RPGRIP1L, are not obese, but suffer from brain and renal malformations [Devuyst & Arnould, 2008]. Hence, the proposed co-regulatory function of both FTO and RPGRIP1L in leptin receptor clustering at the ciliary pole demand further investigation, to identify the underlying molecular mechanisms.

#### 1.4.2 Human FTO phenotypes

#### Loss-of-function mutations

The importance of a functional FTO protein for the human organism was indicated by the analysis of a rare loss-of-function mutation in the genomic sequence of *FTO* in a palestinian arab family [Boissel *et al.*, 2009]. The mutation, leading to an amino acid substitution at position 316 of the FTO protein (arginine to glutamine, R316Q), most likely impairs the interaction of FTO with the cosubstrate 2-oxoglutarate and thus renders the protein non-functional. As a result, all of the eight examined patients born with the autosomal recessive mutation died before the age of 3 while suffering from a severe phenotype, characterized by postnatal growth retardation, microcephaly, brain malformations, severe psychomotor delay, functional brain deficits, facial malformations and cardiac deficits [Boissel *et al.*, 2009]. Both, cognitive defects and changes in brain structure are also observed in carriers of the human obesity risk-alleles, however, they do not reach the severity of the *FTO*-deficient patients [Ho *et al.*, 2010; Benedict *et al.*, 2011].

#### FTO trisomy

In contrast to the aforementioned loss-of-function mutation, genomic triplications (trisomies) including the *FTO* gene show the other end of altered gene dosage. Only few cases of partial trisomies of the human chromosome 16q are known so far. Interestingly however, these cases share some phenotypic characteristics including obesity, learning difficulties and aggressive behaviour [Barber *et al.*, 2006; van den Berg *et al.*, 2010]. Due to the fact that the triplications of the proximal arm of chromosome 16 include more than just one gene these observations cannot be unambiguously attributed to *FTO*. Moreover, not all of the investigated patients exhibited for example obesity [Barber *et al.*, 2006].

#### 1.4.3 Murine Fto studies

#### *Fto* deficiency

Triggered by the growing interest in FTO and its function in regulation of body weight, mouse models were employed to investigate the role of murine FTO in energy homeostasis. Germline deletion of FTO through deletion of exons 2 and 3 of the murine Fto gene causes severe defects. Fto-deficient mice exhibit postnatal growth retardation accompanied by a 50% reduction in survival rate [Fischer et al., 2009]. Furthermore, Fto-deficient mice have both reduced lean and fat mass compared to wildtype littermates, caused by increased energy expenditure and increased systemic sympathetic tone and despite reduced homecage activity and relative hyperphagia. These characteristics, are at least partly in line with human FTO-deficiency [Boissel et al., 2009], demonstrating again the importance of functional FTO protein for mammalian organisms. Notably, heterozygous loss of FTO renders mice tolerant to high fat feeding, while severe defects are rescued by one functional *Fto* allele [Fischer *et al.*, 2009]. Recently, these findings were confirmed for the germline deletion of exon 3 in a conditional mouse model [McMurray et al., 2013]. Furthermore, the conditional model enabled the adult onset, global FTO deletion in mice through usage of a tamoxifen inducible Cre-recombinase (Cre-ER). Since FTO expression was only altered after 6 weeks of age, these mice overcame the postnatal growth retardation and premature death of germline FTO deletion. 3 weeks after tamoxifen treatment, adult onset Fto-deficient mice start loosing weight, mainly due to a loss of lean mass possibly caused by increased protein utilization [McMurray *et al.*, 2013]. During the course of the following weeks, this initial loss of weight was compensated by an increase in fat mass, despite any changes in absolute food intake or energy expenditure.

#### Fto overexpression

To this end, the exact function of the single nucleotide polymorphisms in the human *FTO* gene are not known. Two studies, however, showed increased *FTO* 

mRNA expression in peripheral blood cells of homozygous rs9939609 risk-allele carriers suggesting that *FTO* genomic variation may cause increased FTO expression [Karra *et al.*, 2013; Berulava & Horsthemke, 2010].

In mice, global overexpression of FTO causes obesity in a dose dependent manner [Church *et al.*, 2010]. Both on normal chow as well as on high fat diet, these mice have an increased body weight and fat mass. Since no changes in energy expenditure or locomotor activity are detected, the observed elevated food intake is the most probable cause for the body weight changes [Church *et al.*, 2010]. The increase in food intake in those mice is in line with the reported alterations of energy intake in human *FTO* variants, further supporting the notion that human variation is associated with increased FTO expression or activity.

#### Peripheral tissue function

FTO is expressed in peripheral tissues [Gerken *et al.*, 2007; Frayling *et al.*, 2007; Stratigopoulos *et al.*, 2008]. To date, however, studies on peripheral FTO function are scarce. In a mouse model of reduced FTO function (point mutation I367F), gene expression analysis of white adipose tissue (WAT) revealed the downregulation of several genes involved in inflammation, while multiple genes clustering with the control of fat metabolism were found to be deregulated [Church *et al.*, 2009]. Several genes with known function in fatty acid metabolism, as well as carbohydrate metabolism were upregulated in muscle of FTO<sup>I367F</sup> animals. The observed gene expression changes may be related to some of the phenotypic observations for this mouse model, such as increased lean mass, reduced fat mass and changes in metabolic rate. Cause and effect, as well as the connection between FTO enzymatic function and expression changes, however, remain unanswered [Church *et al.*, 2009].

In human visceral and subcutaneous adipose tissue, *FTO* mRNA levels inversely correlate with body mass index and age [Kloeting *et al.*, 2008]. Moreover, *FTO* mRNA expression is downregulated during human adipocyte differentiation [Tews *et al.*, 2011]. Furthermore, a reduced lipolytic activity was reported for female

rs9939609 risk-allele carriers in vivo and in vitro [Wåhlén et al., 2008].

Recently, a reduced *de novo* lipogenesis was observed for human adipocytes after lentiviral knock down of *FTO* [Tews *et al.*, 2013]. More strikingly, however, was the browning of white adipocytes, both in *Fto*-deficient mice, as well as in human adipocytes after shRNA mediated *FTO* knock down [Tews *et al.*, 2013]. Concomitantly, significant upregulation of UCP-1 was detected in *Fto*-deficient mouse adipose tissue and *FTO*-deficient human adipocytes. In *FTO*-deficient human adipocytes, this led to increased mitochondrial uncoupling in comparison to control cells. Reminiscent of a UCP-1 upregulation in brown adipocytes, *Fto*deficient mice have a higher energy expenditure [Fischer *et al.*, 2009]. Therefore, loss of FTO and the resulting functional browning of white adipocytes may serve as an explanation for the increased energy expenditure in *Fto*-deficient mice.

#### Fto in the central nervous system

*FTO* is ubiquitously expressed, however, by far the highest levels of *FTO* are detected in the central nervous system [Gerken *et al.*, 2007; Frayling *et al.*, 2007; McTaggart *et al.*, 2011; Fredriksson *et al.*, 2008]. Within the brain, FTO is found in the majority of neurons [McTaggart *et al.*, 2011]. Due to the high expression in feeding related nuclei of the hypothalamus (paraventricular nucleus PVN; arcuate nucleus ARC; ventromedial nucleus VMH; dorsomedial nucleus DMH), an important role for FTO in the regulation of energy homeostasis was proposed [Gerken *et al.*, 2007; Tung *et al.*, 2010].

Brain specific *Fto* deletion in mice recapitulates several phenotypic characteristics of whole body *Fto*-deficiency [Gao *et al.*, 2010; Fischer *et al.*, 2009]. Comparable to *Fto*-deficient mice, brain specific loss of FTO leads to postnatal growth retardation, decreased IGF-1 serum concentrations and reduced body weight due to a reduction in lean mass. Since the Nestin-cre line used to generate the brain specific knock out model was reported to suffer from a hypopituitarism phenotype which could potentially cause several of the observed alterations [Galichet *et al.*, 2010], the results of this study have to viewed cautiously. Several studies adressed the role of FTO within the feeding related nuclei of the hypothalamus through virus mediated manipulation of FTO expression. Overexpression of FTO in the rat arcuate nucleus resulted in a decreased daily food intake, while a reduction in FTO caused an increase in food intake [Tung *et al.*, 2010]. Virus mediated knock out of *Fto* in the mediobasal hypothalamus of a conditional mouse model, however, led to the opposite result, causing a decrease in food intake [McMurray *et al.*, 2013]. Since the latter study targeted a larger area of the hypothalamus, the behavioural outcome of *Fto* knock down may depend on the affected neuronal population.

Recently, for the first time, FTO genomic variation was investigated regarding human brain function. In line with previous findings, carriers of the risk-allele (rs9939609 'A' allele) displayed attenuated suppression of hunger following a standard test meal [den Hoed et al., 2009; Karra et al., 2013]. Moreover, regardless of feeding state, neuronal activity assessed by functional MRI in response to food images was altered in homozygous rs9939609 risk-allele carriers [Karra et al., 2013]. Changes in BOLD signal were detected in homeostatic, as well as hedonic brain areas. Furthermore, while the neuronal response to pictures of highly palatable food in control subjects positively covaried with increasing acyl-ghrelin levels, it negatively covaried in risk-allele carriers [Karra et al., 2013]. Acyl-ghrelin is known to potently stimulate hunger and to increase food intake [Uchida et al., 2013]. Hence, altered responses to acyl-ghrelin, or changes in acyl-ghrelin levels could potentially alter energy intake in FTO risk-allele carriers. Postprandialy, rs9939609 SNP carriers show an increased acyl-ghrelin to ghrelin ratio, due to a failure in reduction of acyl-ghrelin levels after a meal [Karra *et al.*, 2013]. The same increase in acyl-ghrelin to ghrelin ratio was observed in vitro, if FTO was overexpressed. In Fto-deficient mice, on the other hand, this ratio is decreased [Karra *et al.*, 2013]. Hence, FTO may play a critical role in regulating ghrelin and acyl-ghrelin levels. Moreover, it may modulate the responses of homeostatic, as well as hedonic brain areas and thus shape hunger and/or satiety responses.

#### 1.4.4 Molecular function of FTO

#### Cellular localisation

*FTO* is ubiquitously expressed [Gerken *et al.*, 2007; Frayling *et al.*, 2007; Fredriksson *et al.*, 2008]. The highest levels are, however, reported for the central nervous system and especially for feeding related brain areas [Gerken *et al.*, 2007; Frayling *et al.*, 2007; Tung *et al.*, 2010; McTaggart *et al.*, 2011; Stratigopoulos *et al.*, 2008; Fredriksson *et al.*, 2008]. Hence, it was proposed that FTO plays a critical role in the central nervous system. FTO primarily localizes to the nucleus of a cell [Gerken *et al.*, 2007; McTaggart *et al.*, 2011]. Only limited evidence so far suggests the presence of FTO in the cytoplasma depending on feeding state [Vujovic *et al.*, 2013]. Within the nucleus, it colocalizes in nuclear speckles with splicing factors, such as SART1 (U4/U6.U5 tri-snRNP-associated protein 1), SC35 (serine/arginine-rich-splicing factor 2) and Pol II-S2P (RNA polymerase II phosphorylated at Ser2) [Jia *et al.*, 2011]. Therefore, despite direct evidence for a connection to mRNA processing, FTO was proposed to play a role in splicing processes.

In mice, FTO is reported to be coexpressed with the satiety mediator oxytocin [Olszewski *et al.*, 2009, 2011]. Furthermore, overexpression of FTO *in vitro* leads to increased oxytocin mRNA levels [Olszewski *et al.*, 2011].

Since FTO was associated with the development of obesity and aberrant feeding behaviour [Cecil *et al.*, 2008; Timpson *et al.*, 2008; Speakman *et al.*, 2008; Wardle *et al.*, 2009; Haupt *et al.*, 2009; Tanofsky-Kraff *et al.*, 2009], *FTO* expression may vary with nutritional status. So far, however, findings are contradictory. In rats, fasting (48h) led to increased *Fto* transcript levels [Fredriksson *et al.*, 2008], whereas the same 48h fast in mice and long term food restriction in rats (60% of ad libitum) cause decreases in *Fto* mRNA [Gerken *et al.*, 2007; Wang *et al.*, 2011]. In a different restriction scheme in mice (food only available from 13:00 to 15:00h each day), however, *Fto* transcript levels were significantly increased in the arcuate and ventromedial hypothalamus [Boender *et al.*, 2012]. Other studies failed to detect differences for *Fto* mRNA in mice for both long term (40h) [Stratigopoulos *et al.*, 2012].

2008] or overnight fasting [McTaggart *et al.*, 2011]. On the protein level, FTO levels were unchanged in response to a overnight fast [McTaggart *et al.*, 2011], whereas reduced levels were measured after long term food restriction (60% of ad libitum) in rat hypothalamus and brainstem [Wang *et al.*, 2011]. Of note, the reduction of FTO protein caused by food restriction depends on leptin receptors and functional STAT3 signaling. A reduction of FTO levels due to caloric restriction was not observed on a leptin-deficient background [Wang *et al.*, 2011]. Furthermore, centrally administered leptin reduced *Fto* mRNA levels in mouse hypothalamus, a result reproduced by application of leptin on a hypothalamic slice preparation [Wang *et al.*, 2011].

Vice versa, FTO was proposed to influence leptin signaling through alteration of leptin receptor clustering [Stratigopoulos *et al.*, 2011]. Furthermore, overexpression of FTO in rat arcuate nucleus increased STAT<sub>3</sub> mRNA levels by 4-fold [Tung *et al.*, 2010]. Moreover, global *Fto* overexpression in mice resulted in reduced fasting plasma levels of leptin at 8 weeks of age, but not at 20 weeks [Church *et al.*, 2010]. Hence, the relationship between leptin and FTO, as well as the regulation of FTO expression itself seems to be complex and demands further investigation.

#### FTO in amino acid sensing

In addition to the aforementioned observations, FTO has been reported to rely on nutrient availability. Glucose deprivation, as well as total amino acid deprivation cause both a reduction in *Fto* mRNA and protein in a hypothalamic cell culture (N46 cells) [Cheung *et al.*, 2013]. Further experiments have proven that essential amino acid deprivation is sufficient to downregulate FTO, presenting a potential link between energy metabolism and FTO expression [Cheung *et al.*, 2013].

Loss of *Fto* leads to growth defects, both *in vitro* and *in vivo*. Postnatal growth retardation is observed in *Fto*-deficient mice, while *Fto*-deficient MEFs (mouse embryonic fibroblasts) have reduced growth rates and translation levels [Gulati *et al.*, 2013; Fischer *et al.*, 2009]. Further analysis revealed a downregulation of the multi-synthetase complex (MSC) in knock out MEFs and a physical interaction of FTO

with several components of the MSC [Gulati *et al.*, 2013]. Through coordination of aminoacyl-tRNA synthetases, the MSC is taking part in the translational regulation. Hence, failure to assemble the complex would lead to reduced translation. Re-expression of *Fto* on a *Fto*-deficient background, however, restored levels of the MSC complex and rescued translational rate [Gulati *et al.*, 2013].

Moreover, loss of *Fto* affects mTORC1 (mammalian target of rapamycin complex 1) signaling, a key-regulatory pathway of translation and growth. *Fto* deficiency leads to reduced phosphorylation of the mTOR effector kinase S6K1 (S6-kinase 1) [Gulati *et al.*, 2013]. Furthermore, the downregulation of mTORC1 in response to amino acid deprivation, a physiologically relevant process, is prevented by over-expression of exogenous FTO [Gulati *et al.*, 2013]. Expression of a catalytically inactive form of FTO (R316Q), however, is not able to block this downregulation of mTORC1. Hence, mTORC1 depends on the enzymatic activity of *Fto* [Gulati *et al.*, 2013]. The apparent amino acid dependent regulation of *Fto* expression and further coupling of FTO activity to the MSC and mTORC1 signaling present a possible model for the integration of FTO in metabolic processes. The exact mechanisms, however, demand further investigation.

#### 2-oxoglutarate dependent nucleic acid demethylase

Interestingly, the *FTO* gene is only present in algae and vertebrates, but is absent in invertebrates, plants, fungi, bacteria or archaea [Fredriksson *et al.*, 2008; Gerken *et al.*, 2007; Sanchez-Pulido & Andrade-Navarro, 2007; Robbens *et al.*, 2008]. Using bioinformatical sequence comparison, FTO was found to be closely related to the bacterial AlkB (alpha-ketoglutarate-dependent dioxygenase) and human AlkB homologs (ABH1, ABH2 and ABH3) [Gerken *et al.*, 2007; Sanchez-Pulido & Andrade-Navarro, 2007; Han *et al.*, 2010]. The FTO protein features the conserved 2-oxoglutarate (2-OG) and Fe(II) binding sites, typical for the 2-OG dependent dioxygenases of the AlkB family of enzymes [Gerken *et al.*, 2007]. Due to its role as an intermediate product of the Krebs-cycle, 2-OG was proposed to link FTO to metabolic processes. Since the 2-OG K<sub>m</sub> for FTO (2.88  $\mu$ M), however, is 10 fold below physiologically relevant concentrations of 2-OG, FTO is unlikely to convey information of the current metabolic status through sensing 2-OG levels [Ma *et al.*, 2012].

AlkB and human AlkB homologs (ABH2 and 3) have been described as DNA repair enzymes, which demethylate cytotoxic 1 - methyladenine and 3 - methylcytosine [Trewick *et al.*, 2002; Aas *et al.*, 2003]. Correspondingly, FTO was demonstrated to demethylate 3 - methylthymine (m<sup>3</sup>T) in single stranded DNA (ssDNA) and 3 - methyluracil (m<sup>3</sup>U), as well as N6 - methyladenosine (m<sup>6</sup>A) in ssRNA [Gerken *et al.*, 2007; Jia *et al.*, 2008, 2011; Meyer *et al.*, 2012]. A C-terminal loop, unique to 2-OG dependent oxygenases, was identified through solving the crystal structure of FTO and probably causes its preference for single stranded rather than double stranded DNA/RNA [Han *et al.*, 2010]. Moreover, its demethylase efficiency is slightly higher for RNA than DNA and m<sup>6</sup>A does not occur in DNA, thus suggesting that RNA is the primary target of FTO [Jia *et al.*, 2008; Ratel *et al.*, 2006].

# 1.5 m<sup>6</sup>A RNA modification

#### 1.5.1 RNA and RNA modifications

RNA (ribonucleic acid) is a central molecule in any organism that may appear in many different forms, serving a plethora of different functions. The relatively short-lived and low-abundant messenger RNA (mRNA) is the carrier molecule for the genetic information encoded in the genome. Approximately 97% of the RNA in a cell, however, belongs to the non protein coding RNA families, including transfer RNA (tRNA), ribosomal RNA (rRNA), small nuclear RNA (snRNA), small-interfering RNA (siRNA), micro RNA (miRNA) and long noncoding RNA (lncRNA) [Sharp, 2009]. The most abundant type of RNA is rRNA, which forms the catalytic domain in ribosomes and hence is a key component of protein synthesis. During protein synthesis, tRNA molecules are the mediators that match the correct amino acid to the corresponding base triplet found within the protein coding mRNA molecule. In both rRNA and tRNA, the secondary and tertiary structure is of importance for their correct function. Small nuclear RNAs play an important role in pre-mRNA splicing in the nucleus [Sharp, 2009]. Small-interfering and micro RNAs on the other hand, represent the means for silencing gene expression at the RNA level through translational/transcriptional silencing or mRNA decay [Sharp, 2009]. Regulation of gene expression is also regulated by long noncoding RNAs, however, their mode of action most probably involves binding of proteins such as transcription factors or formation of protein complexes [Rinn & Chang, 2012].

Modification of the four nucleotides enhances the diversity of RNA species and is needed for the complex functional purposes of RNA. To date, 109 post-transcriptional modifications have been identified in most of the different types of RNA species [Cantara et al. [2011] and 'The RNA Modification Database': http: //mods.rna.albany.edu/, date: 09/20/2013]. Interestingly, the RNA modifications are dynamic and thus may represent yet another level of epigenetic adjustments to environmental input [Yi & Pan, 2011]. Most of the modifications have been described in tRNA and rRNA. However, 13 modifications are reported for mRNA. These modifications include  $N_7$  - methylguanosine (m<sup>7</sup>G), 2'-O - methylnucleotide (N<sub>m</sub>), 5 - methylcytosine (m<sup>5</sup>C), N6 - methyladenosine (m<sup>6</sup>A), N6-methyl-2'- O - methyladenosine ( $m^6A_m$ ).  $m^7G$  and 2'-O - methylnucleotide are modifications found within and being important for the 5'CAP structure of a mRNA molecule [Jia et al., 2012], thus enabling the recruitment of initiation factors and translation, nuclear export, as well as promoting mRNA stability [Sonenberg & Hinnebusch, 2009]. m<sup>6</sup>A and m<sup>5</sup>C, on the other hand, are internal modifications found within the 5'UTR, coding sequence (CDS) or 3' UTR of mRNAs, whose functions so far are largely unknown [Jia et al., 2012].

#### 1.5.2 N6-methyladenosine (m<sup>6</sup>A)

Despite the fact that the N6-methyladenosine (m<sup>6</sup>A) RNA modification has been known since the 1970s, to date the purpose of this most abundant RNA methyla-

tion remains largely unknown [Desrosiers et al., 1974; Harper et al., 1990; Jia et al., 2012]. m<sup>6</sup>A is present in a variety of organisms, including plants [Nichols, 1979; Zhong et al., 2008], yeast [Clancy et al., 2002; Bodi et al., 2010], flies [Levis & Penman, 1978] and mammals [Wei et al., 1975; Shatkin, 1976; Desrosiers et al., 1974; Jia et al., 2011]. Moreover, it has been detected in viral RNA [Krug et al., 1976; Kane & Beemon, 1985]. m<sup>6</sup>A has been found in rRNA and tRNA [Saneyoshi *et al.*, 1969; Iwanami & Brown, 1968]. Despite the scarce knowledge, m<sup>6</sup>A is suggested to be important for mRNA processing, export from the nucleus, stability and translational efficiency [Harper et al., 1990; Pan, 2013; Jia et al., 2012; Niu et al., 2013; Dominissini et al., 2012; Tuck et al., 1999]. The methylation mark is also found in intronic regions of pre-mRNA, showing that it is present before splicing [Carroll *et al.*, 1990]. Moreover, m<sup>6</sup>A on RNA may serve as a label for endogenous RNA that helps the innate immune system to identify foreign RNA molecules [Karikó et al., 2005]. To date, several putative m<sup>6</sup>A binding proteins have been reported [Dominissini et al., 2012]. Two of those proteins are members of the YTH (YT521 homology) family and have been previously described to be involved in alternative splice site selection and mRNA degradation [Rafalska et al., 2004; Harigaya et al., 2006]. Indeed, most recently, YTHDF2 was shown to bind to a subset of m<sup>6</sup>A methylated mRNA transcripts and to subsequently shuttle these transcripts to, for example, processing bodies (p bodies) for RNA degradation [Wang et al., 2013]. Hence, mRNA stability and lifetime depends on m<sup>6</sup>A methylation status and thus will limit the pool of templates available for translation [Wang et al., 2013]. Furthermore, m<sup>6</sup>A sites are overrepresented in transcripts that harbor putative miRNA binding sites and highly expressed miRNAs in the brain have a greater percentage of target transcripts with m<sup>6</sup>A sites, suggesting, that miRNA levels may be involved in the methylation process itself [Meyer et al., 2012]. Despite mRNA, m<sup>6</sup>A is also found in long noncoding RNA, whose mode of action is yet to be finally determined [Meyer *et al.*, 2012].

Before the development of deep sequencing techniques, only two mRNAs were identified that harbor m<sup>6</sup>A sites. One was found to be in the 3'UTR of bovine



Figure 1.3: **Reversible** N6-methyladenosine modification FTO demethylates N6methyladenosine (m<sup>6</sup>A) in a 2-oxoglutarate and Fe(II) dependent manner. The reverse reaction of m<sup>6</sup>A demethylation involves a m<sup>6</sup>A-methyltransferase complex that contains several subunits, one of which is METTL3.

prolactin [Horowitz *et al.*, 1984], whereas several sites were identified in the Rous sarcoma virus RNA [Kane & Beemon, 1985]. Further analysis led to the description of the consensus site: RRACH (R = G or A, H = A, C or U) [Horowitz *et al.*, 1984; Harper *et al.*, 1990; Csepany *et al.*, 1990]. Within each mRNA, however, not all m<sup>6</sup>A sites are methylated. Prevalence for m<sup>6</sup>A in the Rous sarcoma virus RNA is within 20 to 90 % of all sites [Kane & Beemon, 1985] and only about 20 % for bovine prolactin [Horowitz *et al.*, 1984; Narayan *et al.*, 1994].

So far, only one subunit of a nuclear human m<sup>6</sup>A-methyltransferase complex was decribed [Bokar *et al.*, 1994, 1997]. METTL3 (or MTA70) is a homolog of the yeast IME4 (inducer of meiosis), which methylates mRNA in yeast during sporulation (Figure 1.3) [Clancy *et al.*, 2002; Bodi *et al.*, 2010]. Both in plants, as well as in flies, the homologs of METTL3 are important regulators of development [Zhong *et al.*, 2008; Hongay & Orr-Weaver, 2011]. Consistently, knock down of METTL3 affects HepG2 cells, resulting in deregulation of p53 signaling components and apoptosis [Dominissini *et al.*, 2012]. METTL3 colocalizes in the nucleus with nuclear speckles. Hence, the methylation may occur already during transcription [Bokar *et al.*, 1997].

Recently, FTO was shown to demethylate m<sup>6</sup>A in single stranded RNA and single stranded DNA *in vitro* (Figure 1.3) [Jia *et al.*, 2011]. Since m<sup>6</sup>A is not detected in genomic DNA, RNA represents the physiological substrate of FTO [Ratel *et al.*, 2006]. Further experiments confirmed the demethylation of m<sup>6</sup>A in mRNA by FTO [Jia *et al.*, 2011; Meyer *et al.*, 2012]. Like METTL3, FTO localizes primarily in the nucleus and was furthermore reported to colocalize with splicing factors such as SART1 and SC35 in nuclear speckles [Jia *et al.*, 2011; McTaggart *et al.*, 2011; Gerken *et al.*, 2007]. In addition to FTO, a second m<sup>6</sup>A demethylase, alkB alkylation repair homolog (ALKBH)5, has been identified [Zheng *et al.*, 2012]. ALKBH5, like FTO, is ubiquitously expressed, but in contrast to FTO exhibits highest expression levels in peripheral tissues and relatively low levels in the central nervous system [Zheng *et al.*, 2012]. Loss of ALKBH5 in mice affects nuclear mRNA export, RNA metabolism and influences the localization of RNA processing proteins in the nucleus [Zheng *et al.*, 2012]. *Alkbh5*-deficient mice exhibit impaired fertility due to increased apoptosis and abnormal spermatogenesis [Zheng *et al.*, 2012].

Taken together, the identification of the m<sup>6</sup>A methyltransferase METTL3 and the m<sup>6</sup>A demethylases FTO and ALKBH5 demonstrates once more that RNA methylation is probably a dynamic process putatively in control of mRNA processing, nuclear export, turnover, translation and first evidence for a role in mRNA stability [Wang *et al.*, 2013; Pan, 2013; Jia *et al.*, 2012].

#### 1.5.3 The m<sup>6</sup>A methylome

The development of next-generation sequencing enabled the thorough analysis of the whole transcriptome with respect to m<sup>6</sup>A methylation sites, the m<sup>6</sup>A methylome [Dominissini *et al.*, 2012; Meyer *et al.*, 2012]. Approximately 100 nucleotide long RNA fragments were immunoprecipitated with a m<sup>6</sup>A antibody and subsequently subjected to high-throughput sequencing. Both studies identified the m<sup>6</sup>A mark in more than 7000 mRNA transcripts and approximately 300 non coding RNAs in both humans [Dominissini *et al.*, 2012] and mice [Meyer *et al.*, 2012], showing that m<sup>6</sup>A is a common and conserved modification. m<sup>6</sup>A sites were found to be enriched in the 3'UTR near the stop codon, coding sequence and to a lesser extent in the 5'UTR of mRNA transcripts [Dominissini *et al.*, 2012; Meyer *et al.*, 2012]. m<sup>6</sup>A levels are increasing during the course of mouse brain development and show tissue dependent prevalence [Meyer *et al.*, 2012]. Environmental stimuli, such as heat shock, UV irradiation or hepatocyte growth factor did not influence the m<sup>6</sup>A peak positions, however some dynamic modulation was observed upon interferon  $\gamma$  treatment [Dominissini *et al.*, 2012]. Levels of m<sup>6</sup>A-methylation depend on FTO and its enzymatic activity *in vitro* [Dominissini *et al.*, 2012; Meyer *et al.*, 2012]. Hence, FTO most probably plays a critical role in what may represent a novel and dynamic RNA epigenetic process affecting cellular programs important for e.g. energy homeostasis.

#### 1.6 Objectives

The aim of this study was to investigate the potential role of the fat mass and obesity-associated gene (*Fto*) in the dopaminergic system. Since some of the characteristics of *Fto*-deficient mice resemble features of *DRD2*-deficient mice [García-Tornadu *et al.*, 2010; Díaz-Torga *et al.*, 2002; Sibley, 1999; Kelly *et al.*, 1998; Beaulieu & Gainetdinov, 2011] and as both *FTO*, and dopamine have been implicated in the etiology of obesity [Scuteri *et al.*, 2007; Dina *et al.*, 2007; Frayling *et al.*, 2007; Volkow *et al.*, 2013; Wang *et al.*, 2001], FTO might play a critical role in dopaminergic signaling. To investigate this hypothesis, both whole body, as well as DA neuron restricted *Fto*-deficient mice were utilized.

# 2 Materials and Methods

#### 2.1 Animal care

Mice (*Mus musculus*, C<sub>57</sub>Bl/6) were housed in a virus-free facility at 22-24°C on a 12 h light/ 12 h dark cycle. Animals were either fed standard rodent chow (Teklad Global Rodent 2018; 53.5% carbohydrates, 18.5% protein, 5.5% fat (12% calories from fat); Harlan, IN, USA) or a high fat diet (C1057; 32.7% carbohydrates, 20% protein, 35.5% fat (55.2% calories from fat); Altromin, Lage, Germany). All animals had access to water and food *ad libitum*, except 16h fasting prior to glucose tolerance test and refeeding experiments. Procedures and euthanasias were reviewed by the animal care committee, approved by local government authorities (Tierschutzkommission acc. §15 TSchG of the Landesamt für Natur, Umwelt und Verbraucherschutz North Rhine Westphalia) and were in accordance with NIH guidelines.

#### 2.2 Experimental mouse models

For the investigation of the effect of global deficiency, mice with a germline deletion of exon 2 and 3 of the *Fto* gene were employed [Fischer *et al.*, 2009]. For all experiments, whole body *Fto* deficient mice (homozygous knock outs) and wildtype littermates were used. To investigate the role of FTO specifically in dopaminergic neurons, mice expressing the Cre-recombinase under the control of the endogenous *Dat* promoter [Ekstrand *et al.*, 2007] were crossed to mice with a loxP site flanked third *Fto* exon (provided by EUCOMM). If not otherwise stated, DAT-Cre<sup>tg/wt</sup>; *Fto*<sup>f1/f1</sup> and their respective littermate controls DAT-Cre<sup>wt/wt</sup>; *Fto*<sup>f1/f1</sup> were used for experiments.

# 2.3 Genotyping

#### Isolation of genomic DNA

Mouse tail biopsies were taken at weaning age and subsequently digested in 500  $\mu$ l tail lysis buffer (100 mM Tris-HCl pH 8.5, 5 mM EDTA pH 8.0, 0.2% SDS, 200 nM NaCl) containing proteinase K (1/100) at 55°C. DNA was precipitated using 500  $\mu$ l 100% isopropanol and centrifugation at 17.000g. Afterwards, DNA was washed with 750  $\mu$ l 70% ethanol, centrifuged at 17.000g and dried. The DNA pellet was resuspended in TE buffer (10 mM Tris-HCl pH 7.5, 1 mM EDTA) containing RNase (1/100) or ddH<sub>2</sub>O.

#### Polymerase chain reaction

For genotypic analysis, polymerase chain reaction (PCR) was performed on tail DNA using the primers given in table 2.1. For PCR DreamTaq PCR MasterMix and DNA polymerase (Fermentas/Fisher Scientific Germany GmbH, Schwerte, Germany) was used. Standard PCR contained approx. 50 ng DNA, 25 pMol of each primer, 25  $\mu$ M dNTP mix and 1 unit DNA polymerase in a 25  $\mu$ l reaction mix.

Mouse Line	Primer	Sequence 5'-3'
DAT-Cre	DAT_F3	CATGGAATTTCAGGTGCTTGG
	Cre_R2	CGCGAACATCTTCAGGTTCT
	DAT_R1	ATGAGGGTGGAGTTGGTCAG
Fto flox (FLP deleted)	Fto_5b	TCAATCCTGGGCTAACATTTACCA
	Fto_3b	TTTATGGCCTTCGGCTTCAC
Fto flox (non FLP deleted)	Fto_5b	TCAATCCTGGGCTAACATTTACCA
	Fto_3b_euc	GGGATCCTCTAGAGTCCAGAT
	Fto_3b_wt	CAGCGGCGATCTCAGCCTC
Fto deletion	Fto_5b	TCAATCCTGGGCTAACATTTACCA
	Fto_3a	TGGTGACTTCCAACCATTCATC
Fto conventional	Fto_5'	ACCCCTCTCCCCCATCTAAATCCT
	Fto_3'	AAGCCAAGAACAAGTCCATACCTG
	Neo_5′	CTGTGCTCGACGTTGTCACTG
	Neo_3′	GTCCCGCTCAGAAGAACTCGT

	Table 2.1:	Genotyping	g Primer
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#### 2.4 Phenotyping

#### 2.4.1 Body weight

Body weight was assessed weekly for each individual mouse for ages 4-16 (18) weeks. After weaning, animals were either fed a normal chow diet or high fat diet.

#### 2.4.2 Insulin tolerance test

For insulin tolerance test, baseline blood glucose levels (time point o min) were measured using a glucometer (GlucoMen PC, A.Menarini Diagnostics, Italy). Following intraperitoneal administration of insulin (0.75 units  $ml^{-1}$ ; 0,75 units  $kg^{-1}$  body weight), blood glucose levels were measured 15, 30 and 60 minutes after injection. For determination of insulin tolerance, 15, 30 and 60 min values were calculated relative to baseline blood glucose levels for each individual mouse and plotted over time.

#### 2.4.3 Glucose tolerance test

Mice were fasted 16h prior to glucose tolerance test. Fasting state blood glucose levels (time point o min) were determined using a glucometer (GlucoMen PC, A.Menarini Diagnostics, Italy). Following intraperitoneal administration of glucose solution (20%, 10 ml kg<sup>-1</sup> body weight), blood glucose levels were measured at 15, 30, 60 and 120 minutes after injection. For determination of glucose tolerance, blood glucose levels (in mg dl<sup>-1</sup> blood) were plotted over time.

#### 2.4.4 Indirect calorimetry

Energy expenditure was measured using indirect calorimetric measurements in a PhenoMaster System (TSE systems, Bad Homburg, Germany). Animals were allowed to adapt to the single housing in metabolic chambers (7.1 liter) for a training phase of 5 days. During that time, animals were monitored daily to ensure proper adaptation to the drinking and feeding dispensers. Calorimetric measurement was conducted at 22-24°C over a period of 48-72 hours, assessing oxygen consumption, carbon dioxide production and locomotor activity (light barrier frame, TSE systems). Moreover, water and food intake was assessed using automated measuring devices (TSE Systems). Indirect calorimetry was performed with great help and advice of Hella Brönneke and Jens Alber.

#### 2.4.5 Food intake and refeeding response

Daily food intake was either measured automatically during calorimetric measurements (figure 3.15 e and f) or manually using a food hopper (figure 3.17). In either case, mice were allowed to adapt to single housing and food hoppers for 4-5 days. Food intake measurements were conducted for at least 3 consecutive days. All food intake measurements were performed for single caged mice. Refeeding response was measured after a 16h over night fast. Consumed food was measured manually 1, 2, 4, 8 and 24h after returning the food hopper to the home cage.

#### 2.5 Microarray expression analysis

RNA was isolated from midbrain tissue (VTA/SN) using peqGOLD TriFast and following the recommended protocols (peqlab, Erlangen, Germany). Quality of RNA (n=3/genotype) was assessed on a Bioanalyzer chip and subsequently hybridized on GeneChip Mouse Gene 1.0 ST Arrays (Affymetrix, Santa Clara CA, USA). RNA quality check and array hybridization was performed by the Cologne Center for Genomics (CCG, Cologne, Germany). Background correction and normalization for the intensity values were performed using the Affymetrix Powertools (Affymetrix, Santa Clara CA, USA) and robust multi-array average (RMA). Fold change of intensity values, as well as statistics (calculation of p-value and false discovery rate (FDR)) were calculated in R (using the bioconductor software package). Genes were considered significantly dysregulated for p-values  $\leq$  0.05 and FDR  $\leq$  0.25. HeatMap of significantly deregulated genes was generated using

R.

#### 2.6 Quantitative polymerase chain reaction

#### 2.6.1 Preparation of RNA

Fresh brain samples of different brain areas were prepared using a brain slicer (Braintree Scientific, Braintree MA, USA) and snap frozen in liquid nitrogen. RNA was isolated from tissues using peqGOLD TriFast (Peqlab, Erlangen, Germany) according to the manufacturer's protocol and RNA pellets were resuspended in DEPC water. RNA concentrations were assessed by measuring absorption at 260 and 280 nm using a NanoDrop ND-1000 UV-Vis Spectrophotomoter (Thermo Fisher Scientific Inc., Schwerte, Germany). Afterwards, RNA samples were adjusted to equal concentrations for further processing.

#### 2.6.2 Reverse transcription and quantitative PCR

RNA (100 to 200 ng  $\mu$ l<sup>-1</sup> per sample) was reversely transcribed with High-Capacity cDNA Reverse Transcription kit (Applied Biosystems, Foster City CA, USA) and amplified using TaqMan Gene Expression Master Mix with TaqMan Assay-ondemand kits (Applied Biosystems) following the manufacturer's protocol. Realtime probes used for gene expression analysis are listed in table 2.2. Relative expression was determined for target mRNA and samples were adjusted for total mRNA content by quantitative PCR for housekeeping genes (*Gusb*, *Hprt*, *Tfrc*). Calculations were performed by comparative method ( $2^{-\Delta\Delta C_T}$ ) [Livak & Schmittgen, 2001].

Symbol	Transcript Name	Probe
Fos	FBJ murine osteosarcoma viral oncogene homolog	Mm00487425_m1
Dbh	Dopamine beta hydroxylase	Mm00460472_m1
Drd2	Dopamine receptor D2	Mm00438545_m1
Drd3	Dopamine receptor D <sub>3</sub>	Mm00432887_m1
Grin1	glutamate receptor, ionotropic, NMDAR1 (zeta 1)	Mm01336437_m1
Gusb	Beta-glucuronidase	Mm00446953_m1
Hprt	Hypoxanthin-phosphoribosyl-transferase	Mm00446968_m1
		Continued on next page

Table 2.2: Realtime PCR probes

	1 1 8	
Symbol	Transcript Name	Probe
Kcnj6	potassium inwardly-rectifying channel, subfamily J, member 6	Mm00440070_m1
Slc6a3	Dopamine transporter	Mm00438388_m1
Tfrc	Transferrin receptor	Mm00441941_m1
Th	Tyrosine hydroxylase	Mm00447557_m1

Table 2.2 – continued from previous page

#### 2.7 Protein biochemistry

#### 2.7.1 Protein preparation

Tissues, initially frozen in liquid nitrogen, were thawed and homogenized in RIPA buffer (20 mM Tris-HCl pH 8.0, 150 mM NaCl, 1% NP-40, 10 mM NaF, 1 mM sodium vanadate, 1 mM sodium pyrophosphate, 1 protease inhibitor (cOmplete Mini, Roche Diagnostics, Basel, Switzerland) for 10 ml RIPA buffer and, if necessary, 1 PhosSTOP phosphatase inhibitor (Roche Diagnostics, Basel, Switzerland)) using either a Ultra-Turrax homogenizer (IKA Werke, Staufen, Germany) or manually with a pestle. Following homogenization, samples were incubated for 10 min on ice and subsequently centrifuged for 20 min at 4°C. Supernatant was transferred to fresh tubes and kept on -80°C for long term storage.

#### 2.7.2 Western blot

For Western blots, protein samples were boiled for 5 minutes in SDS-PAGE sample buffer (1:3 dilution in 4x SDS loading buffer: 125 mM Tris-HCl pH 6.8, 5% SDS, 43.5% glycerol, 100 mM DTT, and 0.02% bromphenol blue). Proteins were separated by SDS-PAGE and blotted onto PVDF membranes (Bio-Rad, Munich, Germany). Membranes were incubated for at least 1h with 1% blocking reagent in TBS/T at room temperature (Roche, Mannheim, Germany) and subsequently with primary antibody diluted in 0.5% blocking solution for 1 h at room temperature or over night at 4°C. After three washing steps with TBS/T, membranes were incubated for 1 h at RT with the respective secondary antibodies. Antibodies used for Western blot are listed in table 2.3. The signals were visualized after 3 washing steps with TBS/T using Pierce ECL Western Blotting Substrate (Perbio Science, Bonn, Germany) and exposition to Amersham Hyperfilm chemiluminescent film (GE Healthcare, Little Chalfont, UK).

Antibody	Cat.No.	Supplier
β-ACTIN	A5441	Sigma Aldrich Co. LLC.
CALNEXIN	208880	Calbiochem
DAT	SC-14002	Santa Cruz Biotechnology, Inc.
DRD2	ab21218	Abcam, Inc.
	ab32349	Abcam, Inc.
	sc-5303	Santa Cruz Biotechnology, Inc.
DRD <sub>3</sub>	ab42114	Abcam, Inc.
FTO	custom antibody pro-	provided by U. Rüther/Pineda antibody services,
	duced in guinea-pig	Berlin, Germany
GIRK2	ab30738	Abcam, Inc.
GNAI1	#5290	Cell Signaling Technology, Inc.
HSC70	sc-7298	Santa Cruz Biotechnology, Inc.
IKK2	#2370	Cell Signaling Technology, Inc.
NMDAR1	#5704	Cell Signaling Technology, Inc.
TH	ab112	Abcam, Inc.

Table 2.3: Antibodies for Western blot

#### 2.8 Behavioural experiments

#### 2.8.1 Open Field

Open field experiments were performed in open field box for mice (TSE Systems, Bad Homburg, Germany). One day before experiments, mice were injected intraperitoneally (i.p.) with saline and allowed to explore the open field box for 5 minutes. For baseline locomotor activity, mice were injected i.p. with vehicle (saline). The following days, mice were administered cocaine hydrochloride (10 or 20 mg kg<sup>-1</sup> body weight; C5776, Sigma Aldrich) or (-)-quinpirole (30 or 100  $\mu$ g kg<sup>-1</sup> body weight; Q102, Sigma Aldrich). The distance for each mouse was measured over a period of 45 minutes using an automated video-based system in an open field (50x50 cm, VideoMot 2, TSE Systems, Bad Homburg, Germany). Data are expressed as relative increase compared to baseline (saline).

are given for baseline locomotor activity.

#### 2.8.2 Conditioned Place Preference

Conditioned place preference (CPP) experiments were performed in the conditioned place preference box for mice (TSE Systems, Bad Homburg, Germany). Activity and location in the CPP box were monitored by a video recording system (VideoMot 2, TSE Systems).

*Pre-conditioning test (2 days)*: To determine whether a pre-existing bias exists, two single 30 min test sessions (1 session/day) were performed during which mice were allowed to freely explore the CPP box with doors open. Both sessions were video-taped to determine the preferred side.

*Conditioning phase (6 days)*: During the conditioning phase mice of different genotypes received a positive stimulus of 0.5 mg cocaine  $kg^{-1}$  body weight via i.p. injection prior to placement in the non-preferred side of the box (doors closed) and on the intervening days, all mice received an injection of vehicle (saline) prior to placement in the preferred side of the box. The six conditioning sessions lasted 30 min each, one session per day.

*Drug place preference test (1 day)*: One single 30 min test session has been performed during which mice were allowed to freely explore the CPP box with doors open. The session has been video-taped to determine the location of the mice in the CPP box.

*Data analysis*: Data are expressed as relative increase compared to baseline (neutral middle part of CPP box excluded). For statistical analysis a paired *t*-test was performed.

#### 2.8.3 Sucrose preference

To assess sucrose preference, mice were housed individually and restricted to 75% of *ad libitum* food intake. Each cage was fitted with 2 drinking bottles and one additional cage without experimental animal was set up as a control for handling

and evaporation water loss. After 2 days of habituation, the following 3 days water consumption and bottle preference was measured for each mouse. Afterwards, mice were presented with a choice of one bottle of water and one bottle of sucrose, with concentrations increasing over the course of the experiment (0.5, 1, 2, 4, 8%). Each concentration was measured for 2 days, changing the location (bottle 1 or bottle 2) of the sucrose solution after the first 24h to adjust for bottle preference. In between different sucrose concentrations, both bottles were changed to water for a period of 24h. Sucrose preference was calculated as sucrose solution intake relative to total liquid intake.

#### 2.9 Electronmicroscopy

A tissue block containing the midbrain was dissected from each brain. 50  $\mu$ m thick vibratome sections were cut and thoroughly washed in 0.1 M phosphate buffer (PB). To eliminate unbound aldehydes, sections were incubated in 1% sodiumborohydride for 15 min, then rinsed in PB. Next, sections were incubated with primary antobody (a-Tyrosine hydroxylase; dilution 1:1000 in PB) for 24 h at room temperature. Subsequently, sections were incubated in biotinylated goat anti-rabbit immunoglobulin (dilution 1: 250; Vector Laboratories, Burlingame, CA, USA) at room temperature. After a thorough wash in PB, sections were placed in avidinbiotin-complex (ABC Elite Kit, Vector Labs) for 2 hr at room temperature. The tissue-bound peroxidase was visualized by a diaminobenzidine reaction. After the immunostaining, the sections were osmicated (15 min in 1% osmic acid in PB), and dehydrated in increasing ethanol concentrations. During the dehydration, 1% uranyl-acetate was added to the 70% ethanol to enhance ultrastuctural membrane contrast. Dehydration was followed by flatembedding in Araldite. Ultrathin sections were cut on a microtome, collected on Formvar-coated single-slot grids and analyzed with a Tecnai 12 Biotwin (FEI Company) electron microscope. The plasma membranes of selected cells were outlined on photomicrographs and their length was measured with the help of a chartographic wheel. Plasma membrane length values measured in the individual animals were added and the total length was corrected to the magnification applied. Section thickness was determined by using the Small's minimal fold method.

#### 2.10 Immunohistochemistry

For double immunohistochemical stainings, mice were anesthetized and transcardially perfused with saline. The dissected brains were frozen in tissue-freezing medium. 7  $\mu$ m thick coronal sections were fixed in 4% paraformaldehyde (PFA). Following washing in PBS, slices were incubated in 0.3% glycine (in PBS). Subsequently, samples were washed in PBS and treated with 0.03% SDS (in PBS). Prior to antibody treatment, blocking was performed with donkey serum. Incubation with the primary antibody was conducted overnight ( $\alpha$ -Tyrosine hydroxylase, 1:1000, ab112, Abcam);  $\alpha$ -FTO, 1:1000; custom antibody produced in guinea-pig, provided by U. Rüther/Pineda antibody services, Berlin, Germany; Fischer *et al.* [2009]). Preceding secondary antibody treatment, samples were washed in PBS. Secondary antobodies used for immunofluorescent stainings were Cy3  $\alpha$ -guinea pig (Jackson Immuno Research, 706-165-148, donkey, 1:500) and Alexa 488  $\alpha$ -rabbit (Invitrogen, A11008, goat, 1:500). Finally, following 3 washing steps for 10 min in PBS, brain slices were embedded in Vectashield (Vector Laboratories, Burlingame, CA, USA) containing DAPI (4-,6-Diamidin-2-phenylindol).

For staining of c-Fos, mice were anesthetized and transcardially perfused with saline followed by 4% PFA. Brains were dissected, postfixed in PFA for 4 h, soaked in 20% sucrose overnight at 4°C, and frozen in tissue-freezing medium. c-Fos immunoreactivity was labeled with  $\alpha$ -c-Fos antibody (PC38, Calbiochem, EMD Millipore, Billerica MA, USA) and peroxidase coupled secondary antibody ( $\alpha$ -rabbit).

For  $\beta$ -galactosidase stainings, mice were transcardially perfused with saline, and dissected brains were frozen in tissue-freezing medium. X-gal staining was performed using standard protocols. Briefly, coronal sections (8  $\mu$ m thick) were fixed in cold 100% EtOH, washed in PBS and subjected to X-gal staining overnight at  $37^{\circ}$ C (X-gal solution: 5 mM K<sub>3</sub>Fe(CN)<sub>6</sub>, 5 mM K<sub>4</sub>Fe(CN)<sub>6</sub>, 2 mM MgCl<sub>2</sub>, 1 mg ml<sup>-1</sup> X-gal in PBS, pH 7.4). After staining, sections were rinsed in PBS and counterstained with Nuclear Fast Red.

#### 2.11 In situ hybridization

In situ hybridization for GAD67 on fresh frozen sections was performed based on a protocol described previously [Hommel et al., 2006]. Briefly, brains were sliced on a cryostat ( $16\mu$ m) and kept at -80°C until usage. Slices from freezer were dried and subsequently fixed in 4% PFA in PBS for 20 min. After a 3 x 3 minute washing step in PBS, slices were acetylated (2.38 ml triethanolamine, 0.32 ml HCL, 0.45 ml acetic anhydride ad 180 ml  $H_2O$ ) for 10 minutes on a stirrer. Following 3 x 5 minutes wash in PBS, slices were preincubated for 2h at room temperature with hybridization solution (50% deionized formamide, 5x SSC, 5x 50x-Denhardt's solution, 250  $\mu$ g ml<sup>-1</sup> tRNA bakers yeast, 500  $\mu$ g ml<sup>-1</sup> sonicated salmon sperm DNA). Afterwards, slices were incubated over night at 72°C in hybridization mixture (150  $\mu$ l including 400 ng of dig-labeled RNA probe). The following digoxigenin (DIG)labeled probe was used: Gad67 bp 1064-2046 of the mouse coding sequence (PCR amplification primers: 5'GAD67: TGTGCCCAAACTGGTCCT, 3'GAD67: TGGC-CGATGATTCTGGTT). The next day, slices are washed for 2h in 0.2xSSC at 72°C, followed by 5 minutes in 0.2xSSC at room temperature. Fluorescent labeling of the RNA probe was performed using the TSA<sup>™</sup> Plus Cyanine <sub>3</sub>/Fluorescein System kit (Perkin Elmer, Inc., Waltham MA, USA), following the manufacturer's protocols. In situ hybridization was followed by immunostaining for FTO as described in section 2.10. The fluorescence images were captured with a confocal microscope (Leica SP8X, Leica, Wetzlar, Germany).

### 2.12 Electrophysiology

All electrophysiology experiments were performed by Simon Hess in the lab of Peter Kloppenburg (University of Cologne, Cologne, Germany). Experiments were performed on brain slices containing the substantia nigra from 21- to 28-day old female and male  $Fto^{-/-}$  and  $Fto^{\Delta DAT/\Delta}$  mice and their respective littermates as controls. The general experimental procedure has recently been described in detail with additional information in the following paragraphs [Klöckener et al., 2011]. Brain slices were transferred into carbogenated artificial cerebrospinal fluid (aCSF). First, they were kept for 20 min in a 35 °C 'recovery bath' and then stored at room temperature (24 °C) for at least 30 min prior to recording. aCSF contained (in mM): 125 NaCl, 2.5 KCl, 2 MgCl<sub>2</sub>, 2 CaCl<sub>2</sub>, 1.2 NaH<sub>2</sub>PO<sub>4</sub>, 21 NaHCO<sub>3</sub>, 10 HEPES, and 5 Glucose adjusted to pH 7.2 (with NaOH) resulting in an osmolarity of 310 mOsm. For voltage-clamp experiments, the patch pipette was tip filled with internal solution and back filled with gramicidin-containing solution ( $2.5 - 10 \mu g$  ml-1; G5002; Sigma Aldrich) to achieve perforated patch recordings. For stable long-term current-clamp recordings Amphotericin B (  $200 \ \mu g \ ml-1$ ; A4888; Sigma Aldrich) was used as poreforming agent. Gramicidin and Amphotericin B were dissolved in dimethyl sulfoxide (final concentration: 0.4 - 0.5%; DMSO; D8418, Sigma Aldrich) as described previously [Rae et al., 1991; Kyrozis & Reichling, 1995] and was added to the modified pipette solution shortly before use. Drugs were bath-applied at a flow rate of 2 ml min<sup>-1</sup>. Cocaine hydrochloride (10  $\mu$ M; C5776; Sigma Aldrich) and (-)-quinpirole (10 – 1000 nM; Q102; Sigma Aldrich) were added to the normal aCSF shortly before the experiments. In order to quantify DRD2-dependent GIRK currents, we used BaCl<sub>2</sub> (1 mM) which is known to block GIRK channels [Lacey et al., 1988; Takigawa & Alzheimer, 1999; Cruz et al., 2004]. Dopaminergic (DA) neurons in the substantia nigra pars compacta (SNpc) were identified by their slow and regular firing and the presence of a large Ih-dependent "sag"-potential [Ungless et al., 2001; Lacey et al., 1989; Richards et al., 1997]. In voltage-clamp experiments,

dopaminergic neurons were additionally identified by their immunoreactivity for tyrosine hydroxylase (TH) or the dopamine transporter (DAT). All labelled cells which were identified using the aforementioned electrophysiological criteria exhibited DAT or TH immunoreactivity. Upon completion of the recordings, perforatedpatch recordings were converted to the whole cell configuration and biocytin (1%; B4261; Sigma) was allowed to diffuse into the cell for 3 – 5 min. Brain slices were fixed in Roti-Histofix (Po873; Carl Roth, Karlsruhe, Germany) overnight at 4°C and rinsed in TBS. Afterwards, the slices were incubated in TBS-T and 10% normal goat serum (30 min). Brain slices were washed in TBS (3 x 10 min) and subsequently incubated for 2 days at 4°C in rabbit anti-TH (1:1000; ab112; Abcam, Cambridge, UK) or rat anti-DAT (1:500; ab5990; Abcam, Cambridge, UK) that was dissolved in TBS-T and 10% normal goat serum. Afterwards, brain slices were rinsed in TBS (3) x 15 min) and incubated with secondary antibodies: Alexa 633-conjugated streptavidin (1:600; S21375; Invitrogen, Karlsruhe, Germany), dylight 488 anti-rabbit IgG (1:200; ab96883; Abcam) or dylight 488 anti-rat IgG (1:200; ab96887; Abcam) for 2h at RT in TBS-T. Brain slices were rinsed in TBS (5 x 10 min), dehydrated, and then cleared and mounted in Permount. The fluorescence images were captured with a confocal microscope (LSM 510, Carl Zeiss, Göttingen, Germany). Data analysis was performed with Spike2 (Cambridge Electronics, Cambridge, UK), Igor Pro 6 (Wavemetrics) and Graphpad Prism (version 5.0b; Graphpad Software Inc., La Jolla, CA, USA). For each neuron, the firing rate was averaged over a time period of 60s under control conditions and after the drug treatment had reached a steady-state.

#### 2.13 Microdialysis

The intracerebral microdialysis technique enables concentration measurements of neurotransmitters in freely moving animals. In these experiments, the effect of a single cocaine injection on the release of extracellular dopamine levels in the NAc was investigated. Experimental animals were anesthetized by i.p. injection of Ketamin (Albrecht GmbH, Germany) and Rompun (Bayer HealthCare, Germany) and

were stereotactically provided unilateral with a microdialysis guide cannula (CMA Microdialysis AB, Sweden). The tip of the microdialysis guide cannula was positioned just lateral to the NAc (coordinates: 2.0 mm anterior to bregma, 0.9 mm lateral from midline, and 2.9 mm below the surface of the brain; with toothbar set to obtain flat skull position). Dental cement was used to secure the microdialysis guide cannula to two stainless screws inserted in the skull. After surgery, animals were individually housed and allowed to recover for at least two weeks before the microdialysis experiment. The day before the start of intracerebral microdialysis, animals were anesthetized as described above, the dummy of the microdialysis guide cannula was retracted and a microdialysis probe (CMA7 probe (Microdialysis AB, Sweden), 6 kD cut-off membrane, 2 mm length) was inserted. After overnight recovery, the probe was then connected to a microperfusion pump and perfused with Ringer solution at a rate of 1  $\mu$ l min<sup>-1</sup>. After four hours of habituation to the microdialysis perfusion set-up, perfusion samples were collected every 20 minutes. After collecting six baseline samples, cocaine (20 mg kg<sup>-1</sup>) was administered i.p. and another six perfusion samples were collected after drug treatment. For absolute quantification of dopamine levels, a nano Acquitiy UPLC (Waters) was connected to a Xevo<sup>TM</sup> TQ (Waters). An Acquitiv UPLC BEH Phenyl 1.7  $\mu$ m, 1 mm x 100 mm column was used at room temperature. Solvent A was 0.1% formic acid and B acetonitril/0.1% formic acid. A linear gradient from 97% A to 5% in 8 min at a flow rate of 17  $\mu$ l min<sup>-1</sup> was used. 8  $\mu$ l of sample were injected. The TQ was operated in positive ESI MRM (multi reaction monitoring) mode. The source temperature was set at 120°C, desolvation temperature was 200°C and desolvation gas was set to 400 l  $h^{-1}$ . The following MRM transitions were used; m/z 154.1 (M+H+) to 91.04 (quantifier) collision energy 22V, m/z 154.1 to 64.94 (qualifier) collision 30V, m/z 154.1 to 109.05 (qualifier) collision 18V, m/z 154.1 to 119.01 m/z (qualifier) collision 18V, 154.1 to 137.02 (qualifier) collision 10V, cone was in all cases 12V. As data management software MassLynx 4.1 (Waters) and for data evaluation and absolute quantification TargetLynx (Waters) were used. As external standard dopamine hydrochloride (Sigma-Aldrich, Germany) was dissolved in Ringer solution (DeltaSelect, Dreieich, Germany) containing 0.1% perchloric acid. With dopamine eluting at 6.23 min a standard calibration curve was calculated using concentrations ranging from 2.5 – 100 ng ml<sup>-1</sup>. Correlation coefficient; r < 0.995,  $r^2 < 0.992$ ; response type: external standard, area; curve type linear; weighting 1/x. The peak integrations were corrected manually, if necessary. Quality control standards were used during sample analysis and showed between 0.5% and 40% deviation respectively. Blanks after the standard, quality control and sample batch proved to be sufficient. No carry over was detected. For the samples a slight shift in the retention time at 6.35 was observed due to the matrix. Microdialysis was performed with help of Linda A.W. Verhagen and Hella S. Brönneke. UPLC measurements of dopamine was performed by Thomas Franz and Yvonne Masekowitz (Max Planck Institute for Ageing, Cologne, Germany).

#### 2.14 MeRIP pulldown

MeRIP pulldown of provided *Fto*-deficient midbrain RNA was performed by Kate D. Meyer in the lab of Samie R. Jaffrey. Immunoprecipitation of methylated RNAs was performed as described previously [Meyer *et al.*, 2012] using a rabbit anti-m6A antibody (Synaptic Systems, Göttingen, Germany). MeRIP-Seq was done using three biological replicates of midbrain RNA isolated from *Fto*-deficient and wild type (WT) littermate mice. Reads were aligned to the genome using the Burrows-Wheeler Aligner (BWA), and m<sup>6</sup>A peaks were called as previously described [Meyer *et al.*, 2012]. Only the peaks which reached significance in all three replicates for each sample were included in the final peak analysis.

#### 2.15 GO analysis

GO analysis was performed by Yogesh Saletore and Olivier Elemento (Dept. of Physiology and Biophysics, Cornell University NY, USA). Peaks were identified for *Fto*-deficient and WT samples as described above, and the genome coordinates of *Fto*-deficient peaks were intersected with those of WT peaks to determine the peaks that were specific to the *Fto* knockout samples. Pathway analysis was then performed using iPAGE46 and the GO database. Briefly, iPAGE identifies pathways that are informative about the distinction between two or more groups of genes using mutual information. For all highly informative pathways, it calculates hypergeometric enrichment and depletion P values in all gene groups considered and represents these pathways as red-blue heat maps. A similar analysis was performed comparing genes with m<sup>6</sup>A peaks in WT-expressed genes (reads per kilobase per million reads (RPKM) >1) compared to all other expressed genes (RPKM >1).

#### 2.16 Pathway analysis

Pathway analysis was performed for deregulated transcripts in the microarray expression analysis (see section 3.1.2) and hypermethylated transcripts identified in MeRIP pulldown for *Fto*-deficient mice (see section 3.3.1). For pathway analysis, Ingenuity Pathway Analysis software (IPA, Ingenuity Systems, Inc., Redwood City CA, USA) was used.

#### 2.17 Graphical representation of data

If not otherwise mentioned, all graphical representations were created using Graph-Pad Prism (GraphPad Software, Inc., La Jolla CA, USA) and Adobe Illustrator CS4 (Adobe Systems, San Jose CA, USA). Box plot whiskers indicate the minimum and maximum values, centerlines indicate the median and plus signs indicate the means. Sample sizes are indicated in parentheses.

# 2.18 Statistics

Statistical calculations were performed using Microsoft Excel (Microsoft Corp., Redmond WA,USA) and GraphPad Prism (GraphPad Software, Inc., La Jolla CA, USA). Details on statistical analysis are given in the respective figure legends.

# 2.19 Chemicals and Materials

Table 2.4: Chemicals	
Chemical	Supplier
$\beta$ -mercaptoethanol	Applichem, Darmstadt, Germany
0.9% saline (sterile)	AlleMan Pharma GmbH, Pfullingen,
	Germany
Acrylamide	Roth, Karlsruhe, Germany
Agarose	Peqlab, Erlangen, Germany
Agarose (Ultra Pure)	Invitrogen, Karlsruhe, Germany
Ammoniumpersulfat (APS)	Sigma-Aldrich, Seelze, Germany
Bacillol	Bode Chemie, Hamburg, Germany
Bovine serum albumin (BSA)	Sigma-Aldrich, Seelze, Germany
Bromphenol blue	Merck, Darmstadt, Germany
Chloroform	Merck, Darmstadt, Germany
Cocaine hydrochloride	Sigma-Aldrich, Seelze, Germany
Denhardt's Solution	Applichem, Darmstadt, Germany
Desoxy-ribonucleotid-triphosphates (dNTPs)	Amersham, Freiburg, Germany
Developer G153	AGFA, Mortsel, Belgium
DEPC	Applichem, Darmstadt, Germany
Dimethylsulfoxide (DMSO)	Merck, Darmstadt, Germany
di-Natriumhydrogenphosphat	Merck, Darmstadt, Germany
Enhanced chemiluminescence (ECL) Kit	Perbio Science, Bonn, Germany
Ethanol, absolute	Applichem, Darmstadt, Germany
Ethidium bromide	Sigma-Aldrich, Seelze, Germany
Ethylendiamine tetraacetate (EDTA)	Applichem, Darmstadt, Germany
Fixer G354	AGFA, Mortsel, Belgium
Forene (isoflurane)	Abbot GmbH, Wiesbaden, Germany
Formamide	Applichem, Darmstadt, Germany
Glucose 20%	DeltaSelect, Pfullingen, Germany
Glycerol	Serva, Heidelberg, Germany
	Continued on next page

Chemical	Supplier
Glycine	Applichem, Darmstadt, Germany
HEPES	Applichem, Darmstadt, Germany
Hydrochloric acid (37%)	KMF Laborchemie, Lohmar, Germany
Insulin	Novo Nordisk, Bagsvaerd, Denmark
Isopropanol (2-propanol)	Roth, Karlsruhe, Germany
Magnesium chloride	Merck, Darmstadt, Germany
Methanol	Roth, Karlsruhe, Germany
Nitrogen (liquid)	Linde, Pullach, Germany
NP-40	Roche Diagnostics GmbH, Mannheim,
	Germany
Paraformaldehyde (PFA)	Sigma-Aldrich, Seelze, Germany
Phosphate buffered saline (PBS)	Gibco BRL, Eggenstein, Germany
Potassium chloride	Merck, Darmstadt, Germany
Potassium dihydrogenphosphat	Merck, Darmstadt, Germany
Potassium hydroxide	Merck, Darmstadt, Germany
(-)-Quinpirole	Sigma-Aldrich, Seelze, Germany
Sage tea	Bad Heilbrunner Naturheilmittel GmbH
Sodium acetate	Applichem, Darmstadt, Germany
Sodium chloride	Applichem, Darmstadt, Germany
Sodium citrate	Merck, Darmstadt, Germany
Sodium dodecyl sulfate	Applichem, Darmstadt, Germany
Sodium fluoride	Merck, Darmstadt, Germany
Sodium hydrogen phosphate	Merck, Darmstadt, Germany
Sodium hydroxide	Applichem, Darmstadt, Germany
Sodium orthovanadate	Sigma-Aldrich, Seelze, Germany
Sodium pyrophosphate	Sigma-Aldrich, Seelze, Germany
Tetramethylethylenediamine (TEMED)	Sigma-Aldrich, Seelze, Germany
Tissue Freezing Medium	Jung, Heidelberg, Germany
Tramadolhydrochlorid (Tramal)	Grünenthal, Aachen, Germany
Trishydroxymethylaminomethane (Tris)	Applichem, Darmstadt, Germany
Triton X-100	Applichem, Darmstadt, Germany
Trizol	Applichem, Darmstadt, Germany
Tween 20	Applichem, Darmstadt, Germany
Vectashield Mounting Medium with DAPI	Vector, Burlingame, USA
Western Blocking Reagent	Roche Diagnostics GmbH, Mannheim, Germany

Table 2.4 – continued from previous page

# 3 Results

# 3.1 Whole body *Fto* deficiency alters the function of the dopaminergic circuitry

#### 3.1.1 FTO is expressed in midbrain dopaminergic neurons

FTO is ubiquitously expressed with highest levels detected in the brain, especially in feeding related nuclei [Gerken *et al.*, 2007; McTaggart *et al.*, 2011]. To test whether FTO is expressed in dopaminergic neurons, midbrain slices of wildtype C<sub>57</sub>Bl/6 mice were immunohistochemically stained for FTO and tyrosine hydroxylase, the rate limiting enzyme in dopamine synthesis and hence a suitable marker for dopamine neurons in the midbrain (Figure 3.1).



Figure 3.1: **FTO is expressed in dopaminergic neurons of the midbrain** Double immunofluorescent labeling of tyrosine hydroxylase (TH, green) and FTO (red) in wildtype C57Bl/6 midbrain slices. Nuclear staining with DAPI (blue). Representative picture of n >3, scale bar = 10  $\mu$ m.

FTO is present in dopaminergic neurons and, consistently with previous reports, immunoreactivity was found to be primarily localized in the nucleus [Gerken *et al.*, 2007; McTaggart *et al.*, 2011]. Moreover, a slight cytosolic immunoreactivity was observed for FTO. Whether this signal is specific to any FTO function remains elusive.

Furthermore, expression of *Fto* was investigated using a mouse model carrying a knock in of the  $\beta$ -galactosidase gene into the endogenous *Fto* locus (*Fto*::tm1a-(EUCOMM)Wtsi, see Section 3.2.1 for further description). X-gal staining of brain sections confirmed the expression of *Fto* throughout the central nervous system, including the hypothalamus (ARC, VMH, DMH, PVN) and midbrain (VTA, SN)(Figure 6.2 in appendix).

# *Fto* deficiency does not change the number or morphology of midbrain dopaminergic neurons

Since *Fto*-deficient mice suffer from a severe phenotype including growth retardation and decreased postnatal survival rate [Fischer *et al.*, 2009], loss of FTO may potentially impact cell viability. Thus, to test whether the health of dopaminergic cells is affected by *Fto* deficiency, cell number and morphology was assessed in whole body *Fto*-deficient (*Fto*<sup>-/-</sup>) and control (*Fto*<sup>+/+</sup>) mice (see Figure 3.2).

No significant differences in cell number as well as cell area and perimeter were detected for dopamine neurons. Hence, loss of FTO does not alter the general health of dopaminergic neurons.

#### 3.1.2 Microarray analysis of *Fto*-deficient midbrain

#### Expression analysis of *Fto*-deficient midbrain tissue

To generate a general hypothesis for possible effects of *Fto* deficiency on dopaminergic neuron function, gene expression was compared between *Fto*-deficient and control midbrain tissue using microarray analysis. For this purpose, RNA was isolated from midbrain tissue (RNA integrity number determined by bioanalyzer chip  $\geq$ 8.9) and subsequently the RNA was hybridized to an Affymetrix GeneChip


Figure 3.2: Loss of FTO does not alter cell number or morphology of dopaminergic midbrain neurons

(a) Immunohistochemical labeling of FTO and quantification of cells was performed on midbrain sections of control and *Fto*-deficient mice. Experiments performed by Marcelo O. Dietrich and Tamas L. Horvath. Sample sizes are indicated in parentheses, no significant differences were detected. (b) Electron microscopy of wildtype and *Fto*-deficient dopaminergic neurons. *Fto* deficiency does not alter the morphology of dopaminergic neurons as assessed by quantification of cell area and perimeter. Experiments performed by Marcelo O. Dietrich and Tamas L. Horvath. Sample sizes are indicated in parentheses, no significant differences were detected.

Mouse Gene 1.0 ST array. Transcripts were considered significantly deregulated for p-values  $\leq$  0.05 (*t*-test) and a false discovery rate (q-value) of  $\leq$  0.25.

In total, 5785 transcripts were significantly deregulated, of which 2382 were down- and 3403 were up-regulated. The relative changes in transcript expression, however, were relatively low, with the highest downregulation observed for *Cartpt* (-4.807) and the highest up-regulation for *Tdgf1* (+2.774) (see Figure 3.3 and Table 6.2).

Most of the transcripts exhibited minor expression changes (Figure 3.3 fold change (fc) cut off  $\pm 1.80$ ; table 6.2 fc cut off  $\pm 1.50$ ). Among the deregulated mRNAs, several transcripts were identified that are directly or indirectly related to dopaminergic signaling. Significantly downregulated transcripts included the dopamine transporter (*Slc6a*<sub>3</sub>, fc = -2.558), tyrosine hydroxylase (*Th*, fc = -1.880), dopamine

<i>Fto</i> <sup>+/+</sup>	Fto -/-	assignment	fc	р	q
		Cartpt	-4.807	0.013	0.108
		SIc6a3	-2.558	0.035	0.114
		Hist1h1c	-2.355	0.019	0.108
		Aldh1a2	-2.205	0.028	0.112
		Gm5921	-2.184	0.023	0.110
		4930467E23Rik	-2.180	0.003	0.106
		4930467E23Rik	-2.170	0.000	0.106
		E430024C06Rik	-2.169	0.006	0.106
		Txnip	-2.157	0.019	0.108
		Tipin	-2.139	0.009	0.108
		A530053G22Rik	-2.133	0.025	0.110
		4930467E23Rik	-2.111	0.002	0.106
		4930467E23RIK	-2.087	0.001	0.106
		Opalin Ubb b1	-2.085	0.015	0.108
			-2.002	0.010	0.100
		D2Ertd7510	-2.034	0.012	0.106
		Eto	-2.030	0.007	0.100
		Hbb-b1	-1 989	0.001	0.100
		Map	-1.970	0.047	0.120
		Gm12643	-1.970	0.016	0.108
		Lphn2	-1.919	0.012	0.108
		Frzb	-1.896	0.011	0.108
		Th	-1.880	0.041	0.117
		Upp2	-1.874	0.009	0.108
		Dcn	-1.863	0.001	0.106
		Sgk1	-1.861	0.021	0.109
		Hdx	-1.857	0.002	0.106
		Tcf7l2	-1.857	0.040	0.117
		4922502B01Rik	-1.847	0.006	0.106
		Gas5	-1.846	0.021	0.110
		D4Wsu53e	-1.843	0.028	0.112
			-1.834	0.004	0.100
		Aya Umah1	-1.020	0.024	0.110
			-1.815	0.040	0.110
		Tdrd6	-1 807	0.014	0.100
		Acvp1	-1 806	0.043	0.112
		Parl	-1.803	0.044	0.119
		Drd2	-1.301	0.033	0.113
		Drd5	1.456	0.036	0.115
		Hsd11b1	1.804	0.041	0.117
		Bclp2	1.804	0.027	0.112
		Olfr328	1.808	0.016	0.108
		Gm10534	1.821	0.014	0.108
		Klk1b11	1.853	0.016	0.108
		Gm5841	1.879	0.042	0.117
		Ccl12	1.908	0.032	0.113
		Spef2	1.969	0.003	0.106
		Tnnt2	1.991	0.001	0.106
		A730020M07Rik	2.012	0.002	0.106
		Spef2	2.036	0.008	0.107
		Spef2	2.074	0.041	0.117
			2.319	0.019	0.108
			2.004	0.009	0.100
		Tdaf1	2.531	0.009	0.100
		rugii	2.114	0.001	0.100
-1.5	5 -0.5 0.5 1 1.5				

Figure 3.3: Microarray analysis of *Fto*-deficient midbrain tissue

#### Figure 3.3: Microarray analysis of Fto-deficient midbrain tissue

Microarray analysis was performed for control and *Fto*-deficient midbrain tissue. Normalized intensities are presented as a heatmap (each row scaled individually), key indicates Z-Score for color coding. Fold change (fc), p-value (p) and false discovery rate (q-value, q) are shown for a selection of significantly deregulated genes. Highlighted in red are components related to dopaminergic signaling. n = 3 per genotype

type 2 receptor (*Drdr*<sub>2</sub>, fc = -1.301), dopa decarboxylase (*Ddc*, fc = -1.371) and the vesicular monoamine transporter (*Slc18a2*, fc = -1.306). Transcripts of the dopamine type 5 receptor (*Drd*<sub>5</sub>, fc = +1.456) and the dopamine beta hydroxylase (*Dbh*, fc = +2.391) were found to be upregulated.

### Critical components of dopaminergic signaling are deregulated in *Fto*-deficient mice

The overlay of deregulated transcripts using pathway analysis revealed that several components implicated in dopaminergic function were affected in *Fto*-deficient mice (see Figure 3.4). Transcripts of three enzymes involved in the dopamine synthesis were deregulated. The mRNA levels of both the tyrosine hydroxylase, converts L-tyrosine to L-DOPA, and the dopa decarboxylase, converts L-DOPA to dopamine, were reduced in *Fto*-deficient mice, while the transcript levels of the dopamine beta hydroxylase, catalyzes the reaction from dopamine to norepinephrine, was increased (Figure 3.4). These alterations could potentially affect dopamine availability through a reduction in dopamine synthesis and an increase in conversion of dopamine to norepinephrine.

Additionally, a downregulation of the vesicular monoamine transporter, which transports monoamines such as dopamine into synaptic vesicles, could lead to a reduction in dopamine release. On the other hand the downregulation of the dopamine transporter via a reduction in dopamine reuptake from the synaptic cleft, may prolong dopaminergic signaling and thus counteract the potentially decreased levels of secreted dopamine.

Moreover, dopaminergic neurons express dopamine autoreceptors of the D2-like dopamine receptor family (DRD2 and DRD3). One of these, the type 2 dopamine



### Figure 3.4: Schematic overlay of the microarray expression data and the dopaminergic signaling pathway

Key components of dopaminergic signaling and dopamine syntheses exhibit altered expression in midbrain of *Fto*-deficient mice. TH: tyrosine hydroxylase, DDC: dopa decarboxylase, VMAT: vesicular monoamine transporter, DAT: dopamine transporter, AC: adenylyl cyclase, COMT: catechol-O-methyl transferase, MAO: monoamine oxidase. Overlay was created using Ingenuity Pathway Analysis software. Green indicates downregulation and red indicates upregulation of the respective transcripts.

receptor (DRD2), was found to be downregulated on the mRNA level. A reduction in DRD2 autoreceptor signaling could potentially impinge on the regulation of dopamine release through attenuation of the autoreceptor feedback loop [Beaulieu & Gainetdinov, 2011; Bello *et al.*, 2011].

#### Selected deregulated transcripts are not altered on protein level

To confirm the alterations of transcript levels observed in the microarray analysis, quantitative PCR was conducted on a selected subset of deregulated transcripts. To this end, qPCR analysis of *Drd2*, *Th*, and *Slc6a3* verified the observed downregulations for midbrain tissue of *Fto*-deficient mice (Figure 3.5 a, b, c).



#### Figure 3.5: Selected transcripts deregulated in microarray analysis are not altered on protein level

Quantitative PCR on selected deregulated transcripts confirmed the microarray analysis. mRNA levels for (**a**) *Drd2* and (**b**) *Slc6a*<sup>3</sup> are significantly downregulated, whereas a strong tendency is detected for (**c**) *Th*. Western blot analysis, however, reveals no changes on protein level for DRD2, DAT and TH. Western blot for DRD2 (**a**) was performed using three different antibodies. Sample blot shows  $\alpha$ -DRD2 ab21218 (Abcam, Inc.) with two bands corresponding to the long (DRD2L, 51 kDa) and short form (DRD2S, 47 kDa) of DRD2. Sample sizes indicated in parentheses, \**P*<0.05, unpaired two-tailed *t*-test.

Since mRNA levels may not necessarily reflect protein levels, western blot analysis was performed for DRD2, TH and DAT. In contrast to the changes on the mRNA level, no alterations of protein levels were observed (Figure 3.5 a, b, c).

#### 3.1.3 Fto-deficient mice exhibit attenuated responses to cocaine

#### Cocaine fails to increase locomotor activity in Fto-deficient mice

Many addictive substances affect dopaminergic signaling [Beaulieu & Gainetdinov, 2011; Koob & Volkow, 2010]. One of the most prominent drugs of abuse is cocaine, which potently blocks the dopamine transporter [Beaulieu & Gainetdinov, 2011]. Due to the resulting prolonged dopaminergic signaling, the primary effect of cocaine administration is an increase in locomotor activity. For this reason, many studies use cocaine to test the functionality of the dopaminergic system, utilizing locomotor activity as the primary readout [Koob & Volkow, 2010; Seale & Carney, 1991].

To test whether the functionality of the dopaminergic system is altered, locomotor activity after intraperitoneal (i.p.) cocaine administration was assessed in *Fto*-deficient and control mice. After baseline measurement of locomotor activity (saline injection), mice were challenged with two different cocaine concentrations



Figure 3.6: Cocaine fails to increase locomotor activity in *Fto*-deficient mice Control and Fto-deficient mice were injected i.p. with 10 mg kg<sup>-1</sup> and 20 mg kg<sup>-1</sup> cocaine. Data is represented as percent relative to baseline saline injection (sample sizes indicated in parentheses, \*P<0.05, \*\*P<0.01, unpaired two-tailed *t*-test).

(10 mg kg<sup>-1</sup> and 20 mg kg<sup>-1</sup> body weight). While wildtype control mice significantly increased their locomotor activity at both 10 mg kg<sup>-1</sup> (216 $\pm$ 34%) and 20 mg kg<sup>-1</sup> (361 $\pm$ 47%) cocaine, *Fto*-deficient mice failed to increase their locomotor activity (10 mg kg<sup>-1</sup>: 113 $\pm$ 31%, 20mg kg<sup>-1</sup>: 117 $\pm$ 30%, Figure 3.6). These results indicate that dopaminergic function is severely attenuated, rendering *Fto*-deficient mice insensitive to the locomotor stimulatory effect of cocaine.

#### Cocaine fails to increase Fos expression in Fto-deficient mice

To assess the observed insensitivity to cocaine on the network level, *Fto*-deficient mice were treated with 20 mg kg<sup>-1</sup> cocaine i.p. and subsequently midbrain, NAc and CPu tissue was analyzed for *Fos* expression. *Fos*, as one of the immediate early genes, is a widely used marker for neuronal activity [Knight *et al.*, 2012; Dragunow & Faull, 1989]. As such, cocaine-induced stimulation of dopamine signaling is able to induce *Fos* expression as a result of the modulation of neuronal activity.

*Fos* mRNA expression significantly increased 2h after i.p. cocaine treatment in wildtype control mice in all brain areas investigated (Figure 3.7). Conversely, in *Fto*-deficient mice cocaine failed to increase the *Fos* mRNA levels (Figure 3.7, also



Figure 3.7: Cocaine fails to increase *Fos* expression in *Fto*-deficient mice Midbrain, caudate putamen (CPu) and nucleus accumbens (NAc) of control and *Fto*-deficient mice were dissected 2h after either saline (Sal) or 20 mg kg<sup>-1</sup> cocaine (Coc) i.p. injection. *Fos* expression was measured using qPCR and is represented as relative increase compared to saline (Sal) injected control animals. (\*P<0.05, \*\*P<0.01, unpaired two-tailed *t*-test, sample sizes are indicated in parentheses).

confirmed on the protein level see Figure 6.1 in appendix). Of note, *Fos* mRNA levels were elevated under baseline conditions (saline) in the NAc of *Fto*-deficient mice. Thus, the *Fos* expression analysis was consistent with the observed failure of *Fto*-deficient mice to increase their locomotor activity in response to cocaine.

# Cocaine evoked extracellular levels of dopamine are reduced in *Fto*-deficient mice

In order to test whether the loss of FTO affected dopamine release and/or reuptake, extracellular levels of dopamine were measured in the NAc of *Fto*-deficient and control mice via implantation of a microdialysis probe and subsequent detection of dopamine via ultra performance liquid chromatography (UPLC) coupled to mass spectrometry. During the experiment, mice were challenged with either 10 or 20 mg kg<sup>-1</sup> body weight cocaine i.p. injection.

In both *Fto*-deficient and control mice extracellular levels of dopamine increased in response to cocaine administration, due to the blockade of the dopamine transporter preventing dopamine reuptake. Comparing *Fto*-deficient and control mice, no differences in the relative increase in extracellular dopamine levels were de-





Levels of extracellular dopamine in response to 10 mg kg<sup>-1</sup> (**a**) and 20 mg kg<sup>-1</sup> (**b**) i.p. cocaine administration were measured in the NAc of control (n=6) and *Fto*-deficient (n=7) mice using microdialysis. Dopamine was subsequently detected by ultra performance liquid chromatography (UPLC). Graph shows mean  $\pm$  s.e.m. for each individual measurement time point (\**P*<0.05, unpaired two-tailed *t*-test).

tected for the 10 mg kg<sup>-1</sup> cocaine treatment (Figure 3.8 a). At a higher cocaine dosage (20 mg kg<sup>-1</sup>) however, dopamine levels significantly varied between *Fto*-deficient and control mice (Figure 3.8 b). In comparison to the lower cocaine dosage, control mice had even further elevated dopamine content in the NAc in response to 20 mg kg<sup>-1</sup> cocaine injection. *Fto*-deficient mice, on the other hand, displayed similar relative increases at both cocaine concentrations. Hence, dopamine release appears to have reached a maximum at 10 mg kg<sup>-1</sup> cocaine in *Fto*-deficient mice. Unfortunately, whether these differences are due to alterations in dopamine synthesis rates, dopamine release or dopamine reuptake cannot be addressed using the microdialysis technique.

# 3.1.4 Attenuation of the DRD2/DRD3 autoreceptor feedback loop in *Fto*-deficient mice

#### DRD2/DRD3 receptor dependent responses are altered in Fto-deficient mice

To investigate the effects of *Fto* deficiency on the cellular level, neuronal activity of single cells was measured in midbrain slices of *Fto*-deficient and control mice using the patch-clamp technique. No differences in the general properties of dopaminergic neurons were detected, except a slightly reduced conductance density for *Fto*-deficient mice (Table 6.1 in appendix). While under baseline conditions, dopaminergic neurons fired tonically at a rate of approximately 2 Hz, bath application of cocaine (10  $\mu$ M) potently reduced the firing rate of these neurons in control mice on average by 86% (Figure 3.9 a). In *Fto*-deficient mice, however, cocaine's ability to reduce the firing rate of dopaminergic neurons was significantly attenuated (reduction by 46%, Figure 3.9 a).

Since dopamine neurons express autoreceptors, blocking of the dopamine transporter by cocaine increases the amount of extracellular dopamine, which then binds to these D2-like receptors, leading to the activation of an autoinhibitory feedback loop that silences the neurons in a G protein-coupled inwardly rectifying potassium channel (GIRK) dependent manner [Lüscher & Slesinger, 2010].



Figure 3.9: Altered DRD2/DRD3 receptor dependent responses in *Fto*-deficient mice (a) Relative firing rate of SNpc dopaminergic neurons in patch clamp recordings during bath application of cocaine (10  $\mu$ M, 10 min). Sample trace shows recording of firing rate before, during and after bath application of cocaine (sample sizes indicated in parentheses, \**P*<0.05, unpaired two-tailed *t*-test). (b) Bath application of the D2-D3-receptor agonist quinpirole (10 nM) on control and *Fto*-deficient dopamine neurons (sample sizes indicated in parentheses, \**P*<0.05, unpaired one-tailed *t*-test). (c) In line with the attenuated reduction in firing rate, quinpirole (1  $\mu$ M) mediated increase in conductance density is significantly reduced in *Fto*-deficient mice (sample sizes indicated in parentheses, \**P*<0.05, unpaired one-tailed *t*-test). All electrophysiological experiments were conducted by Simon Hess.

To further assess whether the observed alteration in autoinhibition was directly related to receptor function, the selective DRD<sub>2</sub>/DRD<sub>3</sub> agonist quinpirole (10 nM) was applied during patch clamp recordings of midbrain dopaminergic neurons. In line with the previous finding, quinpirole potently inhibited firing in control neurons, while the response in *Fto*-deficient neurons was significantly attenuated (Figure 3.9 b). Consistently, the quinpirole (1  $\mu$ M) evoked conductance density, a measure of the membrane's ability to pass current, was significantly reduced in *Fto*-deficient mice (Figure 3.9 c).

Taken together, these results demonstrate that the DRD2/DRD3 dependent autoreceptor feedback loop was affected by the loss of FTO. Since the primary function of the autoreceptor feedback loop is the opening of GIRKs, the attenuated ability to reduce the firing rate in *Fto*-deficient mice may be a result of a reduction in DRD2/DRD3 or GIRK expression. Moreover, malfunction of the intracellular coupling of the dopamine receptors to GIRKs could potentially represent the underlying cause of the attenuated cocaine and quinpirole-mediated reduction in firing rate.

#### Reduced GIRK dependent current density in Fto-deficient mice

To directly assess the GIRK mediated and dopamine autoreceptor dependent changes in membrane conductance, brain slices were incubated with quinpirole (300 nM) to fully activate the DRD2/DRD3 autoreceptor feedback loop. Subsequently, bath application of barium chloride (1 mM), a potent potassium channel blocker, was used to measure the change in current density mediated by GIRKs (Figure 3.10). Confirming the previous results, the increase in quinpirole-dependent current density was attenuated in *Fto*-deficient mice. Furthermore, these quinpirole mediated changes were almost completely reversed by the blockade of GIRK channels, demonstrating that GIRK currents are the main driver of dopamine autoinhibition. The GIRK dependent current density was significantly lower in *Fto*-deficient mice, further supporting the notion that the DRD2-DRD3 dependent feedback loop depends on GIRK function and FTO expression (Figure 3.10).



Figure 3.10: **Reduced GIRK dependent current density in** *Fto*-**deficient mice** DRD2 mediated activation of GIRK channels is attenuated in *Fto*-deficient dopamine neurons. GIRK currents were measured by activation of D2 receptors by quinpirole (300 nM) and subsequent blocking of GIRKs by BaCl<sub>2</sub> (1 mM) (sample sizes indicated in parentheses, \**P*<0.05, unpaired two-tailed *t*-test). All electrophysiological experiments were conducted by Simon Hess.

#### Attenuated quinpirole dependent decrease in locomotor activity in

#### Fto-deficient mice

As on the cellular level, *Fto*-deficient mice showed an attenuated response to quinpirole, the ability of quinpirole to reduce locomotor activity was tested in freely moving animals [Mattingly *et al.*, 1993; Bello *et al.*, 2011]. Intraperitoneal injection of quinpirole dose dependently decreased locomotor activity in both *Fto*-deficient, as well as control mice (Figure 3.11). *Fto*-deficient mice, however, exhibited an attenuated response to quinpirole, retaining a higher relative locomotor activity than control littermates. Locomotor activity was significantly higher at 100  $\mu$ g kg<sup>-1</sup> i.p. quinpirole injection and showed a tendency for 30  $\mu$ g kg<sup>-1</sup> as compared to contols (Figure 3.11).

Taken together, *Fto*-deficient mice displayed a significant attenuation of cocaine and quinpirole evoked locomotor responses. Furthermore, cocaine's ability to induce *Fos* expression was blunted and *Fto*-deficient mice exhibited a reduction in cocaine evoked extracellular levels of dopamine in the NAc (20 mg kg<sup>-1</sup> cocaine i.p.). On the cellular level, *Fto*-deficiency altered the ability of the DRD2/DRD3-GIRK dependent autoreceptor feedback loop to inhibit dopamine neuron firing.



Figure 3.11: Attenuated quinpirole dependent decrease in locomotor activity in *Fto-*deficient mice

Control and *Fto*-deficient mice were injected i.p. with 30  $\mu$ g kg<sup>-1</sup> and 100  $\mu$ g kg<sup>-1</sup> quinpirole. Data is represented as percent relative to baseline saline injection. (\**P*<0.05, unpaired two-tailed *t*-test, sample sizes are indicated in parentheses).

# 3.2 Dopamine neuron restricted loss of FTO attenuates the function of the DRD2/DRD3 dependent autoreceptor feedback loop

#### 3.2.1 Generation of dopamine neuron restricted Fto knock out mice

Conventional whole body deletion of *Fto* causes a severe phenotype that, with respect to dopaminergic function, affects dopamine neurons as well as target neurons of the midbrain dopamine system. Hence, the loss of *Fto* most probably alters preas well as postsynaptic signaling events. Therefore, mice with a dopamine neuron restricted *Fto* deletion (*Fto*<sup> $\Delta$ DAT</sup>) were generated using the Cre-loxP system, to investigate the role of FTO specifically in dopaminergic neurons.

#### Mouse models for dopamine neuron restricted Fto deletion

To generate a dopamine neuron restricted FTO knock out, mice with a loxP site flanked exon 3 of the *Fto* gene (knock out first allele EUCOMM, *Fto*::tm1a-(EUCOMM)Wtsi; Figure 3.12 a) were crossed to FLP-deleter mice and subsequently to transgenic mice expressing the Cre recombinase under the control of the endogenous dopamine transporter (*Dat*) promoter (Figure 3.12 b; Ekstrand *et al.* [2007]).



#### Figure 3.12: Schematics of Cre-dependent deletion of Fto

(a) *Fto*::tm1a(EUCOMM)Wtsi mice provided by the European Conditional Mouse Mutagenesis program carry a flippase recognition target (FRT) site flanked knock in of the  $\beta$ -galactosidase gene in conjunction with a neomycin resistance cassette (knock out first allele). Furthermore, loxP sites were introduced flanking the third exon of the *Fto* gene. Prior to FLP deletion, the knock out first construct was used for  $\beta$ -galactosidase stainings. The conditional allele was generated through crossing of mice with FLP-recombinase, deleting the  $\beta$ -galactosidase and neomycin cassette and restoring endogenous *Fto* expression levels. (b) Subsequent crossing of mice carrying the conditional allele with mice expressing the Cre recombinase under the control of the endogenous *Dat* promoter Ekstrand *et al.* [2007] led to the generation of dopamine neuron restricted *Fto* knock outs (*Fto*<sup>ΔDAT</sup>) and controls (*Fto*<sup>fl/fl</sup>).

The dopamine transporter is regarded as a selective marker for dopaminergic neurons [Ciliax *et al.*, 1995; Freed *et al.*, 1995]. Therefore, directing the expression of Cre to DAT expressing neurons caused a dopamine neuron restricted recombination of loxP sites. Deletion of the loxP site flanked third exon of *Fto* leads to a frame shift, causing a premature translational stop signal. Moreover, exon 3 encodes for approximately 40% of the FTO protein. The remaining truncated *Fto* mRNA is likely to undergo degradation via nonsense-mediated decay mechanisms. Hence, excision of the third *Fto* exon was expected to efficiently delete FTO.



Figure 3.13: Validation of DA neuron specific Fto deletion

#### Figure 3.13: Validation of DA neuron specific Fto deletion

(a) Midbrain dopaminergic neurons were stained in  $Fto^{\Delta DAT/\Delta}$  and  $Fto^{+/+}$  mice using an antibody directed against the tyrosine hydroxylase (TH), a marker for dopaminergic neurons in the midbrain. Further labeling of FTO revealed the absence of FTO in dopamine neuron restricted *Fto* knock out mice. (b) Quantification of FTO immunofluorescence in TH positive neurons in the midbrain (n = 3 for each  $Fto^{\Delta DAT}$  and  $Fto^{fl/fl}$ , \*\*\**P*<0.001, unpaired two-tailed *t*-test). (c) Western blot analysis of liver, pancreas, skeletal muscle and rest brain (nonmidbrain). (d) Western blot analysis of DAT expression between  $Fto^{\Delta DAT}$  mice carrying a copy of the Cre recombinase in the endogenous *Dat* locus and controls.

#### Validation of DA neuron specific *Fto* deletion

To verify the efficient and selective loss of FTO in  $Fto^{\Delta DAT}$  mice, immunohistochemical stainings of midbrain sections were performed. To identify the genetically targeted neurons, tyrosine hydroxylase (TH, Figure 3.13 a, green) was used as a marker for dopamine neurons in the midbrain. Immunolabeling of FTO confirmed the presence of FTO in approximately 90% of midbrain TH expressing neurons of control mice (Figure 3.13 a, b; FTO labeled in red, representative staining shows midbrain sections of  $Fto^{\Delta DAT/\Delta}$  and  $Fto^{+/+}$  mice). In  $Fto^{\Delta DAT}$  mice, FTO immunoreactivity was only observed in 1.14% of TH neurons (Figure 3.13 a, b; quantification was performed for  $Fto^{\Delta DAT}$  and  $Fto^{fl/fl}$  controls).

To exclude unspecific deletion of the loxP-flanked third exon in untargeted peripheral or remaining brain tissue, Western blot analysis was performed. For analysis of liver, pancreas and skeletal muscle (SM), tissue derived from  $Fto^{\Delta DAT/\Delta}$  was used, while Western blot of rest brain (non-midbrain) tissue was conducted for  $Fto^{\Delta DAT}$  mice. No aberrant loss of FTO was observed for all non-targeted tissues tested. Hence, the targeted deletion of FTO in dopaminergic neurons was considered efficient and specific (Figure 3.13 c).

In DAT-cre mice the cre-recombinase cDNA was cloned into the endogenous *Dat* locus between exon 1 and 2 [Ekstrand *et al.*, 2007]. Using this strategy, the endogenous transcription site was used for cre expression, while not affecting the *Dat* coding region with its translational start codon in exon 2. To ensure that this strategy was not affecting the endogenous DAT expression, western blot on mid-



Figure 3.14: Fto deletion in DA neurons does not affect FTO expression in midbrain GABAergic neurons Combined *in situ* hybridization for *Cad6z* (red) a marker for CABAergic neu-

Combined *in situ* hybridization for *Gad67* (red), a marker for GABAergic neurons, and immunofluorescent staining of FTO (green) revealed no loss of FTO in GABAergic neurons of  $Fto^{\Delta DAT}$  mice.

brain lysates of  $Fto^{\Delta DAT}$  and  $Fto^{fl/fl}$  was performed. This analysis confirmed no differences in DAT expression between genotypes (Figure 3.13 d).

#### Fto deletion in DA neurons does not affect FTO expression in midbrain

#### **GABAergic** neurons

To further exclude unspecific deletion of *Fto* within the midbrain, FTO expression was assessed in GABAergic neurons of midbrain slices. For this purpose, combined *in situ* hybridization for *Gad67* (glutamat decarboxylase; marker for GABAergic neurons) and FTO immunohistochemistry was performed. No loss of FTO in GABAergic neurons of the midbrain was observed (Figure 3.14).

Taken together, FTO was shown to be efficiently and specifically deleted in mid-

brain dopaminergic neurons of  $Fto^{\Delta DAT}$  mice. Neither FTO expression in peripheral or remaining brain tissue was affected nor was FTO unspecifically deleted in non-dopaminergic neurons.

# 3.2.2 Dopamine restricted *Fto* knock out does not influence basic metabolic parameters

#### Dopamine neuron restricted loss of FTO does not affect body weight

Whole body *Fto*-deficient mice have a lower body weight, due to a reduced lean and fat mass [Fischer *et al.*, 2009]. Since dopamine signaling is implicated in the etiology of obesity, alteration of dopaminergic function through loss of FTO may impact body weight regulation [Volkow *et al.*, 2013]. Therefore, the body weight of  $Fto^{\Delta DAT}$  and control mice was monitored over the course of 16-18 weeks (Figure 3.15 a, b). No significant differences were detected for both males and females on either a normal chow diet (NCD) or a high fat diet (HFD).

Consistently, no differences in metabolic rate (depicted as  $O_2$ -consumption, 12-13 weeks of age) were found for males on either NCD or HFD (Figure 3.15 c, d). Moreover, food intake was unchanged for male  $Fto^{\Delta DAT}$  mice as compared to controls on both NCD and HFD (Figure 3.15 e, f).

# Dopamine neuron restricted loss of FTO does not affect insulin and glucose tolerance

To investigate glucose metabolism in  $Fto^{\Delta DAT}$  mice, insulin and glucose tolerance tests were performed at 12 weeks (ITT) and 13 weeks (GTT) of age. No differences in either insulin sensitivity or glucose tolerance were observed between male  $Fto^{\Delta DAT}$  and control mice on either high fat (Figure 3.16 a, c) or normal chow diet (Figure 3.16 b, d).

Hence, insulin's ability to reduce blood glucose levels, as well as the insulin mediated counter response to elevated glucose levels are not altered in  $Fto^{\Delta DAT}$  mice. These results are consistent with the paucity of body weight differences for  $Fto^{\Delta DAT}$  mice.





Figure 3.15: Basic metabolic parameters are unchanged in  $Fto^{\Delta DAT}$  mice (a) Body weight of male  $Fto^{\Delta DAT}$  and control mice was monitored until 16 weeks of age on both normal (NCD) and high fat diet (HFD). (b) Body weight of female  $Fto^{\Delta DAT}$  and control mice was monitored until 18 weeks of age on both normal (NCD) and high fat diet (HFD). (c) O<sub>2</sub> consumption of male  $Fto^{\Delta DAT}$  and control mice on a HFD. (d) O<sub>2</sub> consumption of male  $Fto^{\Delta DAT}$  and control mice on a NCD. (e) Food intake of male  $Fto^{\Delta DAT}$  and control mice on a HFD. (f) Food intake of male  $Fto^{\Delta DAT}$  and control mice on a NCD (sample sizes are indicated in parentheses).



Figure 3.16: Unchanged insulin and glucose tolerance in  $Fto^{\Delta DAT}$  mice

(a) Insulin tolerance test was performed on male  $Fto^{\Delta DAT}$  (n=24) and control (n=22) mice fed a HFD. (b) Insulin tolerance test was performed on male  $Fto^{\Delta DAT}$  (n=18) and control (n=14) mice fed a NCD. (c) Glucose tolerance test was performed on male  $Fto^{\Delta DAT}$  (n=23) and control (n=24) mice fed a HFD. (d) Glucose tolerance test was performed on male  $Fto^{\Delta DAT}$  (n=23) and control (n=16) and control (n=12) mice fed a NCD.

#### Dopamine neuron restricted loss of FTO does not affect food intake and

#### refeeding responses

In order to further investigate feeding behavior in  $Fto^{\Delta DAT}$  mice, the refeeding response to a 16h over night fast was assessed. In line with the previous results (Figure 3.15 e, f), baseline food intake was unaltered between  $Fto^{\Delta DAT}$  and control mice (Figure 3.17 a).

Following the 16h over night fasting period, the cumulative food intake was measured 1h, 2h, 4h, 8h and 24h after refeeding. During early hours of refeeding,  $Fto^{\Delta DAT}$  mice showed a slightly increased food intake as compared to their control



Figure 3.17: Food intake and refeeding response are unaltered in  $Fto^{\Delta DAT}$  mice (a) Baseline food intake was unaltered in male  $Fto^{\Delta DAT}$  mice on NCD. (b) Refeeding behavior was assessed in response to a 16h over night fast. Food intake was measured 1, 2, 4, 6, and 24h after refeeding in male  $Fto^{\Delta DAT}$  and control mice fed a NCD (RM two-way ANOVA,  $F_{1,14} = 1.06$ , P = 0.3196).

littermates, however, no significant changes were observed ( $F_{1,14} = 1.06$ , P = 0.3196; Figure 3.17).

#### Dopamine neuron restricted loss of FTO does not affect sucrose preference

Both anhedonia and depression are closely related to dopaminergic function [Nestler & Carlezon, 2006; Krishnan & Nestler, 2008]. To test, whether dopamine neuron restricted deletion of *Fto* affected anhedonia in mice,  $Fto^{\Delta DAT}$  and control mice were subjected to a sucrose preference test, a measure for anhedonia in animals [Strekalova *et al.*, 2004]. With increasing concentrations, both  $Fto^{\Delta DAT}$  and control mice significantly increased their preference for sucrose (0.5 - 8% sucrose solution, RM two-way ANOVA,  $F_{4,60} = 42.68$ , P < 0.0001, Figure 3.18). Between genotypes,  $Fto^{\Delta DAT}$  mice exhibited slightly higher sucrose preference values. However, these differences were not significant (RM two-way ANOVA,  $F_{1,15} = 0.4338$ , P = 0.5201), showing that anhedonia is not affected in  $Fto^{\Delta DAT}$  mice (Figure 3.18).



#### Figure 3.18: Sucrose preference is unaltered in $Fto^{\Delta DAT}$ mice

Sucrose preference was assessed for  $Fto^{\Delta DAT}$  and control mice. Sucrose consumption was monitored for each sucrose concentration (0.5, 1, 2, 4 and 8% sucrose solution) for 2 consecutive days and calculated relative to total liquid consumption.  $Fto^{fl/fl}$  (n = 10);  $Fto^{\Delta DAT}$  (n = 7).

#### 3.2.3 Altered DRD2/DRD3 dependent responses in $Fto^{\Delta DAT}$

### Attenuated DRD2/DRD3 autoreceptor feedback loop in $Fto^{\Delta DAT}$ mice

To investigate whether  $Fto^{\Delta DAT}$  mice exhibited comparable alterations on the cellular level as *Fto*-deficient mice, patch-clamp recordings were performed and firing rate was measured for dopaminergic midbrain neurons challenged with 10  $\mu$ M cocaine or 10 nM quinpirole. In line with the results obtained for *Fto*-deficient mice (see Figure 3.9 a, b),  $Fto^{\Delta DAT}$  mice exhibited attenuated cocaine and quinpirole dependent reductions in firing rate compared to control mice, demonstrating that the DRD2/DRD3 mediated autoinhibition was malfunctional (Figure 3.19 a, b). Furthermore, the quinpirole (10 nM) dependent conductance density was reduced, demonstrating that activation of presynaptic DRD2/DRD3 receptors in *Fto*<sup> $\Delta DAT$ </sup> mice is not able to elicit the same relative current flow (Figure 3.19 c). Hence, the loss of FTO in dopaminergic neurons cell autonomously affects the DRD2/DRD3 autoreceptor feedback loop.

#### Reduced GIRK dependent current density in $Fto^{\Delta DAT}$ mice

To further assess whether the change in feedback inhibition could be attributed to GIRK currents, GIRK-dependent current density was measured as described



Figure 3.19: Attenuated responses of midbrain neurons to cocaine and quinpirole in  $Fto^{\Delta DAT}$  mice

(a) Relative firing rate of SNpc dopaminergic neurons in patch clamp recordings during bath application of cocaine (10  $\mu$ M, 10 min, sample sizes indicated in parentheses, \**P*<0.05, unpaired one-tailed *t*-test). (b) Bath application of the D2-D3-receptor agonist quinpirole (10 nM) on control and *Fto*<sup>ΔDAT</sup> dopamine neurons. (sample sizes indicated in parentheses, \*\**P*<0.01, unpaired two-tailed *t*-test). (c) In line with the attenuated reduction in firing rate, quinpirole (10 nM) mediated increase in conductance density is significantly reduced in *Fto*<sup>ΔDAT</sup> mice (sample sizes indicated in parentheses, \**P*<0.05, unpaired two-tailed *t*-test). All electrophysiological experiments were conducted by Simon Hess.

in section 3.1.4. Consistent with the attenuated responses to bath application of cocaine and quinpirole on firing rate and mirroring the results obtained for *Fto*-deficient mice (Figure 3.10), the GIRK dependent current density was significantly reduced in *Fto*<sup> $\Delta$ DAT</sup> mice (Figure 3.20).

Hence, the autoreceptor feedback loop is malfunctional through the attenuation of DRD2-DRD3-GIRK dependent changes in conductance. Whether a reduction in GIRK channel availability or whether attenuated activation of these channels due to changes further upstream in the signaling pathway are responsible for these observations remains unclear.



Figure 3.20: **Reduced GIRK dependent current density in**  $Fto^{\Delta DAT}$  **mice** DRD2 mediated activation of GIRK channels is attenuated in  $Fto^{\Delta DAT}$  dopamine neurons. GIRK currents were measured by activation of D2/D3 receptors by quinpirole (300 nM) and subsequent blocking of GIRKs by BaCl<sub>2</sub> (1 mM) (sample sizes indicated in parentheses, \*\**P*<0.01, unpaired two-tailed *t*-test). All electrophysiological experiments were conducted by Simon Hess.

#### Altered baseline and cocaine evoked locomotor activity in $Fto^{\Delta DAT}$ mice

Since dopamine is involved in motor control, malfunction of the dopaminergic autoinhibitory feedback loop may alter locomotor activity. To probe motor function, baseline and cocaine-induced locomotor activity was assessed for  $Fto^{\Delta DAT}$  mice in the open field paradigm. For baseline locomotor activity, the distance travelled over the course of 45 minutes was assessed in saline injected mice. These measurements revealed baseline hyperlocomotion for  $Fto^{\Delta DAT}$  mice as compared to controls (Figure 3.21 a).

When challenged with cocaine,  $Fto^{\Delta DAT}$  mice exhibited a hypersensitivity towards lower cocaine concentration (10 mg kg<sup>-1</sup>), while no differences at the higher concentration (20 mg kg<sup>-1</sup>) were observed (Figure 3.21 b).

### Attenuated quinpirole dependent decrease in locomotor activity in $Fto^{\Delta DAT}$ mice

To directly address the impact of the activation of the DRD2/DRD3 autoreceptors on locomotor activity,  $Fto^{\Delta DAT}$  mice and control mice were challenged with i.p. injections of 30 and 100  $\mu$ g kg<sup>-1</sup> quinpirole. In line with the previous results obtained for *Fto*-deficient mice,  $Fto^{\Delta DAT}$  mice exhibited an attenuated response in the quinpirole-dependent decrease of locomotor activity (Figure 3.22).



Figure 3.21: Altered baseline and cocaine evoked locomotor activity in  $Fto^{\Delta DAT}$  mice (a) Baseline locomotor activity during open field experiments in  $Fto^{\Delta DAT}$  mice (sample sizes indicated in parentheses, \**P*<0.05, unpaired two-tailed *t*-test) (b) Cocaine induced locomotor activity in the open field paradigm after 10 mg kg<sup>-1</sup> BW and 20 mg kg<sup>-1</sup> cocaine i.p. injection in  $Fto^{\Delta DAT}$  compared to control mice. Cocaine evoked locomotor activity is expressed as percent increase compared to baseline activity following saline injection (sample sizes indicated in parentheses, \**P*<0.05, unpaired two-tailed *t*-test).



Figure 3.22: Attenuated quinpirole dependent decrease in locomotor activity in  $Fto^{\Delta DAT}$  mice

Control and  $Fto^{\Delta DAT}$  mice were injected i.p. with 30  $\mu$ g kg<sup>-1</sup> and 100  $\mu$ g kg<sup>-1</sup> quinpirole. Data is represented as percent relative to baseline saline injection (\**P*<0.05, unpaired two-tailed *t*-test, sample sizes are indicated in parentheses).

After both 30 and 100  $\mu$ g kg<sup>-1</sup> quinpirole administration  $Fto^{\Delta DAT}$  mice retained significantly more of their locomotor activity. Hence, the ability of the DRD2/DRD3 agonist quinpirole to reduce activity of the dopaminergic neurons and thereby reducing the dopaminergic network tone was significantly attenuated. These results are consistent with the proposed cell autonomous reduction in DRD2/DRD3-GIRK dependent autoinhibition in  $Fto^{\Delta DAT}$  mice and are in line with the results obtained for Fto-deficient mice.

# Hypersensitivity of $Fto^{\Delta DAT}$ mice to cocaine in the conditioned place preference

Finally, to assess the function of the dopaminergic system with respect to processing reward-related behavior,  $Fto^{\Delta DAT}$  mice were tested in the conditioned place preference paradigm.  $Fto^{\Delta DAT}$  mice featured several aspects of the previously reported DRD2 autoreceptor knock out mouse, including increased baseline and cocaine-induced locomotor activity and the attenuated responses to quinpirole both on the cellular as well as the behavioral level [Bello *et al.*, 2011]. Therefore, the conditioned place preference was performed with a very low dose cocaine bait (0.5 mg kg<sup>-1</sup>), a concentration that was able to affect place preference in DRD2 autoreceptor knock out mice [Bello *et al.*, 2011]. While this concentration failed to show any effect in control mice, place preference in  $Fto^{\Delta DAT}$  mice was significantly enhanced (Figure 3.23).

This result is in line with the concept that decreased inhibitory tone in dopaminergic neurons would result in enhanced responses to conditioned stimuli and again supports the notion that loss of FTO cell autonomously attenuates the DRD<sub>2</sub>/DRD<sub>3</sub>-GIRK-dependet autoinhibitory feedback loop.



Figure 3.23: Low dosage of cocaine shifts preference of  $Fto^{\Delta DAT}$  mice in conditioned place preference

Reward processing was assessed in the conditioned place preference paradigm for  $Fto^{\Delta DAT}$  and control mice using a low dose cocaine bait (0.5 mg kg<sup>-1</sup>, sample size indicated in parenthesis, \**P*<0.05, paired two-tailed *t*-test).

# 3.3 *N*6-methyladenosine in mRNA depends on FTO demethylase function

# 3.3.1 Methylated RNA immunoprecipitaion (MeRIP) sequencing identifies demethylation targets of FTO

On the molecular level, FTO was identified as a Fe(II) and 2-oxoglutarate dependent demethylase that is able to demethylate 3 - methyluracil and N6 - methyladenosine (m<sup>6</sup>A) *in vitro* [Jia *et al.*, 2011; Gerken *et al.*, 2007]. Recently, the m<sup>6</sup>A mark was identified in over 7600 mRNA transcripts *in vivo* [Meyer *et al.*, 2012; Dominissini *et al.*, 2012]. To investigate the potential role of this enzymatic capability of FTO with respect to dopaminergic function, the m<sup>6</sup>A methylation profile was assessed in *Fto*-deficient mice. To this end, mRNA of midbrain and striatal (CPu and NAc) tissue was isolated and subsequently processed using established methylated RNA immunoprecipitaion (MeRIP) protocols, followed by next generation sequencing [Meyer *et al.*, 2012]. In total, 42.000 m<sup>6</sup>A peaks were found, and 5000 peaks in over 1500 transcripts were unique to *Fto*-deficient mice (Table 6.3). In line with previously published results, one or more m<sup>6</sup>A marks were found in the 5' UTR, CDS or 3'UTR of individual transcripts (Table 6.3, Meyer *et al.* [2012]).



### Figure 3.24: Gene ontology analysis of transcripts with m<sup>6</sup>A hypermethylation in *Fto-*deficient mice

Gene ontologies of m<sup>6</sup>A hypermethylated midbrain and striatal mRNA transcripts cluster in categories of synaptic transmission and cell-cell signaling in *Fto*-deficient mice. Gene ontology analysis was performed by Yogesh Saletore and Olivier Elemento

#### Gene ontology analysis of transcripts hypermethylated in Fto-deficient mice

Since the loss of FTO leads to a hypermethylation of a subset of  $m^6A$  modified mRNAs, gene ontology analysis was performed to investigate the potential connection between the observed phenotype of *Fto*-deficient mice and the hypermethylated transcripts. This analysis showed that in comparison to the whole transcriptome, gene ontologies related to synaptic transmission and cell-cell signaling were overrepresented in *Fto*-deficient mice (Figure 3.24).

In wildtype control mice, however, enrichment of these categories identified in *Fto*-deficient mice were not found, suggesting that FTO targets a functionally distinct subset of transcripts (Figure 3.25).

#### 3.3.2 m<sup>6</sup>A in mRNA influences translation of methylated transcripts

To identify putative candidate transcripts, whose m<sup>6</sup>A methylation in *Fto*-deficient mice might be functionally implicated in dopamine signaling, pathway analysis was performed to generate an overlay of dopaminergic signaling and hypermethylated mRNAs (Table 6.3, Figure 3.26). A number of hypermethylated transcripts in *Fto*-deficient mice encode for proteins that are components of dopaminergic signaling, including DRD<sub>3</sub>, GIRK<sub>2</sub>, NMDAR<sub>1</sub>, GNAO<sub>1</sub> and SYN<sub>1</sub> (Figure 3.26). Several of these components were selected for further analysis.

The type 3 dopamine receptor (DRD3) is expressed both pre- and postsynaptically [Beaulieu & Gainetdinov, 2011]. MeRIP-seq identified a m<sup>6</sup>A methylation site within the coding sequence of the *Drd3* transcript (Figure 3.27 a, Table 6.3). Using quantitative PCR, significant upregulation of *Drd3* mRNA levels were detected in *Fto*-deficient midbrain and CPu (Figure 3.27 b). On the protein level, however, a significant downregulation was observed for DRD3 in *Fto*-deficient mice (Figure 3.27 c, d).

Comparable results were obtained for the G protein coupled inwardly rectifying potassium channel 2, whose transcript was m<sup>6</sup>A methylated within the 5'UTR (Figure 3.28 a). This 5' UTR, however, is only present in the Girk2A and Girk2B,



Figure 3.25: Gene ontology analysis of transcripts m<sup>6</sup>A methylated in control mice m<sup>6</sup>A methylated mRNA transcripts, isolated from wildtype midbrain and striatum, do not cluster in gene ontologies of synaptic transmission or cellcell signaling. Gene ontology analysis was performed by Yogesh Saletore and Olivier Elemento

but not Girk2C transcripts. qPCR analysis of total *Kcnj6* revealed a significant upregulation of mRNA levels in *Fto*-deficient midbrain tissue (Figure 3.28 b; isoform unspecific *Kcnj6* qPCR probe). Consistent with the previous results for DRD3, GIRK2 protein levels were significantly downregulated in both midbrain and CPu of *Fto*-deficient mice (Figure 3.28 c, d).

For the N-methyl-D-aspartate (NMDA) receptor subunit 1, hypermethylated m<sup>6</sup>A



Figure 3.26: **Pathway analysis of m<sup>6</sup>A hypermethylated transcripts in** *Fto*-deficient mice Overlay of dopaminergic signaling and m<sup>6</sup>A hypermethylated transcripts identified via MeRIP-Seq in *Fto*-deficient midbrain and striatal tissue was performed to identify putative candidates functionally related to the phenotype observed in *Fto*-deficient mice

sites were detected in both the 5' and 3' UTR of *Fto*-deficient mice (Figure 3.29 a, only 3' UTR shown). *Grin1* transcripts showed significant upregulation in *Fto*-deficient midbrain but not CPu (Figure 3.29 b), while protein levels were significantly downregulated in both midbrain and CPu (Figure 3.29 c, d).

Whilst the upregulation of m<sup>6</sup>A hypermethylated on mRNA level was detected for additional transcripts (*Gnai1, Ikbkb, Gnao1, Gnb5*; Figure 3.30 a, 3.31 a, 3.32), downregulation of the protein level was not confirmed for GNAI1 nor IKK2 (Figure 3.30 b, c, 3.31 b, c), suggesting a more complicated mechanism through which m<sup>6</sup>A methylation functionally impacts specific transcripts.



#### Figure 3.27: FTO demethylation target Drd3

(a) MeRIP-Seq identified a hypermethylated m<sup>6</sup>A site in the coding sequence of the *Drd*<sub>3</sub> mRNA transcript of *Fto*-deficient mice. MeRIP pulldown was performed by Kate Meyer. (b) Quantitative PCR of *Drd*<sub>3</sub> mRNA isolated from *Fto*-deficient and control midbrain and dorsal striatum (CPu). (c) Western blot analysis of DRD<sub>3</sub> protein in *Fto*-deficient and control midbrain and CPu lysates. (d) Quantification of DRD<sub>3</sub> western blot analysis. (\**P*<0.05, \*\**P*<0.01, \*\*\**P*<0.001; unpaired two-tailed *t*-test, sample sizes are indicated in parenthesis).



Figure 3.28: FTO demethylation target Kcnj6

(a) MeRIP-Seq identified a hypermethylated m<sup>6</sup>A site in the 5' UTR of *Kcnj6* mRNA transcripts of *Fto*-deficient mice. MeRIP pulldown was performed by Kate Meyer. (b) Quantitative PCR of *Kcnj6* mRNA isolated from *Fto*-deficient and control midbrain and dorsal striatum (CPu). (c) Western blot analysis of GIRK2 protein in *Fto*-deficient and control midbrain and CPu lysates (bands in blot correspond to GIRK2A and GIRK2B isoforms). (d) Quantification of GIRK2 western blot analysis. (\**P*<0.05, \*\**P*<0.01; unpaired two-tailed *t*-test, sample sizes are indicated in parenthesis).



#### Figure 3.29: FTO demethylation target Grin1

(a) MeRIP-Seq identified hypermethylated m<sup>6</sup>A sites in the 5' and 3' UTR of *Grin1* (glutamate receptor, ionotropic, N-methyl-D-aspartate 1) mRNA transcripts of *Fto*-deficient mice (5' UTR not depicted). MeRIP pulldown was performed by Kate Meyer. (b) Quantitative PCR of *Grin1* mRNA isolated from *Fto*-deficient and control midbrain and dorsal striatum (CPu). (c) Western blot analysis of NMDAR1 (N-methyl-D-aspartate receptor subunit 1) protein in *Fto*-deficient and control midbrain and CPu lysates. (d) Quantification of NM-DAR1 western blot analysis. (\**P*<0.05, \*\*\**P*<0.001; unpaired two-tailed *t*-test, sample sizes are indicated in parenthesis).





MeRIP-Seq identified a hypermethylated m<sup>6</sup>A site in the 5' UTR of *Gnai1* mRNA transcripts of *Fto*-deficient mice. (a) Quantitative PCR of *Gnai1* mRNA isolated from *Fto*-deficient and control midbrain and dorsal striatum (CPu). (b) Western blot analysis of GNAI1 protein in *Fto*-deficient and control CPu lysates. (c) Quantification of GNAI1 western blot analysis. (\*P<0.05, \*\*P<0.01; unpaired two-tailed *t*-test, sample sizes are indicated in parenthesis).





MeRIP-Seq identified hypermethylated m<sup>6</sup>A sites in the coding sequence and 3' UTR of *lkbkb* mRNA transcripts of *Fto*-deficient mice. (a) Quantitative PCR of *lkbkb* mRNA isolated from *Fto*-deficient and control midbrain and CPu. (b) Western blot analysis of IKK2 protein in *Fto*-deficient and control CPu lysates. (c) Quantification of IKK2 western blot analysis. (\*\*\*P<0.001; unpaired two-tailed *t*-test, sample sizes are indicated in parenthesis).


## Figure 3.32: FTO demethylation targets Gnao1 and Gnb5

MeRIP-Seq identified hypermethylated m<sup>6</sup>A sites in the coding sequence and 5' UTR of *Gnao1* and the 5' UTR of *Gnb5* mRNA transcripts of *Fto*-deficient mice. (a) Quantitative PCR of *Gnao1* mRNA isolated from *Fto*-deficient and control midbrain and dorsal striatum (CPu). (b) Quantitative PCR of *Gnb5* mRNA isolated from *Fto*-deficient and control midbrain and CPu. (\*P<0.05, \*\*\*P<0.001; unpaired two-tailed *t*-test) Sample sizes are indicated in parenthesis.

## 4 Discussion

The worldwide increase in prevalence of obesity is going to be one of the major challenges of modern society, causing a plethora of health problems and placing a burden on health care systems [Cawley & Meyerhoefer, 2012; Finkelstein *et al.*, 2009; Caballero, 2007]. The reason for the increase in obesity which started in the middle of the  $20^{th}$  century, is unlikely to be caused by rare mutations. It is rather a cause of environmental changes including sedentary life style and the constant availability of highly palatable food in conjunction with a genetic susceptibility to gain weight in such conditions [Swinburn *et al.*, 2011; Caballero, 2007].

This susceptibility is believed to be shaped by common genetic variations and the sum of their individual effects on body weight [Loos, 2012]. Hence, identification of these single nucleotide polymorphisms (SNPs) underlying common obesity has become a primary goal. Some of the SNPs can directly impact the function of genes through changes in the coding sequence, while others are situated in intronic regions and may indirectly affect gene function.

In 2007, a cluster of SNPs was identified within the first intron of the human *FTO* gene and these SNPs were subsequently the targets of extensive studies, due to their robust association with obesity related traits [Frayling *et al.*, 2007; Dina *et al.*, 2007; Scuteri *et al.*, 2007]. To date, the exact function of these SNPs within the first intron as well as the exact function of the *FTO* gene product are not known. Hence, the aim of this thesis was the investigation of FTO by means of genetic manipulations in mice to identify FTO's function and depending pathways, to ultimately shed light on the connection between *FTO* genomic variation and common obesity.

Whole body FTO deletion in mice causes a severe phenotype that partly resembles the phenotype of *Drd2*-deficient mice, including growth retardation, reduced

IGF-1 levels, lean phenotype, increased energy expenditure and reduced voluntary locomotor activity [Fischer *et al.*, 2009; Klinker *et al.*, 2013; Kim *et al.*, 2010; García-Tornadu *et al.*, 2010; Díaz-Torga *et al.*, 2002; Sibley, 1999; Kelly *et al.*, 1998; Beaulieu & Gainetdinov, 2011]. Moreover, both FTO and DRD2 are linked to the etiology of obesity [Scuteri *et al.*, 2007; Dina *et al.*, 2007; Frayling *et al.*, 2007; Volkow *et al.*, 2013; Wang *et al.*, 2001]. For this reason, the potential role of FTO in dopaminergic signaling was investigated.

## 4.1 *Fto* deficiency alters D2-like receptor–dependent responses

### 4.1.1 FTO is expressed in midbrain dopaminergic neurons

Although *Fto* is ubiquitously expressed, it's highest levels are detected within the central nervous system [Gerken *et al.*, 2007; McTaggart *et al.*, 2011]. In line with these results, endogenous *Fto* expression in midbrain dopaminergic neurons was confirmed using a mouse model with a knock in of the  $\beta$ -galactosidase gene into the endogenous *Fto* locus (Section 3.1.1). Moreover, FTO immunoreactivity was demonstrated for midbrain dopaminergic neurons (Section 3.1.1). Hence, FTO potentially plays a role in dopaminergic neurons and dopaminergic signaling.

Since the loss of FTO leads to increased mortality in both men and mice, *Fto* deficiency may affect cell viability [Fischer *et al.*, 2009; Boissel *et al.*, 2009]. In *Fto*-deficient mice, however, no changes in number or morphology of dopaminergic neurons were observed, showing that viability of dopamine neurons is not affected by the loss of FTO (Section 3.1.1).

## 4.1.2 Whole body *Fto*-deficiency attenuates responses to cocaine

To investigate the function of the dopaminergic circuitry, *Fto*-deficient mice were challenged with cocaine injections. Cocaine is a potent psychostimulatory substance, whose primary effect is the blockade of the dopamine transporter and hence many of its effects impinge on dopaminergic signaling [Beaulieu & Gainetdinov,

2011; Hyman et al., 2006; Nestler, 2001]. Loss of FTO had severe impacts on the cocaine evoked responses in mice. Firstly, the cocaine mediated increase in locomotor activity was blunted (Section 3.1.3). Secondly, cocaine-induced Fos expression in midbrain and striatal tissue was attenuated (Section 3.1.3). And thirdly, although cocaine was able to stimulate increases in extracellular dopamine in the NAc, significant differences were detected between control and *Fto*-deficient mice at higher cocaine dosages (Section 3.1.3). Since all neurons are affected in Fto-deficient mice, the individual contributions of pre- and postsynaptic loss of FTO in these experiments are not known. Failure to increase locomotor activity and Fos expression may stem from a failure of cocaine to block the dopamine transporter and would resemble aspects of a dopamine transporter mutant mouse insensitive to cocaine [Chen *et al.*, 2006]. The fact that dopamine levels increased in response to cocaine in *Fto*-deficient mice, however, suggests that other factors may contribute to the observed cocaine insensitivity, though not ruling out an alteration of dopamine transporter function. As DAT protein levels were demonstrated to be unchanged in *Fto*-deficient mice, loss of FTO might indirectly affect DAT function.

## 4.1.3 Impairment of D2-like autoreceptor signaling

Dopaminergic neurons express D2 and D3 autoreceptors that are activated by dopamine and trigger a feedback loop that subsequently terminates dopamine signaling through the activation of GIRK channels and hyperpolarization of dopamine neurons [Beaulieu & Gainetdinov, 2011; Lüscher & Slesinger, 2010]. While dopamine neurons fire tonically in a slice preparation, cocaine administration leads to a decrease in firing by increasing extracellular dopamine levels and activating the autoinhibitory feedback loop. Consistently, cocaine decreased the firing rate of dopamine neurons in the midbrain of control mice (see Section 3.1.4). In *Fto*-deficient mice, however, the ability of cocaine to reduce firing of dopamine neurons was significantly attenuated (Section 3.1.4).

Since cocaine acts indirectly via increasing extracellular levels of dopamine, the

DRD<sub>2</sub>/DRD<sub>3</sub> selective agonist quinpirole was used to directly address the function of the autoinhibitory feedback loop. In line with the previous experiments, activation of the feedback loop by quinpirole potently reduced the firing rate of dopamine neurons in control mice, while this response was significantly attenuated in *Fto*-deficient mice (Section 3.1.4). Consistently, the quinpirole and GIRK dependent conductance density was decreased in *Fto*-deficient mice. On the behavioral level, injection of quinpirole in control mice caused a reduction in locomotor activity via inhibiting dopamine neuron activity. Consistently with the impairment observed on the cellular level, quinpirole's ability to reduce locomotor activity was significantly attenuated in *Fto*-deficient mice, demonstrating that the impaired autoinhibitory feedback directly translates into a behavioral phenotype.

Taken together, *Fto* deficiency led to a malfunction of the DRD2-DRD3-GIRKdependent autoinhibitory feedback loop of dopaminergic neurons and impaired, in conjunction with postsynaptic alterations, responses of the dopaminergic circuitry to cocaine and quinpirole.

# 4.2 Conditional loss of Fto resembles D2 autoreceptor deficiency

## 4.2.1 Successful generation of dopamine neuron specific knock out mice

To investigate the role of FTO in altering the dopaminergic circuitry, dopamine neuron restricted knock out mice were utilized in addition to whole body *Fto*-deficient mice. To generate a specific deletion of FTO in dopaminergic cells, mice carrying the Cre recombinase under the control of the endogenous *Dat* promoter were crossed to mice with a loxP site flanked third exon of *Fto* (Section 3.2.1). Successful generation of *Fto*<sup> $\Delta$ DAT</sup> mice was confirmed using immunohistochemical investigation of midbrain slices. Here, tyrosine hydroxylase (TH) immunolabeling was used to identify dopaminergic neurons. These experiments showed that the majority of dopamine cells in the VTA/SN of mice expressed FTO (approximately 90%). After

Cre-mediated recombination in  $Fto^{\Delta DAT}$  mice, however, only 1.14% of TH positive neurons were found to express FTO, demonstrating the efficient deletion of FTO in dopaminergic neurons. Using Western blot analysis on peripheral tissues, the specificity of FTO deletion was further confirmed (Section 3.2.1).

### 4.2.2 Cell-autonomous impairment of D2-like autoreceptor signaling

On the cellular level, the responses of  $Fto^{\Delta DAT}$  to cocaine and quinpirole mirrored those obtained in *Fto*-deficient mice. The ability of both cocaine and quinpirole to inhibit the firing of midbrain dopamine neurons was significantly attenuated (Section 3.2.3). Moreover, the GIRK channel-dependent conductance density was reduced in  $Fto^{\Delta DAT}$  as compared to control mice. These results show that the dopamine neuron restricted knock out resembled whole body FTO deletion on the cellular level and that the autoinhibitory feedback loop was cell-autonomously affected by loss of FTO.

The duration of dopamine signaling is limited by the presynaptic autoinhibition. Hence, attenuation of the feedback loop that terminates dopamine signaling, prolongs synaptic dopamine transmission [Bello *et al.*, 2011]. Targeted disruption of D2 autoreceptors in mice demonstrated that blunted autoreceptor function results on the single cell level in comparable loss of inhibitory currents in response to quinpirole bath application as observed for *Fto*-deficient and *Fto*<sup> $\Delta$ DAT</sup> mice [Bello *et al.*, 2011]. In addition, D2 autoreceptor knock out mice displayed increased baseline and cocaine-induced locomotor activity, whereas quinpirole failed to reduce locomotor activity. Moreover, increased conditioned place preference in response to very low dose cocaine injections was observed in D2 autoreceptor knock out mice, showing that these mice are hypersensitive to the locomotor and rewarding effects of cocaine [Bello *et al.*, 2011].

In comparison,  $Fto^{\Delta DAT}$  mice displayed increased baseline as well as cocaine induced locomotor activity at low concentrations, while no significant difference were detected at higher concentrations. Hypersensitivity to cocaine in  $Fto^{\Delta DAT}$  mice was

further assessed in the conditioned place preference paradigm, challenging the mice with a very low dose of cocaine (0.5 mg kg<sup>-1</sup>, Section 3.2.3). While control mice were indifferent to the treatment,  $Fto^{\Delta DAT}$  mice responded to the subthreshold dosage by increasing their preference for the baited side. Hence, in line with the assumption that dopamine neuron restricted loss of FTO resembles the hypersensitivity observed in D2 autoreceptor knock out mice, very low dosages of cocaine were able to elicit a response in the conditioned place preference paradigm. Furthermore, dopamine neuron restricted knock out of FTO significantly attenuated quinpirole's ability to inhibit locomotor activity (Section 3.2.3). In contrast to D2 autoreceptor knock out mice, quinpirole still retained a portion of its agonist potential and markedly decreased locomotor activity in  $Fto^{\Delta DAT}$  mice as compared to baseline levels [Bello *et al.*, 2011]. Therefore,  $Fto^{\Delta DAT}$  mice share several features of D2 autoreceptor deficiency, but are not a phenocopy of the D2 autoreceptordeficient mice. Dopamine neuron restricted loss of FTO rather leads to a loss of autoinhibition through more complex mechanisms as compared to loss of D2 autoreceptors. In line with this notion, no differences in DRD2 expression were detected in *Fto*-deficient mice, showing that attenuation of autoinhibition would involve other components of the feedback loop or may indirectly affect DRD2 autoreceptor function.

Dopamine signaling has been implicated in the etiology of obesity [Volkow *et al.*, 2013; Wang *et al.*, 2001], hence, attenuation of dopamine autoinhibitory feedback may impact body weight regulation. Since *Fto*-deficient mice suffer from a complex phenotype, alterations of body weight regulation in these mice may stem from multiple sources, thereby making it impossible to draw unambiguous conclusions [Fischer *et al.*, 2009]. Therefore, basic metabolic parameters were assessed in *Fto*<sup> $\Delta$ DAT</sup> mice. To this end, no alterations in body weight, food intake, insulin sensitivity, glucose tolerance, re-feeding response or sucrose preference were detected, demonstrating that loss of FTO specifically in dopaminergic neurons, while affecting dopamine autoinhibition, does not impact energy homeostasis. These results

are consistent with the findings obtained for D2 autoreceptor-deficient mice, that do not exhibit changes in body weight [Bello *et al.*, 2011]. Both of these findings suggest that D2 autoreceptor function is not critical for body weight regulation. Possibly, postsynaptic adaptations at the network level compensate in every day life for the aberrant autoreceptor function, thereby preventing malfunctional body weight regulation. Only as the dopaminergic circuitry is pushed by non-natural stimuli, such as cocaine, the attenuated autoinhibtory feedback leads to behavioral alteration. In contrast, in whole body *Fto*-deficient mice loss of FTO affects postsynaptic sites of dopamine action as well. Hence, these mice share several phenotypic characteristics of whole body *Drd2*-deficient mice, such as growth retardation, reduced IGF-1 levels, lean phenotype, increased energy expenditure and reduced voluntary locomotor activity [Fischer *et al.*, 2009; Klinker *et al.*, 2013; Kim *et al.*, 2010; García-Tornadu *et al.*, 2010; Díaz-Torga *et al.*, 2002; Sibley, 1999; Kelly *et al.*, 1998; Beaulieu & Gainetdinov, 2011].

Taken together, loss of FTO in dopaminergic neurons attenuates function of the DRD2-DRD3-GIRK-dependent autoinhibitory feedback loop that ensures termination of dopamine synaptic transmission. While this led to a hypersensitivity to locomotor and reward stimulating effects of cocaine in  $Fto^{\Delta DAT}$  mice, Fto-deficient mice were insensitive to cocaine. Therefore, in addition to control of presynaptic dopamine signaling, FTO is likely to affect postsynaptic signaling events in target neurons of the dopaminergic system as well.

## 4.2.3 Relation of whole body and dopamine restricted FTO deficiency to D2 receptor studies

Although DRD2 was not downregulated on the protein level in *Fto*-deficient mice (Section 3.1.2), FTO deficiency resembles several aspects of DRD2 deficiency. In addition to the previously described similarities, both *Fto*- and *Drd2*-deficient mice exhibit comparable loss of cocaine-induced locomotor activity and *Fos* induction [Welter *et al.*, 2007]. Likewise,  $Fto^{\Delta DAT}$  mice resemble characteristics of DRD2

autoreceptor-deficient mice [Bello *et al.*, 2011]. Hence, the phenotypic differences between *Fto*-deficient and  $Fto^{\Delta DAT}$  mice mirrors the differences between DRD2 whole body knock out and DRD2 autoreceptor-deficient mice [Bello *et al.*, 2011; Welter *et al.*, 2007; Chausmer *et al.*, 2002; Kelly *et al.*, 1998].

Despite the paucity of DRD2 protein downregulation in *Fto*-deficient mice, the striking similarities to loss of DRD2s suggests to view loss of FTO in the context of D2 receptor studies. Postsynaptic DRD2 receptor availability influences drug abuse, with increased levels of DRD2 corresponding with lower self administration in monkeys and rodents and decreased levels of DRD2 observed in human drug abusers [Volkow et al., 2009; Morgan et al., 2002; Thanos et al., 2001]. Decreased postsynaptic DRD2 availability was suggested to cause repetitive drug abuse to compensate for the decreased postsynaptic dopamine signaling [Volkow *et al.*, 1999]. Similarly, obese subjects exhibit decreased DRD2 levels in the striatum and are believed to compensate for the decreased receptor availability and decreased downstream activation of striatal DRD2 signaling via compulsive increase in intake of highly palatable food that stimulates dopamine release [Volkow et al., 2013; Stice et al., 2008; Wang et al., 2001]. Consistently, rapid development of compulsive overeating in rats has been observed after virus-mediated knock down of striatal DRD2 [Johnson & Kenny, 2010]. A different theory suggests downregulation of postsynaptic DRD2s as a compensatory response to increased dopaminergic transmission [Bello et al., 2011; Stice et al., 2008]. In line with this notion, reduced levels of DRD2/DRD3 in human midbrain are associated with higher impulsivity and increased stimulant craving due to increased substance-mediated DA release [Buckholtz et al., 2010]. Moreover, DRD2 autoreceptor-deficient mice exhibit increased responses to the rewarding properties of cocaine [Bello et al., 2011]. Although, cause and consequence of the changes in D<sub>2</sub> receptor expression are still a matter of debate, both obesity and addiction share deregulations of DRD2 availability [Volkow *et al.*, 2013]. Therefore, FTO, via regulating presynaptic dopamine autoreceptor feedback and/or postsynaptic dopamine signaling, may impinge on obesity or addictive behavior. Consistently,  $Fto^{\Delta DAT}$  mice exhibited cocaine supersensitivity in the conditioned place preference paradigm. Dopamine neuron restricted loss of FTO, however, had no influence on body weight or food intake, which is consistent with the paucity of body weight differences for DRD2 autoreceptor-deficient mice. Hence, in detail investigation of postsynaptic loss of FTO is warranted, that ultimately may affect food intake via attenuation of dopamine signaling in striatal dopamine target neurons, thereby resembling downregulation of DRD2 in human drug abusers and obese subjects [Volkow *et al.*, 2009; Wang *et al.*, 2001].

## 4.3 FTO demethylates m<sup>6</sup>A in messenger RNA

To date, the exact molecular function of FTO is not known. Growing evidence suggests that FTO demethylates *N6*-methyladenosine in messenger RNA [Meyer *et al.*, 2012; Dominissini *et al.*, 2012; Jia *et al.*, 2011]. First evidence demonstrated a role for m<sup>6</sup>A in mRNA stability [Wang *et al.*, 2013]. Whether this modification serves additional functions in mRNA processing, splicing, translation and/or other cellular functions remains elusive. Moreover, additional enzymatic functions of FTO, other than m<sup>6</sup>A demethylation, cannot be excluded at this point.

## 4.3.1 FTO acts as a m<sup>6</sup>A demethylase in vivo

To investigate whether FTO demethylates m<sup>6</sup>A in mRNA *in vivo* and thereby potentially impacts dopaminergic signaling, the m<sup>6</sup>A methylation pattern was assessed for *Fto*-deficient and control mice. In line with previous studies, a total of 42.000 m<sup>6</sup>A peaks were identified in mRNA isolated from midbrain and striatal tissue [Meyer *et al.*, 2012; Dominissini *et al.*, 2012]. This widespread occurrence of m<sup>6</sup>A in brain tissue is in line with previously reported results [Meyer *et al.*, 2012]. In comparison to control tissue over 5000 additional m<sup>6</sup>A peaks in over 1500 transcripts were identified in *Fto*-deficient mice, demonstrating that FTO demethylates m<sup>6</sup>A in mRNA *in vivo*. Moreover, loss of FTO only affected a subset of m<sup>6</sup>A sites and consequently only a subset of all methylated transcripts. For this reason, it seems that FTO is acting only on specific transcripts and potentially affects specific pathways or cellular functions. Indeed, gene ontology analysis of those transcripts hypermethylated in *Fto*-deficient mice (FTO demethylation targets) revealed an enrichment of categories related to synaptic transmission and cell-cell signaling, while methylated transcripts in control mice did not cluster within these categories. This supports the notion that FTO plays a critical role in the central nervous system and is in line with the severe brain malformations observed for loss of FTO in humans [Gao et al., 2010; Boissel et al., 2009; Gerken et al., 2007]. FTO demethylase activity was directed against a specific subset of transcripts, however, this analysis only included specific parts of the brain. Hence, different transcripts may be affected in other brain areas. Moreover, other demethylases may act in parallel on yet different subsets of mRNA in a tissue specific manner. Supporting this concept is the recent identification of AlkBH<sub>5</sub>, a second m<sup>6</sup>A demethylase, that is highly expressed in peripheral tissues rather than the central nervous system [Zheng et al., 2012]. Hence, FTO, AlkBH5 and yet unidentified demethylases may alter methylation status and as a consequence mRNA function in a tissue specific manner.

Albeit the yet unknown function of the m<sup>6</sup>A mark, hypermethylated transcripts in *Fto*-deficient midbrain and striatal tissue were further investigated for a potential involvement in the dopamine signaling related phenotype observed in *Fto*-deficient and  $Fto^{\Delta DAT}$  mice. Overlay of hypermethylated transcripts with dopaminergic signaling using pathway analysis revealed several transcripts encoding proteins important for neuronal signaling in general, such as GNAO1 and NMDAR1(zeta-1), and dopaminergic signaling specifically, such as DRD3, GIRK2, GNAO1, PDE1b, CACNA1A -1C -1D and SYN1 (Section 3.3.2).

## 4.3.2 Selected candidate transcripts are affected on protein level

Following the identification of hypermethylated transcripts that putatively impact dopaminergic signaling, several candidates were selected for further investigation. All investigated candidates showed no differences or minor increases on the transcript level. Several candidates, however, were downregulated on the protein level (DRD3, GIRK2, NMDAR1), suggesting a role for the m<sup>6</sup>A mark in regulating translation. These observations are in line with a reduced global translation reported for *Fto*-deficient cells and the loss of lean mass in adult onset *Fto*-deficient mice [Gulati *et al.*, 2013; McMurray *et al.*, 2013]. Furthermore, downregulated protein levels are in agreement with the recent finding that m<sup>6</sup>A affects mRNA stability via binding of YTHDF2 to methylated transcripts and subsequent recruitment to RNA decay sites [Wang *et al.*, 2013]. Thereby, the pool of available mRNA templates is limited and would subsequently lead to a reduction in translation and protein levels. Hypermethylation as caused by loss of FTO would thus lead to decreased mRNA stability and lifetime and as a consequence reduced protein levels as observed for DRD3, GIRK2 and NMDAR1 in *Fto*-deficient mice.

Since not all investigated hypermethylated transcripts exhibited downregulation on protein level, the m<sup>6</sup>A modification does not necessarily influence translation, suggesting complex mechanisms underlying the role of m<sup>6</sup>A in mRNA. Binding of YTHDF2 was reported to only occur for a subset of m<sup>6</sup>A methylated transcripts and therefore the YTHDF2-dependent regulation of mRNA stability does not affect all m<sup>6</sup>A modified mRNAs [Wang *et al.*, 2013]. Both GNAI1 and IKK2 transcripts were hypermethylated in *Fto*-deficient mice, but showed normal protein expression. Hence, these candidates may represent transcripts that, although they exhibit m<sup>6</sup>A hypermethylation, are not bound by YTHDF2 and are not removed from the mRNA translation pool. Moreover, it cannot be ruled out that the observed downregulations merely present indirect effects through downregulation of proteins involved in RNA processing, metabolism or translation. Furthermore, m<sup>6</sup>A may influence splicing patterns, thus affecting expression and protein levels of certain isoforms.

Since only midbrain and striatal tissue were analyzed in these experiments, it remains to be determined whether the hypermethylated transcripts identified in this study reflect a general population that is demethylated by FTO or whether different subsets of transcripts are affected in different brain areas. Furthermore, detailed investigation of the role of m<sup>6</sup>A in regulating mRNA stability and translation is warranted in order to define the exact context of FTO action.

With respect to dopaminergic signaling, the downregulation of DRD<sub>3</sub>, GIRK<sub>2</sub> and NMDAR<sub>1</sub> protein levels may, at least partly, explain the mechanism underlying the attenuation of the DRD<sub>2</sub>-DRD<sub>3</sub>-GIRK dependent autoinhibitory feedback loop in *Fto*-deficient and *Fto*<sup> $\Delta$ DAT</sup> mice.

## The dopamine D3 receptor

The DRD<sub>3</sub>, like the DRD<sub>2</sub>, is found presynaptically on dopamine neurons [Diaz *et al.*, 2000]. While the D<sub>2</sub> receptor is known to reduce firing rate of dopaminergic neurons through coupling to potassium channels of the GIRK family and subsequent membrane hyperpolarization [Bello *et al.*, 2011; Lacey *et al.*, 1987], evidence on D<sub>3</sub> receptors with regards to this function are so far contradictory. Both the coupling and the paucity of coupling to GIRKs has been reported for DRD<sub>3</sub> autoreceptors [Kuzhikandathil *et al.*, 1998; Davila *et al.*, 2003]. Nevertheless, both DRD<sub>3</sub> and DRD<sub>2</sub> may share the ability to reduce dopamine neuron firing as a mean of feedback inhibition.

Furthermore, the whole body deletion of DRD3 in mice led to increased locomotor activity, increased grooming and enhanced reactivity to drug-paired cues [Accili *et al.*, 1996; Xu *et al.*, 1997; Le Foll *et al.*, 2005; Narita *et al.*, 2003; Francès *et al.*, 2004]. All of these behaviors are related to dopamine levels and consistently, DRD3-deficient mice have higher levels of extracellular dopamine [Koeltzow *et al.*, 1998; Joseph *et al.*, 2002]. In contrast, DRD2-deficient mice have unaltered dopamine levels, suggesting that control of basal dopamine levels depends on DRD3 rather than DRD2 function [Dickinson *et al.*, 1999]. *Fto*-deficient mice are hypoactive, whereas  $Fto^{\Delta DAT}$  mice were relatively hyperactive [Fischer *et al.*, 2009]. As baseline locomotor activity would partialy depend on baseline dopamine levels, detailed investigation of absolute dopamine values may aid in further outlining the exact outcome of conditional and whole body loss of FTO [Giros *et al.*, 1996; Zhou & Palmiter, 1995]. Taken together, decreased availability of DRD3 autoreceptors due to FTO deficiency may directly affect the feedback loop, leading to the attenuation of dopamine neuron autoinhibition in *Fto*-deficient and *Fto*<sup> $\Delta$ DAT</sup> mice.

In humans variation within the *DRD*<sup>3</sup> gene affecting dopamine binding affinity has been linked to impulsivity and substance abuse [Agrawal *et al.*, 2013; Huang *et al.*, 2008; Limosin *et al.*, 2005; Retz *et al.*, 2003; Krebs *et al.*, 1998; Duaux *et al.*, 1998]. Moreover, *DRD*<sup>3</sup> variation was linked to some aspects of ADHD related to violent behavior [Retz *et al.*, 2003]. Therefore, FTO may likewise impinge on behaviors such as impulsivity through affecting *DRD*<sup>3</sup> transcript methylation. In line with this notion, first associations of genomic variation in *FTO* with ADHD have been reported [Choudhry *et al.*, 2013; Velders *et al.*, 2012]. Thus, investigation of *Fto*-deficient mice led to the identification of a putative candidate transcript, *Drd*<sup>3</sup>, linking human *FTO* genotypes to psychiatric diseases such as ADHD. Consequently, investigation of human *FTO* and *DRD*<sup>3</sup> genotypes may hold the potential to identify synergistic or antagonistic actions with respect to psychiatric and obesity related traits.

## G protein-coupled inwardly rectifying potassium channel 2

G protein-coupled inwardly rectifying potassium channels (GIRK) are mediating slow inhibitory currents, both pre- and postsynaptically [Lüscher & Slesinger, 2010]. Furthermore, they shape the resting membrane potential and thus influence the excitability of neurons [Mark & Herlitze, 2000]. The four known GIRK subunits (GIRK1-4) form homo- or heterotetrameric channels [Lüscher & Slesinger, 2010]. Within the brain, the dominant form of this channel is compromised by GIRK1 and GIRK2. Knock out studies in mice have demonstrated that GIRK2 (*Kcnj6*) is the primary channel subunit mediating inhibitory currents [Lüscher & Slesinger, 2010]. Hence, one of the consequences of the downregulation of GIRK2 in *Fto*deficient mice is the reduction of dopamine autoreceptor-mediated inhibitory currents. Furthermore, *Girk2*-deficient mice exhibited reduced anxiety, increased activity, reduced cocaine self-administration and reduced conditioned taste aversion [Arora *et al.*, 2010; Pravetoni & Wickman, 2008; Hill *et al.*, 2003; Morgan *et al.*, 2003].

While a reduction in cocaine self-administration is reminiscent of the cocaine insensitivity in *Fto*-deficient mice, increased activity of *Girk2*-deficient mice is opposing the hypoactivity of whole body FTO knock out mice [Fischer et al., 2009]. Therefore, Fto-deficient mice do not resemble all aspects of GIRK2 deficiency, but are rather subject to a number of alterations (including DRD<sub>3</sub>, NMDAR<sub>1</sub> and GIRK<sub>2</sub>) shaping their phenotype. GIRKs are not only coupling to autoreceptors, but also to other non-dopaminergic receptors in dopamine neurons, thereby representing one of the major factors controlling dopamine neuron function [Lüscher & Slesinger, 2010]. Widely expressed, both pre- and postsynaptic, GIRKs are important mediators of long term depression (LTD) and long term potentiation (LTP), synaptic mechanisms underlying various forms of learning behaviors [Lüscher & Slesinger, 2010]. Hence, the reduced GIRK availability in midbrain dopaminergic neurons of *Fto*-deficient and  $Fto^{\Delta DAT}$  mice would not only affect autoreceptor inhibition of dopamine neurons, but also impact the responsiveness of dopaminergic neurons to various other synaptic inputs (e.g. GABAergic). Additionally, postsynaptic loss of GIRKs in target neurons of the dopamine circuitry in *Fto*-deficient mice would attenuate LTD and/or LTP and thus prevent the encoding of motivational value by dopaminergic signaling [Volkow et al., 2013; Kauer & Malenka, 2007; Hyman et al., 2006].

In humans, GIRK channels are implicated in diseases such as epilepsy, Down's syndrome, Parkinson's disease and addiction, demonstrating their importance for neuronal function [Lüscher & Slesinger, 2010].

Taken together, FTO dependent regulation of GIRK2 availability would not only affect dopamine neuron function via coupling of GIRKs to both DRD2 and DRD3 autoreceptors, but may also represent a possible reason for the strong contrast between whole body and dopamine neuron restricted FTO deficiency, via postsynaptic alterations of GIRK expression.

#### N-methyl-D-aspartate receptor subunit 1

The NMDAR1 (Grin1) subunit is a critical component of N-methyl-D-aspartate receptors, which belong to the family of voltage-gated ionotropic receptors [Paoletti et al., 2013; Kauer & Malenka, 2007]. NMDARs are activated by membrane depolarization in conjunction with co-binding of the excitatory neurotransmitters glutamate and either glycine or D-serine [Paoletti et al., 2013]. Within the brain, NMDARs are important mediators of LTD and LTP. Opening of NMDARs leads to an influx of sodium and importantly calcium, which triggers intracellular signaling molecules, such as the CamKII protein kinase (in LTP) or phosphatases (in LTD) [Paoletti et al., 2013; Kauer & Malenka, 2007]. Both LTP and LTD depend on changes in  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AM-PAR) availability, which is regulated by NMDAR signaling [Kauer & Malenka, 2007]. Deletion of the critical NMDAR1 subunit caused a complete loss of NMDA receptor function [Forrest et al., 1994; Tsien et al., 1996]. Hence, reduced availability of NMDAR1 in *Fto*-deficient mice would lead to an attenuation of the synaptic alterations in LTP and LTD underlying dopaminergic signaling, thereby impairing fundamental mechanisms of synaptic plasticity [Kauer & Malenka, 2007; Hyman et al., 2006]. Once again, loss of these mechanisms may represent one possible cause for the insensitivity of *Fto*-deficient mice to cocaine-induced increases in synaptic dopamine levels. Since NMDARs are also expressed on dopaminergic neurons [Wang et al., 2010; Paquet et al., 1997], dopamine neuron restricted FTO knock out mice may also exhibit a deregulation of NMDAR1 signaling in DA neurons, implicated in synaptic plasticity and addiction [Zweifel *et al.*, 2008].

In humans, malfunctional NMDAR dependent synaptic plasticity has been linked to various psychiatric diseases, including schizophrenia, mood disorders, Huntington's and Alzheimer's disease [Lakhan *et al.*, 2013]. Therefore, malfunctional FTO-dependent regulation of NMDA receptor availability may play a role in these neuropsychiatric diseases and could possibly represent a link to the observed associations of human *FTO* variants with major depressive disorder or ADHD [Samaan *et al.*, 2012; Rivera *et al.*, 2012; Velders *et al.*, 2012; Choudhry *et al.*, 2013]. Furthermore, the importance of NMDA receptors for synaptic plasticity, poses the question, whether human *FTO* variation affects learning and memory. Limited evidence suggests that *FTO* risk alleles worsen memory performance and negatively impact cognitive decline [Alosco *et al.*, 2013; Bressler *et al.*, 2013].

Taken together, via its proposed function as a m<sup>6</sup>A demethylase, FTO may regulate *Grin1* transcript methylation, reducing NMDAR1 availability and thus would downregulate a major component of the mechanistic machinery needed for synaptic plasticity in learning, memory and addiction [Zweifel *et al.*, 2008; Kauer & Malenka, 2007].

Most probably, additional hypermethylated transcripts not covered by the current study are affected on protein level in *Fto*-deficient mice. Therefore, it is likely that, in addition to DRD<sub>3</sub>, GIRK<sub>2</sub> and NMDAR<sub>1</sub>, other components involved in the function of dopaminergic signaling participate in the attenuation of the DRD2-DRD3-GIRK-dependent autoreceptor function observed for *Fto*-deficient and  $Fto^{\Delta DAT}$  mice. Moreover, it cannot be ruled out at this point that loss of FTO affects processes involved in the development of the central nervous system in general and formation of synapses in particular. Adult onset loss of FTO in mice overcomes many of the aspects of the germline Fto knock out phenotype, including postnatal growth retardation [McMurray et al., 2013; Fischer et al., 2009]. The first three postnatal weeks of life in mice (third trimester of pregnancy in humans) are known as the critical time frame for central nervous system development, during which circuits are wired and/or rewired [Bouret, 2010]. Hence, developmental defects observed for growth may also affect the development of the neuronal circuitry and hypermethylation of transcripts leading to deregulation on the protein level may underly these developmental alterations.

So far, all of the above described observations on FTO-dependent m<sup>6</sup>A hypermethylation and subsequent alterations of protein levels have been conducted in *Fto*-deficient mice. Further experiments will need to address whether comparable results are observed for dopamine neuron restricted loss of FTO and hence dissect pre- and postsynaptic effects of FTO demethylase activity.

## 4.4 Relation to studies of human FTO genomic variation

Genomic variation of FTO in humans is associated with obesity related traits. To date the mechanisms causing this relation remain elusive. Although the exact function of the N6-methyladenosine modification in mRNA is largely unknown, a putative regulation of expression through demethylation by FTO may represent a mechanism by which physiological networks such as the homeostatic and hedonic circuitry are controlled. FTO expression has been demonstrated to depend on amino acid availability [Cheung et al., 2013]. Hence, environmental changes e.g. leading to starvation could affect FTO expression and subsequently change the methylation pattern in a given tissue or neuronal circuitry affecting a whole set of genes simultaneously. These changes in methylation and subsequent expression changes may alter network properties, setting a new baseline for the responsiveness of for example the hedonic circuitry, potentially rendering an organism more susceptible to e.g. rewarding stimuli. *Fto*-deficient as well as dopamine neuron restricted FTO knock out mice exhibited alterations of the dopaminergic circuitry. FTO expression decreases with a reduction of amino acid availability [Cheung et al., 2013; Gulati et al., 2013]. Hence, starvation may reflect a knock down of FTO that would potentially lead to an attenuation of the dopamine autoinhibitory feedback loop, subsequently hypersensitizing dopaminergic pathways and setting a new baseline that could increase the responsiveness to rewarding stimuli. Further supporting this hypothesis are studies of human FTO 'risk-allele' carriers demonstrating altered responsiveness of different brain areas, including nuclei of the reward circuitry, to food representations [Karra et al., 2013]. Hence, FTO may be an important relay enzyme, conveying environmental changes to hedonic and energy homeostasis centers in the brain, finally leading to an adaptation of behavior.

The human FTO phenotype is predominately related to energy intake, with FTO 'risk-allele' carriers showing elevated consumption of highly palatable food [Haupt et al., 2009; Speakman et al., 2008; Cecil et al., 2008; Timpson et al., 2008]. Moreover, 'risk-allele' carriers display deviant food responsiveness and satiety [Wardle et al., 2009, 2008; Velders et al., 2012]. Despite the robust associations with obesity related traits, FTO variants were furthermore associated with addictive behavior, ADHD and depression [Sobczyk-Kopciol et al., 2011; Velders et al., 2012; Choudhry et al., 2013; Rivera et al., 2012; Samaan et al., 2012]. These, however, are inverse associations rendering the obesity 'risk-allele' protective against depression, certain addictive behavior and ADHD. Earlier studies established that ADHD and depression are associated with increased body weight [Luppino et al., 2010; Cortese & Vincenzi, 2012]. Therefore, the inverse associations of FTO variants with these conditions are surprising. Malfunction of the dopaminergic circuitry has been previously linked to psychiatric disorders such as addictive behavior, ADHD and depression [Swanson et al., 2007; Beaulieu & Gainetdinov, 2011; Koob & Volkow, 2010]. Intake of highly palatable food and the concomitant pleasure felt by its consumption affect the dopaminergic circuitry as well. Hence, Velders and colleagues proposed a mechanism through which overeating and enjoyment of food represent self-medication that ameliorates the symptoms of ADHD, addiction and depression [Velders et al., 2012]. As a result, carriers of the obesity risk allele for FTO would benefit from protective aspects of the increased intake of highly palatable food via rewarding stimulation of the dopaminergic circuitry and attenuation of psychiatric symptoms such as depression.

## 4.5 Conclusions

In summary, loss of FTO leads to the attenuation of the DRD2-DRD3-GIRK-dependent autoreceptor feedback loop in both *Fto*-deficient and *Fto*<sup> $\Delta$ DAT</sup> mice. While this leads to a cocaine hypersensitivity in *Fto*<sup> $\Delta$ DAT</sup> mice, *Fto*-deficient mice are insensitive to the stimulatory effects of cocaine. On the molecular level, FTO was

demonstrated to act as a m<sup>6</sup>A demethylase in midbrain and striatal tissue, acting only on a subset of all m<sup>6</sup>A methylated transcripts and thus suggesting that FTO acts on specific pathways implicated in neuronal signaling. As a consequence of loss of FTO and m<sup>6</sup>A hypermethylation, protein levels of DRD<sub>3</sub>, GIRK<sub>2</sub> and NMDAR<sub>1</sub> were found to be downregulated and would, at least partly, explain malfunction of the autoreceptor feedback loop in dopaminergic neurons. Moreover, this finding is in perfect agreement with the recent demonstration that m<sup>6</sup>A mRNA methylation leads to shuttling of transcripts to mRNA degradation sites in a YTHDF2-dependent manner and hence limiting the template pool of mRNA transcripts [Wang *et al.*, 2013].

Despite the yet unknown consequence of human *FTO* genomic variation on FTO function and/or expression, the malfunction of the dopaminergic circuitry in *Fto*-deficient and  $Fto^{\Delta DAT}$  mice warrants the detailed investigation of dopaminergic function in human *Fto* SNP carriers. Aberrant function of the dopaminergic circuitry may underly the associations of human *FTO* variation with addictive behavior, ADHD and depression [Sobczyk-Kopciol *et al.*, 2011; Velders *et al.*, 2012; Choudhry *et al.*, 2013; Rivera *et al.*, 2012; Samaan *et al.*, 2012]. Moreover, malfunction of dopaminergic signaling could represent a major component causing changes in food responsiveness and preference, thereby influencing eating behavior and, at least partly, causing the increase in energy intake described for human *FTO* risk allele carriers [Karra *et al.*, 2013; Velders *et al.*, 2012; Wardle *et al.*, 2009; Haupt *et al.*, 2009; Cecil *et al.*, 2008; Timpson *et al.*, 2008; Speakman *et al.*, 2008].

Importantly, this study defined molecular targets (DRD<sub>3</sub>, GIRK<sub>2</sub> and NMDAR<sub>1</sub>) and a pathway (dopamine signaling and dopamine autoreceptor function) for FTO demethylase activity in mice, indicating potential targets for human *FTO* studies. This warrants the broadening of the scientific scope for FTO investigation beyond obesity and towards reward processing, reward based decision making and psychiatric diseases such as depression, ADHD and addiction.

## 4.6 Perspectives

The investigation of both whole body *Fto*-deficient and dopamine neuron restricted knock out mice revealed a FTO-dependent alteration of the DRD2-DRD3-GIRKdependent autoinhibitory feedback loop of midbrain dopaminergic neurons. Comparison of both mouse models suggests that in addition to the changes in dopamine neuron function, loss of FTO may attenuate postsynaptic signaling events as well. Hence, conditional deletion of FTO in both pre- and postsynaptic sites of dopaminergic signaling through usage of Cre lines expressing the recombinase under the control of the Drd1, Drd2 or Adora2a (targeting DRD2 expressing neurons in striatum and not dopaminergic neurons, [Durieux et al., 2009]) promoters may aid in further delineating the effect of FTO on the dopaminergic circuitry. Furthermore, a double knock out of FTO in both DRD1 and DRD2 expressing neurons, leading to a loss of FTO in almost every pre- and postsynaptic dopamine signaling site, would be best suited to investigate FTO's function in the reward circuitry and may restore features of *Fto*-deficient mice with respect to dopamine network function. Since human FTO phenotypes are associated with increased energy intake, additional studies could address FTO function in other feeding related nuclei, such as the PVN and LH. Especially the LH, as it represents an integrative center for homeostatic and hedonic pathways, may prove a viable target for specific FTO manipulations [Berthoud, 2011; Simerly, 2006; Saper et al., 2002]. In addition, these investigations should be used to assess the putative tissue specificity of FTO by comparison of methylation patterns identified in different brain areas.

To date, human studies addressing *FTO* phenotypes have focused primarily on its associations with obesity related traits. However, it becomes more and more evident that FTO may play a role in more than just homeostatic, feeding related nuclei. Therefore, the notion that the loss of FTO in mice alters dopamine neuron function cell autonomously as well as on the network level should aid in generating hypotheses for the study of human *FTO* phenotypes. Based on this notion, investigation of human *FTO* 'risk-allele' carriers should be expanded to reward processing and reward based decision making, developing the appropriate behavioral tests and functional MRI paradigms. Moreover, identification of pathways altered by the loss of FTO in rodents may aid in selecting additional risk factors for polygenic obesity for a combined investigation with *FTO* variants. Thus, the combined effects, being synergistic or opposing, could be investigated to better understand the complex interplay of risk factors for polygenic obesity shaping each individual's susceptibility to gain weight.

## 5 Bibliography

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Figure 6.1: **Reduction in cocaine-induced c-Fos immunoreactivity in** *Fto*-deficient mice Immunohistochemistry of cortical areas (**a**, cingulate and sec. motor cortex) and the CPu (**b**) revealed blunted cocaine induced c-Fos expression in *Fto*-deficient mice (20 mg kg<sup>-1</sup> cocaine). No increase in c-Fos immunoreactivity is observed in *Fto*-deficient mice following cocaine injection, whereas the number of c-Fos positive cells markedly increased in control mice when challenged with cocaine. Scale bar = 200  $\mu$ m.

Table 6.1: Electrophysiolog	gical properties of Fto-d	eficient dopamine neurons
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	Whole-cell capacitance [pF]	Firing rate [Hz]	Conductance density [S F <sup>-1</sup> ]
Fto <sup>+/+</sup>	49.5±1.0	2.1±0.1	55.3±2.6
	(n=37)	(n=41)	(n=34)
Fto <sup>+/+</sup>	49.7±1.4	1.8±0.2	48.1±2.4*
	(n=34)	(n=31)	(n=31)

Asterisk indicates significant difference (\*P<0.05)



#### Figure 6.2: Confirmation of *Fto* expression by $\beta$ -galactosidase staining

 $\beta$ -galactosidase staining of animals with a knock-in of the ?-galactosidase cDNA into the endogenous *Fto* locus (EUCOMM, *Fto*<sup>tm1a(EUCOMM)Wtsi</sup>) confirmed *Fto* expression in murine midbrain. In addition, expression was detected in numerous other brain regions including the paraventricular nucleus (PVN), arcuate nucleus (ARC), ventromedial hypothalamus (VMH) and dorsomedial hypothalamus (DMH).

Campin         4.6004101         0.0005041         0.0005041           Bitshis         -2.540406         0.00050712         0.132506           Bitshis         -2.540406         0.00050712         0.132506           Company         -0.0005070         0.0125070         0.0005070           Status         -0.0005070         0.0005070         0.0005070           Expond_c6840         -0.0005070         0.0005070         0.0005070           Data         -0.0005070         0.0005070         0.0005070           Opalm         -0.0005070         0.0005070         0.0007050           Data	Assignment	fc	pv	qv
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Pin	D3Ertd751e	-2.02987844	0.006774102	0.105745966
	Fto	-2.020632093	0.000627479	0.105745966
	Hbb-b1	-1.988793289	0.007844134	0.107008823
Camada	Mgp	-1.970365583	0.046597259	0.119725282
op/basis         - 0.9999999         0.017/1288         0.0797288           Th         - 8.50/15698         0.01099196         0.15/979124           Th         - 8.50/15698         0.0059791         0.15/979124           Dar         - 8.50/15691         0.0059791         0.15/9574           Dar         - 8.50/15691         0.00779199         0.15/95661           Spla         - 8.50/15691         0.000779         0.15/95661           Spla         - 8.50/15691         0.000779         0.15/95661           Spla         - 8.50/15691         0.000779         0.15/95661           Lipha         - 9.50/95612         0.15/95661         0.15/95661           DyNasys         - 8.51/9561         0.0207/1593         0.111/12241         0.015/123           Casy         - 8.51/9561         0.0205612         0.111/12241         0.015/123           Casy         - 8.51/9561         0.015/1241         0.015/1241         0.015/1241         0.017/1241           Casy         - 8.51/9561         0.015/1241         0.015/1241         0.017/1241         0.015/1241           Casy         - 7.56/9571         0.015/1241         0.017/1241         0.015/1241         0.017/1241         0.015/1241         0.015/1241	Gm12643	-1.970128867	0.016207701	0.107723281
approx.         bit         bit         bit         bit         bit           Fib         -15688895         concepting         concepting         concepting           Fib         -15698495         concepting         concepting         concepting           Dan         -15698495         concepting         concepting         concepting           Dan         -15698495         concepting         concepting         concepting           Spit         -15698495         concepting         concepting         concepting           Spit         -15698495         concepting         concepting         concepting           Spit         -15698495         concepting         concepting         concepting           Apart         -15698495 <td< td=""><td>Lphp2</td><td>-1 010282040</td><td>0.011715228</td><td>0 107722281</td></td<>	Lphp2	-1 010282040	0.011715228	0 107722281
	Erzh	1.919303949	0.011/19220	0.107723201
1n       -1.797/411       0.0093930       0.10760372         Den       -1.869.660,45       0.000779499       0.1095037         Den       -1.869.660,45       0.000708595       0.10950477         Skit       -1.869.650,497       0.000708595       0.10950477         Hdn       -1.859.050,297       0.10650377       0.10650377         Jap2320B/Rk       -1.843.7999       0.0009578       0.10952432         Qavasse       -1.843.898.05       0.02445934       0.10952492         DaVasse       -1.843.898.05       0.02445934       0.10974956         Aça       -1.859.0561       0.02445934       0.10974956         Aça       -1.859.0561       0.02445934       0.10974936         Aça       -1.859.0561       0.02445934       0.10974936         Aça       -1.859.0561       0.02970580       0.11473284         Acypri       -1.859.0561       0.02970580       0.11473284         Acypri       -1.859.0561       0.02970580       0.11473284         Acypri       -1.859.0561       0.02970580       0.119719284         Acypri       -1.859.0571       0.0239.0597       0.11693.177         Acypri       -1.959.0571       0.0239.0597       0.11971938 <td>T12D</td> <td>-1.090100970</td> <td>0.010925045</td> <td>0.10//23201</td>	T12D	-1.090100970	0.010925045	0.10//23201
Uppa         4.7394475         0.00%79395         0.1079496           Dan         -1.8504695         0.00779499         0.1079496           Skit         -1.85046950         0.0027955         0.10974996           Skit         -1.85046907         0.0027955         0.10974996           Skit         -1.85956029         0.00297978         0.10974996           Cass         -1.85956029         0.0029798         0.10974996           Cass         -1.840198616         0.00297978         0.10974996           Cass         -1.84019303         0.002197956         0.111712284           Cang         -1.83939818         0.0021904753         0.111712284           Cang         -1.8509073         0.012974956         0.111712284           Cang/637         -1.8509073         0.012904573         0.11861190           Idraf         -1.8601703         0.023904573         0.11861190           Idraf         -1.8601703         0.023904573         0.11861190           Idraf         -1.8601703         0.023904573         0.11861190           Idraf         -1.7696174         0.023904573         0.11861190           Idraf         -1.7696174         0.023904573         0.11872284	In	-1.879714211	0.040934926	0.116939704
Drn         -1.860x6085         0.00073490         0.01090001           Hdx         -1.860x6097         0.001708986         0.01906001           Hdx         -1.8570x9414         0.001708986         0.01967966           40232080/Rk         -1.8570x9414         0.001708987         0.01995214           40232080/Rk         -1.8471909         0.00197878         0.01995214           Cars         -1.8472378         0.001978953         0.011972344           D4Wax5p         -1.8432378         0.0029578         0.01995214           Cars         -1.859378         0.00295613         0.01197234           Cars         -1.859378         0.00295613         0.01197234           Cars         -1.859378         0.00295061         0.01197244           Cardof         -1.859514         0.0129744         0.01097244           Cardof         -1.9596734         0.0219987         0.01384983           Cardof         -1.9596734         0.0219987         0.01384983           Cardof         -1.9596794         0.0139947         0.01384974           Cardof         -1.9596794         0.0139947         0.01384974           Cardof         -1.9596794         0.01394787         0.01384974	Upp2	-1.873942475	0.008795025	0.107600372
Spkin         1.86000000000000000000000000000000000000	Dcn	-1.863080485	0.000779499	0.105745966
Hdx     -185090414     coorpsb/98     0.0079696       (dp2apabb/Rik     -2847099     coorps778     0.10794966       (dp3apabb/Rik     -2847099     coorps7783     0.10794966       (dp3apabb/Rik     -2847099     coorps7783     0.117127461       (Dm3y     -28460325     coorps77833     0.117127461       (Dm3y     -284960325     coorps77833     0.117127461       (Dm3y     -284960325     coorps77833     0.10101030       Hmgb1     -2859513     coorps77833     0.10101300       Cardo     -2859513     coorps7683     0.10752361       Cardo     -2859513     coorps7683     0.11795697       Tdrdd     -88651936     coorps6883     coorps7684     0.10795087       Cardo     -2794977     coorps6883     coorps768     coorps7686       Cardo     -79695124     coorps6981     coorps768     coorps768       Cardo     -79695124     coorps6981     coorps7686     coorps7686       Cardo     -79695124     coorps76864     coorps7686     coorps7686       Cardo     -79695777     coords76931     coorps76961     coorps76961       Cardo     -79695791     coorps76961     coorps72986       Cardo     -79695791     coorps79961     coorps7	Sgk1	-1.861067007	0.021007515	0.109360201
Tcfyla	Hdx	-1.857029414	0.001708938	0.105745966
1.1.2.5.1.0         0.1.0000000000000000000000000000000000	Tcf7l2	-1.856506029	0.040466175	0.116683307
42-25/2001/02         - 1.00/1999         0.00939/70         0.00948904           Casis         - 1.8(319/32)         0.00912/10/23         0.10942142           D4/Warsje         - 1.8(319/32)         0.00912/10/23         0.10923142           Aga         - 1.8(319/32)         0.00912/10/23         0.1117/23.04           Aga         - 1.8/279318         0.02449234         0.1117/23.04           BC049675         - 0.16/65/02         0.1117/23.04         0.00976082           BC049675         - 1.8/55/061         0.0397604         0.1117/95067           Aryp         - 1.8/64/57/06         0.03976082         0.1117/95067           Tdrdd         - 1.8/96/69         0.0397694         0.1117/95067           Cakinb         - 1.7/96/8743         0.0397694         0.1118/868           Z/p455         - 1.7/96/9712         0.03924975         0.1128/873           Cakinb         - 1.7/96/9712         0.03924975         0.1128/873           Cakinb         - 1.7/96/9712         0.03924975         0.1128/873           Cakinb         - 1.7/96/9712         0.03924975         0.1138/873           Cakinb         - 1.7/96/9712         0.03924975         0.1138/873           Cakinf        7/96/9712         0.0	1022502BoxRik	-1.8471000	0.00505778	0.105745066
Casisy         1-4001/3000         0.0005/34/2           QHW14529         1-43139235         0.00145331         0.1007/3506           Cm3         1-8319235         0.00445331         0.1007/3506           Aga         1-8329335         0.0096157         0.116331753           ECup607         1.16531753         0.0096057         0.116331753           ECup6075         1-8519096         0.0077064         0.119792361           Tdrdd         1-8607871         0.03304575         0.0185449           Acypt         1-8607906         0.0379264         0.119796907           Part         1-709613401         0.03304575         0.01864869           Cdarld         1-7969577         0.01520411         0.11795486           Carld         1-797890377         0.0250491         0.1179548           Consy         1-754895773         0.0250491         0.1179548           Consy         1-76785733         0.0246951         0.11179548           Consy         1-77489377         0.0250491         0.1179548           Consy         1-77489377         0.0256951         0.1179248           Consy         1-77489377         0.02586971         0.1179248           Consy         1-774893773	Case	-1.04/1999	0.00595770	0.103743900
Lq Maigè         1-Akja 3939         0.027/1893         0.1117j2284           Cmm         -1-Szyyjj15         0.024439241         0.1016/1200           Aga         -1-Szyyjj15         0.0396137         0.1117j8284           BC04j69js         -1-Sityj051         0.0396137         0.1117j82961           Acypi         -1-Sityj051         0.03970802         0.1117j8297           Acypi         -1-Sotyj051         0.03970802         0.1117j82907           Acypi         -1-Sotyj051         0.03970802         0.1117j82907           Acypi         -1-Sotyj051         0.0390475         0.118/8869           Acypi         -1-Sotyj051         0.11398907         0.118/8869           Cahnb         -7-94493462         0.007520488         0.109708833           Cardo         -179589777         0.0320411         0.1097318           Cardo         -179589777         0.0326911         0.1179849           Cardo         -179589773         0.02869591         0.1179849           Cardo         -179589773         0.02869591         0.1179849           Cardo         -179589773         0.02869591         0.11797343           Cardo         -179589773         0.02869591         0.117972345	Gass	-1.840150818	0.02120043	0.109523432
Curn3         -1.85g480125         0.004459214         0.105745966           Aga         -1.8599358         0.00945957         0.11651209           Hmgbr         -1.816993545         0.0396157         0.11651209           Tdrd6         -1.856916702         0.0276082         0.11172284           Acyp1         -1.866916702         0.0276082         0.11172284           Acyp1         -1.866916702         0.0276082         0.11172284           Acyp1         -1.866916702         0.02370875         0.11848689           Culn13         -1.79661301         0.03304575         0.112848754           Culn14         -7.79669714         0.02320957         0.112849754           Con37         -1.778503777         0.01250911         0.10773286           Con37         -1.77859377         0.01250911         0.10773286           Con37         -1.77859371         0.02865971         0.10894243           Con47         -1.76857173         0.0286591         0.1179188           Dmajcr13         -1.7989737         0.0286591         0.11791831           Chards         -1.798773         0.0245591         0.10773381           Chards         -1.79848732         0.0267933         0.10772381      C	D4wsu53e	-1.843239238	0.027718953	0.111732284
Aga         -18297318         0.02442921         0.100f02209           Hmgh         -18599355         0.0396157         0.11351753           BCoujogis         -185379061         0.037824554         0.107732381           Acypi         -186057956         0.043072694         0.11789907           Part         -18057831         0.03394974         0.11861499           Tdrdi         -179649742         0.007520488         0.109708833           Caknob         -794493462         0.007520481         0.109768367           Cardo         -179689377         0.0320475         0.11387933           Cardo         -1796497173         0.0230411         0.10972388           Cardo         -179689377         0.02369587         0.1184754           Cardo         -1796891773         0.02869591         0.1117848           Cardo         -179589773         0.02869591         0.11179848           Cardo         -179589773         0.02869591         0.11179848           Cardo         -179589773         0.02869591         0.11179244           Cardo         -179589773         0.0261051         0.11179244           Cardo         -179589783         0.04155591         0.110772381           Card	Cnn3	-1.834080125	0.004454321	0.105745966
Hingh         -1.81999354         0.0396177         0.11633173           BCupégis         -1.8539061         0.031842534         0.1177284           Tdrdd         -1.80519702         0.0370082         0.1177284           Arypi         -1.80519703         0.033940734         0.118641199           Tdrds         -1.79613401         0.03004753         0.11284864           Cdknrb         -1.79848774         0.03204975         0.11284754           Cdanda         -1.798487749         0.03230497         0.11284754           Cardad         -1.79848774         0.0320678         0.12974296           Cardad         -1.7984977         0.02306951         0.1128874           Cardad         -1.79848713         0.0285951         0.1128874           Cardad         -1.79848713         0.0285951         0.11972384           Omagory         -1.79848713         0.0245757         0.1099413           Charda         -1.79848713         0.0245757         0.1199245           Cardad         -1.79848713         0.0245574         0.1199245           Charda         -1.7948972         0.04455515         0.1199245           Charda         -1.7948972         0.04455515         0.11992455	Aga	-1.82793318	0.024429234	0.110161209
PCqp/sp3         -1.81590/f1         0.01384234         0.01792381           Acyp1         -1.80615703         0.03304257         0.11796557           Parl         -1.80627831         0.03304257         0.11284578           Cdhrab         -1.9469342         0.03304257         0.11284578           Cdhrab         -1.94493462         0.003304575         0.11284578           Cdhrab         -1.974939474         0.003312957         0.11284578           Cardó         -1.78675124         0.003312957         0.11385733           Cardó         -1.78675124         0.002369591         0.105743966           Cardy         -1.75658743         0.02865931         0.1178848           Coxiy         -1.756797173         0.02865931         0.11792381           Ufca         -1.7587873         0.02465951         0.11792384           Ufca         -1.79485215         0.0258516         0.117712381           Carbarpla         -1.79485215         0.0245515         0.11791293           Carbarpla         -1.79485732         0.04157351         0.10772381           Carbarpla         -1.79485732         0.0245673         0.10772381           Carbarpla         -1.79485732         0.0245535         0.117939455	Hmgb1	-1.819993545	0.03966157	0.116331753
Tacké       -1.806916702       0.02700802       0.11792384         Acypri       -1.806278931       0.0330497241       0.11861199         Tdrdg       -1.796613401       0.033049755       0.1284869         Zdp155       -1.789487749       0.03304975       0.112848754         Calknib       -1.798497749       0.03304977       0.11284754         Cardo       -1.789487749       0.03320957       0.11284754         Cardo       -1.7894777       0.01320911       0.07732381         Cardo       -1.7989377       0.023696931       0.109949243         Cox17       -1.795487313       0.02469756       0.11039143         Dajci 3       -1.795487173       0.02469371       0.10994143         Cox17       -1.79485125       0.02795816       0.11793244         Dajci 3       -1.79485125       0.0279581       0.11039143         Cox160000       -1.79485121       0.0267535       0.11039143         Cox17       -1.79485121       0.0269513       0.10773281         Cox16002786       -1.79489719       0.04147351       0.1773281         Cox16002786       -1.7928778       0.04147351       0.10773281         Chrma6       -1.792867729       0.041475351       0.10	BC049635	-1.81539061	0.013824254	0.107723281
Acypi       -1.8x6157036       0.03072694       0.11786997         Parl       -1.8x027891       0.03304971       0.1188469         Cdknib       -7.794493462       0.007303675       0.11248275         Cdknib       -7.794493749       0.031343676       0.10773381         Canda       -1.76595124       0.00250598       0.107732816         Canda       -1.76595737       0.01303977       0.11328733         Canda       -1.765877137       0.02869591       0.11792843         Canta       -1.758877137       0.02869591       0.11792843         Omajora       -1.758877137       0.02869591       0.11792843         Ufc       -1.758877137       0.02869591       0.1039413         Ufc       -1.758877137       0.0286951       0.11792843         Ufc       -1.75887733       0.02469576       0.1039413         LOC100027986       -1.74393813       0.02469576       0.11939415         LOC100027986       -1.743948732       0.04473351       0.10973381         Chrada       -1.73948732       0.04473351       0.10773381         Chrada       -1.73948732       0.04473351       0.10773381         Gmbg99       -1.74046049       0.01595995       0.10773381	Tdrd6	-1.806916702	0.027600802	0.111732284
Part         -1.8027831         0.033949741         0.118614199           Tdrdy         -1.796613401         0.033043755         0.118614199           Cdkntb         -1.79493462         0.007520488         0.107008823           Zfp455         -1.795497749         0.013330567         0.114482754           Cardó         -1.795497749         0.0236098         0.10773281           Cardó         -1.795497749         0.0236098         0.10773281           Cardó         -1.795497749         0.02360991         0.1117884           Omiosor         -1.7755773         0.02866931         0.11029413           Cardó         -1.795497173         0.028669371         0.10894243           Ufci         -1.795497173         0.02467576         0.11029413           Gatmáp         -1.793948732         0.02467576         0.11029413           Choraó         -1.74852215         0.027838164         0.11029413           Choraó         -1.793898732         0.04147351         0.10773381           Chraá         -1.79489713         0.04147351         0.10773381           Chraá         -1.72464030         0.01983393         0.10773381           Chraá         -1.724640403         0.011689997         0.10973281	Acvp1	-1.806157036	0.043072694	0.117869507
Int.         Int. <th< td=""><td>Parl</td><td>-1 80278821</td><td>0.042040741</td><td>0.118614100</td></th<>	Parl	-1 80278821	0.042040741	0.118614100
1003       -1.99403462       0.00753045/75       0.11242675         Cahrib       -1.99403462       0.0025302697       0.112428754         Candó       -1.9768975124       0.002509411       0.10774396         Candó       -1.975897377       0.01500411       0.107743963         Coxty       -1.751857433       0.033142751       0.113287933         Coxty       -1.756877173       0.022868371       0.10954423         Dnajc13       -1.754891373       0.022868371       0.10954423         Ulct       -1.754891373       0.022868371       0.10984423         Ulct       -1.754891373       0.022868371       0.10984123         Coxtoouty966       -1.719452215       0.02856515       0.111711039         Coxtoouty986       -1.719349732       0.041473351       0.107723281         Coxtoouty986       -1.72807029       0.041473351       0.107723281         Chrua6       -1.73527753       0.0268427       0.10983258         Coxtoouty987       -1.72464003       0.01695935       0.107723281         Chrua5       -1.7246403       0.0195932       0.107723281         Chrua5       -1.7246403       0.01954594       0.11030976         Ulsp2       -1.72464043       0.010	Tanta	-1.002/0031	0.043949741	0.110014199
Cahnib         -1.9949142         0.007240485         0.107008623           Zip455         -1.796497749         0.03233957         0.11248754           Cardó         -1.796497749         0.03230957         0.11248754           Cardó         -1.79649773         0.015209411         0.10773281           Cardó         -1.7618743         0.03214751         0.13389933           Cardío         -1.7618743         0.02365931         0.1124874           Diajcri3         -1.75687773         0.02865931         0.1092443           Ulfcr         -1.756877737         0.02467576         0.110291413           Cardoný         -1.74885213         0.02467576         0.110291413           Olfcrid         -1.74889732         0.02467576         0.110291413           Corvory966         -1.749393141         0.0095131         0.107723281           Corvory9786         -1.72489729         0.04145751         0.117930455           Resp18         -1.72489729         0.041457351         0.107723281           Chrma6         -1.72486729         0.0048259         0.107723281           Chrma5         -1.72465924         0.00382594         0.119390455           Gm8595         -1.79480771         0.0058575         0.109		-1./90013401	0.033004575	0.112040009
Zdp35       -1.758497749       0.03233967       0.112482754         Cardé       -1.756867124       0.0005098       0.10572566         Ano3       -1.77589737       0.015209411       0.107723281         Coxty       -1.756877173       0.022868371       0.113287933         Ufc1       -1.754895133       0.02467376       0.110994443         Ufc1       -1.754895213       0.02467376       0.110994433         Coxty       -1.74852513       0.02467376       0.110994433         Ufc1       -1.754895213       0.02467376       0.110994133         Cabarapla       -1.73948772       0.04473351       0.10773381         LOCtoouzy86       -1.73948772       0.041473351       0.10773381         Chrma6       -1.73547783       0.041473351       0.10773381         Chrma5       -1.724064003       0.01659905       0.10773381         Gm8527       -1.724069749       0.03038254       0.1109976         Ufsp2       -1.70680546       0.01659995       0.10773381         Gm8593       -1.70649549       0.0038254       0.11072382         Gm8594       -1.706495459       0.005745966       2810021602R84       0.11072382         Stro21Co2R84       -1.7040877 <td< td=""><td>Cdkn1b</td><td>-1.794493462</td><td>0.007520488</td><td>0.107008823</td></td<>	Cdkn1b	-1.794493462	0.007520488	0.107008823
Cardé         -1.78675124         0.00206798         0.105745066           Anog         -1.778590377         0.01520411         0.10773381           Cox17         -1.765185743         0.02866531         0.11175844           Dnajc13         -1.75687773         0.02268871         0.10594413           Ufc1         -1.754855213         0.02467576         0.110291413           CStm6         -1.74852215         0.02783614         0.11752284           LOCrooxp7966         -1.74895723         0.04156515         0.11712033           Gabarapl2         -1.739485732         0.04156515         0.11712033           Chrna6         -1.7287783         0.045425046         0.10990455           Chrna5         -1.724064003         0.010583339         0.10773381           Chrna5         -1.724064003         0.010583339         0.10773381           Chrna5         -1.724064003         0.01058339         0.10773281           Chrna5         -1.724064003         0.01058339         0.10773381           Chrna5         -1.724064003         0.01058339         0.10773381           Chrna5         -1.724064003         0.0105831         0.10773381           Chrna5         -1.70405071         0.020316805         0.105	Zfp455	-1.789487749	0.032329567	0.112482754
Anog         -1.77289377         0.01520411         0.107723281           Cox17         -1.765185743         0.033412781         0.113287933           Gm10507         -1.7651723466         0.028669531         0.11328793           Dhajc13         -1.754882131         0.02286371         0.109594443           Gstm6         -1.7454852215         0.027838164         0.11173284           LOC1cooL7986         -1.7393141         0.009610351         0.107723281           Cabaraple         -1.72368722         0.044755615         0.11712093           Chrna6         -1.72456922         0.02083339         0.107723281           Chrna5         -1.72466903         0.01659395         0.107723281           Chrna5         -1.72466922         0.0208427         0.109683258           Gm8959         -1.71669546         0.01659955         0.10772381           Chrna5         -1.7045619         0.03348594         0.1193976           U15p2         -1.70459149         0.43497794         0.105745966           Cars82         -1.7040113         0.002316895         0.105745966           Armcx6         -1.704214797         0.02516861         0.11072282           Rabp31         -1.604187556         0.002650535         <	Card6	-1.786765124	0.00206798	0.105745966
Coxiy         -1.76518743         0.033412781         0.113287933           Gm10507         -1.761722466         0.02860931         0.1178848           Dhajci 3         -1.75897173         0.022868371         0.10894143           Ufc 1         -1.748525215         0.02467376         0.110294143           Costmó         -1.748252215         0.027838164         0.110721381           Corvozy986         -1.74303141         0.00610351         0.17721381           Cabaraplz         -1.73527783         0.045425046         0.119390455           Chrnaó         -1.72867029         0.04473351         0.10772381           Chrnaó         -1.72867029         0.04473351         0.10772381           Chrnaó         -1.72867029         0.0208427         0.10983258           Gm6959         -1.71660946         0.01165995         0.10772381           Gm7827         -1.70800769         0.030382594         0.111920776           Ufsp         -1.7046013         0.03038259         0.10774384           Stitozi CozRik         -1.70400137         0.026516801         0.11828666           Rambp31         -1.70406137         0.026516801         0.11827480           Armcx5         -1.70125705         0.0801531	Ano3	-1.772890377	0.015209411	0.107723281
Gnilogor         -1.761722466         0.02806951         0.11178848           Dnajci3         -1.756871473         0.022868371         0.01994243           Gstm6         -1.748525215         0.027838164         0.111732284           Gstm6         -1.74393141         0.009610351         0.17723281           LOCicooly986         -1.74393747         0.04545545         0.11773284           Chrna6         -1.73527783         0.04545546         0.119390455           Chrna6         -1.724869729         0.01473351         0.10772381           Chrna6         -1.7246903         0.01953339         0.10772381           Gm7827         -1.72469034         0.030382594         0.109723281           Gm7827         -1.706694549         0.030382594         0.10772381           Ulfsp2         -1.707315875         0.003938259         0.10772381           Ulfsp2         -1.707315875         0.003938254         0.10774396           Vlfsp2         -1.705094549         0.030382594         0.10774396           SolozalCo2Rik         -1.704077         0.026516851         0.10774366           SolozalCo2Rik         -1.704077         0.026516851         0.10774366           Armcsy         -1.704077         0.02650533	Cox17	-1.765185743	0.033412781	0.113287933
Dnajcr3         -1.756877173         0.02286371         0.109894243           Ufc1         -1.754885213         0.02467576         0.11073284           LOC100047986         -1.743952215         0.027838164         0.11073284           LOC100047986         -1.74393141         0.009610351         0.107723281           Gabarapla         -1.739488732         0.04155615         0.11073284           Chrna6         -1.73527783         0.045425046         0.109703281           Chrna5         -1.728870729         0.014473351         0.107723281           Chrna6         -1.728807529         0.010583339         0.107723281           Chrna5         -1.712069026         0.011655995         0.107723281           Chrna5         -1.716905964         0.011655995         0.107723281           Syttr7         -1.708207619         0.030382594         0.111930776           Ufsp         -1.706904549         0.043497794         0.118218066           Ranbp31         -1.706904549         0.043497794         0.118218066           Rarbp31         -1.70105705         0.008016321         0.10702382           Afreck         -1.70214379         0.41495542         0.11712093           Tappc2l         -1.696020177         0.	Gm10507	-1.761722466	0.028696391	0.11178848
Ufci       -1.75485213       0.02467576       0.110291413         Gstm6       -1.754852215       0.0227838164       0.110291413         LOC tooo47986       -1.73933141       0.009610351       0.107723281         Gabarapla       -1.739489732       0.044555615       0.117112093         Chrma6       -1.7324870729       0.044453514       0.107723281         Chrma5       -1.72464003       0.010593339       0.107723281         Gm827       -1.72464003       0.010593339       0.107723281         Gm7827       -1.724650546       0.010593339       0.107723281         Gm8599       -1.70660546       0.010593595       0.107723281         Vifsp2       -1.707515875       0.000899751       0.105745966         Stity7       -1.796894549       0.043497794       0.111030776         Ufsp2       -1.707315875       0.000899751       0.105745966         Z810021GO2Rik       -1.70407877       0.02516801       0.11107282         Armcx5       -1.704107877       0.02516801       0.110712093         Trappc2l       -1.696020177       0.00550533       0.105745966         Z/P759       -1.69613578       0.00158299       0.105745966         Sum01       -1.68613578	Dnaic13	-1.756877173	0.022868371	0.109894243
Citta         17,4453215         0.02475/76           Citta         17,4453215         0.02475/8164         0.111732284           LOC toooq7986         1-7,4303141         0.009610351         0.107723281           Cabarapla         1-7,39489732         0.041565015         0.117112033           Chrna6         1-7,327783         0.041473351         0.107723281           Chrna6         1-7,2464003         0.010583339         0.107723281           Gm7827         1-7,24669054         0.011655995         0.107723281           Gm7827         1-7,21265922         0.02038427         0.10983258           Gm7827         1-7,208207619         0.030382594         0.111990776           Ufsp2         1-7,07315875         0.00889751         0.105745966           Sittoo21Go2Rik         1-70640013         0.002316895         0.105745966           Ranbp31         1-704107877         0.026516801         0.11072282           Armcx5         1-70105705         0.00801521         0.105745966           Zip759         0.043195542         0.11072282         0.105745966           Zip759         1-696020177         0.00560335         0.105745966           Zip759         1-696020177         0.00590335         0.105745966	Ufer	-1 754885213	0.02467576	0 110201413
Control         1-74025215         0.0205074         0.11712224           LOC1cood27986         1-743033141         0.009610351         0.107723281           Gabaraplz         1-73527783         0.041565615         0.117112093           Chrma6         1-73527783         0.04125046         0.10390455           Resp18         1-7248870729         0.014473351         0.107723281           Chrma5         1-72464003         0.010583339         0.107723281           Gm7827         1-721265922         0.02038427         0.10983258           Gm8599         1-71690546         0.01059595         0.107723281           Ul5p2         1-70731875         0.000899751         0.10774366           2810021G02Rik         1-70460113         0.00236953         0.10745966           Armcx5         1-70125705         0.00809551         0.10745966           Armcx5         1-70125705         0.00816321         0.107008823           Ret         1-700214379         0.041955542         0.117112093           Trappcal         1.696020177         0.00650935         0.105745966           Zip759         1-69118756         0.00236982         0.105745966           Sumo1         1-688251688         0.0015745966	Cetm6	-1 748252215	0.027828164	0.111722284
Loc. toxing/geo         -1/43/93141         0.009051         0.10773201           Gabarapla         -1/3934732         0.041565615         0.11112003           Chrna6         -1.73527783         0.042425046         0.10973281           Chrna5         -1.724887929         0.01473351         0.107723281           Chrna5         -1.724064003         0.02038427         0.1098328           Gm8959         -1.716890546         0.011695995         0.107723281           Gm8959         -1.708207619         0.030382594         0.11930776           Ul5p2         -1.70460113         0.00089751         0.105745966           28t0021G02Rik         -1.70400173         0.002316895         0.105745966           Ak5         -1.70407877         0.026516801         0.11072282           Armcv5         -1.70125705         0.00816521         0.105745966           Armcv5         -1.70214379         0.041955542         0.117112093           Trappcal         -1.6690177         0.0050355         0.105745966           Zip759         -1.669118756         0.002369892         0.105745966           Sum01         -1.68821688         0.01576743         0.107723281           Ititop58L19Rik         -1.67950571         0.012012 </td <td>LOC100017086</td> <td>1 = 1000001 11</td> <td>0.000610251</td> <td>0.107700081</td>	LOC100017086	1 = 1000001 11	0.000610251	0.107700081
Labarapiz         -1.739478732         0.04159515         0.117112093           Chrna6         -1.73527783         0.045425046         0.119390455           Resp18         -1.728870729         0.014473351         0.10773281           Chrna5         -1.724064003         0.010583339         0.10773281           Gm7827         -1.72165922         0.0238427         0.109083258           Gm8959         -1.706807619         0.030382594         0.11939076           U/sp2         -1.707315875         0.000899751         0.105745966           2810021C02Rik         -1.70460787         0.02316895         0.118218066           Ak5         -1.704107877         0.025516801         0.1172282           Armcx5         -1.704107877         0.026516801         0.11792282           Armcx5         -1.704007877         0.005695355         0.105745966           Zfp759         -1.691187556         0.0033989         0.105745966           Zfp759         -1.691187556         0.00339839         0.105745966           Zfp759         -1.69118756         0.0033989         0.105745966           Zfp759         -1.69118756         0.0033989         0.105745966           Zfp759         -1.69118756         0.0033989	Calegraphic	-1./43033141	0.009010351	0.10/7/23201
Lnnab         -1.73527783         0.04423544         0.11930455           Resp18         -1.72867729         0.01473351         0.107723281           Gm7827         -1.72165922         0.02038427         0.10983258           Gm8959         -1.71660546         0.011695995         0.10773281           Sytr7         -1.708207619         0.0385294         0.11930776           Ulfsp2         -1.705484549         0.043497794         0.18218066           2810021Go2Rik         -1.706494549         0.043497794         0.18218066           Ranbp31         -1.70400717         0.026516801         0.117072882           Armcx5         -1.704107877         0.026516801         0.117072882           Armcx5         -1.70214797         0.041955542         0.117112093           Tapp221         -1.696020177         0.006509535         0.105745966           Z/p759         -1.69118756         0.002369892         0.105745966           Metl4         -1.689613578         0.0015745966         0.0015745966           Sum01         -1.68951368         0.015756743         0.10773281           Npy2r         -1.681811689         0.015052172         0.10782683           Sum01         -1.679505671         0.01222553	Gabarapiz	-1.739488732	0.041505015	0.117112093
Resp18         -1.728870729         0.014473351         0.107723281           Chrnas         -1.724064003         0.02038339         0.107723281           Gmy8z7         -1.72165922         0.02038427         0.109083258           Gm895         -1.71690546         0.011695995         0.107723281           Sytr7         -1.08207619         0.030382594         0.11930776           Ulsp2         -1.707315875         0.00899751         0.105745966           Ranbp31         -1.70460113         0.00216855         0.105745966           Ak5         -1.704107877         0.026516801         0.111072282           Armcx5         -1.701255705         0.00816321         0.105745966           Zfp759         -1.696020177         0.00650555         0.105745966           Zfp759         -1.691187556         0.00236892         0.105745966           Metl4         -1.689613578         0.001158299         0.105745966           Sumo1         -1.68131689         0.015567743         0.107723281           Npy2r         -1.68131689         0.015062172         0.10772381           Npy2r         -1.681831689         0.015062172         0.10772381           Npy2r         -1.681831689         0.01292112         0.	Chrna6	-1.73527783	0.045425046	0.119390455
Chrnaş         -1.724064003         0.010583339         0.107723281           Gmy8zr         -1.721265922         0.02038427         0.109083258           Gm8359         -1.70690546         0.011695995         0.107723281           Syftr7         -1.708207619         0.30382594         0.1119390776           Ufsp2         -1.70450751         0.000899751         0.105745966           2810021G02Rik         -1.704007877         0.002316895         0.11192282           Akş         -1.704107877         0.002616801         0.11072282           Akr         -1.70214379         0.002615801         0.105745966           Armcrs         -1.70214379         0.002615801         0.105745966           Tappc2al         -1.69020177         0.002690535         0.105745966           Zfy759         -1.689613578         0.0021158299         0.105745966           Zfy759         -1.689613578         0.001158299         0.105745966           Sumo1         -1.689613578         0.001393189         0.105745966           Sumo1         -1.68181689         0.015056172         0.107723281           Npy2r         -1.681831689         0.015052172         0.10773281           Npy2r         -1.681831689         0.0122553	Resp18	-1.728870729	0.014473351	0.107723281
Gmy827         -1.721265922         0.02038427         0.109083258           Gm8959         -1.716690546         0.011695995         0.107723281           Sytr7         -1.708207619         0.030382594         0.111390776           Ulfsp2         -1.707315875         0.000899751         0.105745966           Z810021G02Rik         -1.706984549         0.043497794         0.118318066           Ranbp31         -1.704007877         0.026516801         0.111072282           Armcx5         -1.70125705         0.00816321         0.109745966           Ak5         -1.700214379         0.04195542         0.117112093           Trappcal         -1.696020177         0.006509335         0.105745966           Zfp759         0.1691187556         0.00236892         0.105745966           Mettl4         -1.689613578         0.001158299         0.105745966           Eifzs3y         -1.681318961         0.004339189         0.105745966           Sumo1         -1.68821688         0.015576743         0.107723281           Npy2r         -1.68131689         0.01922553         0.107723281           Npy2r         -1.69505671         0.01920112         0.10780683           Pdgfra         -1.67744119         0.0122553 <td>Chrna5</td> <td>-1.724064003</td> <td>0.010583339</td> <td>0.107723281</td>	Chrna5	-1.724064003	0.010583339	0.107723281
Gm8959       -1.716690546       0.011695995       0.107723281         Sytr7       -1.708207619       0.030382594       0.111930776         Ulfsp2       -1.70731875       0.00899751       0.105745966         2810021G02Rik       -1.70460013       0.002316895       0.105745966         Anbp31       -1.704107877       0.026516801       0.11072282         Armcx5       -1.704107877       0.026516801       0.1107282         Armcx5       -1.700214379       0.041955542       0.107745966         YEpr24       -1.696020177       0.006509535       0.105745966         Mettl4       -1.696020177       0.006309892       0.105745966         Mettl4       -1.69613758       0.00158299       0.105745966         Mettl4       -1.689613378       0.00158299       0.105745966         Sum01       -1.688251688       0.015576743       0.10772381         Npy2r       -1.68131869       0.01920112       0.107872663         Yugra4       -1.679505671       0.01920112       0.107872881         Npy2r       -1.679144119       0.0122253       0.107723281         Itih2       -1.679628055       0.08945402       0.107600372         Sfrs3       -1.672628055       0.08945402 </td <td>Gm7827</td> <td>-1.721265922</td> <td>0.02038427</td> <td>0.109083258</td>	Gm7827	-1.721265922	0.02038427	0.109083258
Sytr7       -1.708207619       0.030382594       0.11930776         Ufsp2       -1.707315875       0.000899751       0.105745966         2810021G02Rik       -1.706984549       0.043497794       0.118218066         Ranbp31       -1.70400113       0.002316895       0.105745966         Ak5       -1.704107877       0.026516801       0.111072282         Armcx5       -1.700214379       0.041955542       0.117112033         Trapc21       -1.696020177       0.006509535       0.105745966         Zfp759       -1.689613578       0.001158299       0.105745966         Mettl4       -1.689613578       0.00155829       0.105745966         Sum01       -1.68851688       0.015576743       0.107723281         Npy2r       -1.661831689       0.015062172       0.10773281         Npy2r       -1.673617683       0.0132553       0.107723281         Npy2r       -1.673617683       0.01343841       0.107723281         Ith2       -1.673617683       0.01343841       0.107723281         Sfrs3       -1.67268055       0.008945402       0.10760372         Gm5512       -1.67267783       0.006677079       0.105745966         Rp3       -1.667642448       0.047670409 <td>Gm8959</td> <td>-1.716690546</td> <td>0.011695995</td> <td>0.107723281</td>	Gm8959	-1.716690546	0.011695995	0.107723281
Ufsp2       -1.707315875       0.000899751       0.105745966         2810021G02Rik       -1.706984549       0.043497794       0.118218066         Ranbp3l       -1.704107877       0.026516801       0.11072282         Aks       -1.704107877       0.026516801       0.11072282         Armcx5       -1.701255705       0.00810321       0.105745966         Trappc2l       -1.69602177       0.006509355       0.105745966         Zfp759       -1.69602177       0.006509355       0.105745966         Zfp759       -1.6961187556       0.002369892       0.105745966         Elfzsay       -1.689613578       0.00158299       0.105745966         Sumo1       -1.689613578       0.01576743       0.107723281         Npv2r       -1.681831689       0.015062172       0.10773281         Npv2r       -1.681831689       0.01222553       0.107723281         Npdfra       -1.673617683       0.011343841       0.107723281         Hih2       -1.67266783       0.01343841       0.107723281         Sfrs3       -1.672668055       0.00845402       0.107600372         Gm5512       -1.67266783       0.06677079       0.105745966         Rp3       -1.667642448       0.047670409<	Syt17	-1.708207619	0.030382594	0.111930776
2810021G02Rik       -1.706984549       0.043497794       0.118218066         Ranbp3l       -1.70400113       0.002316895       0.105745966         Ak5       -1.704107877       0.026516801       0.111072282         Armcx5       -1.701255705       0.008016321       0.107008823         Ret       -1.700214379       0.041955542       0.117112093         Trappc2l       -1.690187556       0.00236892       0.105745966         Zlp759       -1.691187556       0.00236892       0.105745966         Mettl4       -1.689613578       0.00158299       0.105745966         Eifzs3y       -1.688113961       0.004339189       0.105745966         Sumo1       -1.688251688       0.01576743       0.107723281         Npy2r       -1.681831689       0.0120012       0.10773281         Npy2r       -1.6873617683       0.01222553       0.107723281         Npgfa       -1.673617683       0.01343841       0.107723281         Strs3       -1.67266783       0.00845402       0.10760372         Gm5512       -1.67266783       0.006677079       0.105745966         Rp3       -1.667642448       0.047670409       0.1020417	Ufsp2	-1.707315875	0.000899751	0.105745966
Internation         Intersection         Outgraphysic         Outgraphysic         Outgraphysic           Ranbp3l         -1.704600113         0.002316895         0.105745966           Ak5         -1.70125705         0.008016321         0.10702822           Armcx5         -1.700214379         0.04955542         0.117112093           Trappc2l         -1.69018756         0.002669892         0.105745966           Zlp759         -1.6991187556         0.00236892         0.105745966           Zlp759         -1.6991187556         0.002369892         0.105745966           Sumo1         -1.68913578         0.00158299         0.105745966           Sumo1         -1.688151688         0.015576743         0.107723281           Npy2r         -1.681831889         0.015062172         0.10773281           1110058L19Rik         -1.679505671         0.01222553         0.10773281           1110058L19Rik         -1.673617683         0.011343841         0.107723281           Itih2         -1.673617683         0.00845402         0.107600372           Gm5512         -1.672628055         0.00845402         0.107600372           Gm5512         -1.67642448         0.047670409         0.102024917	2810021G02Rik	-1.706984549	0.043497794	0.118218066
Image         Image         Outpating         Outpating         Outpating           Ak5         -1.704107877         0.02510695         0.105745900           Ak7         -1.70125705         0.008016321         0.11072282           Ret         -1.700214379         0.041955542         0.117112093           Trappc2l         -1.696020177         0.006509535         0.105745966           Zfp759         -1.691187556         0.002369892         0.105745966           Mettl4         -1.689613578         0.00158299         0.105745966           Eifz3yy         -1.689113961         0.00439189         0.105745966           Sumo1         -1.68251688         0.015576743         0.10772381           Npy2r         -1.68181689         0.015062172         0.10773281           1110058L19Rik         -1.679505671         0.01920112         0.10773281           1110058L19Rik         -1.673617683         0.011343841         0.107723281           Kfrs3         -1.672628055         0.00845402         0.107600372           Gm5512         -1.67267783         0.006677079         0.10274906           Rpa3         -1.66762448         0.047670409         0.10204917	Ranhnal	-1 704600112	0.002216805	0.105745066
Aksy         -1.704107877         0.020518801         0.11072282           Armxx5         -1.701255705         0.008016321         0.107008823           Ret         -1.700214379         0.041955542         0.117112093           Trappc2l         -1.696020177         0.006509535         0.105745966           Zfp759         -1.689613578         0.001158299         0.105745966           Mettl4         -1.689613578         0.001576743         0.107723281           Sumo1         -1.688251688         0.015062172         0.107723281           Npy2r         -1.681831689         0.015062172         0.10773281           Npy2r         -1.681831689         0.01222553         0.10773281           Pdgfra         -1.673617683         0.011343841         0.107723281           Itih2         -1.672628055         0.00845402         0.10760372           Sfrs3         -1.672628055         0.00845402         0.10760372           Gm5512         -1.67266783         0.01543841         0.10773281           Rp3         -1.667642448         0.047670409         0.10260372	AL-	1./04000113	0.002310093	0.103/43900
Armcx5         -1.701255705         0.008016321         0.107008823           Ret         -1.700214379         0.041955542         0.117112093           Trappc2l         -1.690620177         0.006509535         0.105745966           Zfp759         -1.691187556         0.002369822         0.105745966           Mettl4         -1.689613578         0.001158299         0.105745966           Eif2s3y         -1.68813689         0.01576743         0.107723281           Npy2r         -1.681831689         0.015062172         0.107876683           I110058L19Rik         -1.679505671         0.01222553         0.107723281           Itih2         -1.673617683         0.01343841         0.107723281           Sfrs3         -1.67268055         0.00845402         0.10773281           Sfrs3         -1.67267783         0.00677079         0.105745966           Rpa3         -1.667642448         0.047670409         0.102024917	AK5	-1.704107877	0.020510801	0.111072282
Ret         -1.700214379         0.041955542         0.117112093           Trappc2l         -1.696020177         0.06509535         0.105745966           Zfp759         -1.691187556         0.002369892         0.105745966           Mettl4         -1.689613578         0.001158299         0.105745966           Eifzs3y         -1.68113961         0.00439189         0.105745966           Sumo1         -1.681831689         0.015576743         0.107723281           Npy2r         -1.681831689         0.015062172         0.10773281           1110058L19Rik         -1.679505671         0.01920112         0.10773281           1110058L19Rik         -1.673617683         0.011343841         0.107723281           Sfrs3         -1.672628055         0.00845402         0.10773281           Sfrs3         -1.672628055         0.00845402         0.10760372           Gm5512         -1.67267783         0.006677079         0.105745966           Rpa3         -1.667642448         0.047670409         0.102042917	Armcx5	-1.701255705	0.008016321	0.107008823
Trappc2l         -1.696020177         0.006509535         0.105745966           Zfp759         -1.691187556         0.002369892         0.105745966           Mettl4         -1.689613578         0.00158299         0.105745966           Eifz3yy         -1.689113961         0.004339189         0.105745966           Sumo1         -1.68851688         0.015576743         0.10772381           Npy2r         -1.681831689         0.015062172         0.10773281           1110058L19Rik         -1.679505671         0.01920112         0.10786683           Pdgfra         -1.673617683         0.011343841         0.10772381           Sfrs3         -1.672628055         0.008945402         0.10772381           Sfrs3         -1.67267783         0.00677079         0.105705072           Rpa3         -1.667642448         0.047670409         0.10202917	Ket	-1.700214379	0.041955542	0.117112093
Złp759         -1.691187556         0.002369892         0.105745966           Metłl4         -1.689613578         0.001158299         0.105745966           Eifzsyy         -1.689113961         0.004339189         0.105745966           Sumo1         -1.688251688         0.01576743         0.107723281           Npy2r         -1.681831689         0.01220571         0.10773281           1110058L19Rik         -1.679505671         0.012212         0.10773281           Pdgfra         -1.673617683         0.011343841         0.107723281           Itih2         -1.672628055         0.00845402         0.10760372           Sfrs3         -1.672628055         0.00845402         0.10760372           Gm5512         -1.67267783         0.006677079         0.105745966           Rpa3         -1.667642448         0.047670409         0.10204217	Trappc2l	-1.696020177	0.006509535	0.105745966
Mettl4         -1.689613578         0.001158299         0.105745966           Eif2s3y         -1.689113961         0.004339189         0.105745966           Sumo1         -1.688251688         0.015576743         0.107723281           Npy2r         -1.681831689         0.015062172         0.107723281           1110058L19Rik         -1.679505671         0.01222553         0.107723281           Pdgfra         -1.673617683         0.011343841         0.107723281           Itih2         -1.673617683         0.011343841         0.107723281           Sfrs3         -1.672628055         0.008945402         0.105760372           Gm5512         -1.672067783         0.006677079         0.105745966           Rpa3         -1.667642448         0.047670409         0.10204917	Zfp759	-1.691187556	0.002369892	0.105745966
Eif2s3y       -1.68913961       0.004339189       0.105745966         Sumo1       -1.688251688       0.015576743       0.107723281         Npy2r       -1.681831689       0.015062172       0.107723281         1110058L19Rik       -1.679505671       0.01920112       0.107876683         Pdgfra       -1.673617683       0.011343841       0.107723281         Itihz       -1.672628055       0.008945402       0.10760372         Gm5512       -1.672667783       0.006677079       0.105745966         Rpa3       -1.667642448       0.047670409       0.10204917	Mettl4	-1.689613578	0.001158299	0.105745966
Sumoi         -1.688251688         0.015576743         0.107723281           Npy2r         -1.681831689         0.015062172         0.107723281           1110058L19Rik         -1.679505671         0.01920112         0.107876683           Pdgfra         -1.673617683         0.011343841         0.107723281           Itih2         -1.673617683         0.011343841         0.107723281           Sfrs3         -1.672628055         0.008945402         0.107600372           Gm5512         -1.672667783         0.006677079         0.105745966           Rpa3         -1.667642448         0.047670409         0.120024917	Eif2s3y	-1.689113961	0.004339189	0.105745966
Npy2r         -1.681831689         0.01590743         0.107723281           1110058L19Rik         -1.679505671         0.01920112         0.10782683           Pdgfra         -1.679505671         0.01222553         0.107723281           Itih2         -1.673617683         0.011343841         0.107723281           Sfrs3         -1.672628055         0.008945402         0.107600372           Gm5512         -1.672667783         0.006677079         0.105745966           Rpa3         -1.667642448         0.047670409         0.120024917	Sumot	-1 688251688	0.015576742	0.107722281
Ny 21         -1.001031009         0.015002172         0.107723201           1110058L19Rik         -1.679505671         0.01920112         0.107723201           Pdgfra         -1.679505671         0.0122253         0.107723281           Itih2         -1.673617683         0.011343841         0.107723281           Sfrs3         -1.672628055         0.008945402         0.107600372           Gm5512         -1.667642448         0.047670409         0.10202917	Novor	1 681821680	0.015060150	0.10772202
11100-0619KK         -1.079505071         0.01920112         0.107876683           Pdgfra         -1.679144119         0.01222553         0.107723281           Itih2         -1.673617683         0.01343841         0.107723281           Sfrs3         -1.672628055         0.008945402         0.107600372           Gm5512         -1.672067783         0.006677079         0.105745966           Rpa3         -1.667642448         0.047670409         0.102024917		-1.001031009	0.015002172	0.10//23201
rdgtra         -1.677144119         0.01222553         0.107723281           Itih2         -1.673617683         0.011343841         0.10773281           Sfrs3         -1.672628055         0.008945402         0.107600372           Gm5512         -1.672667783         0.006677079         0.105745966           Rpa3         -1.667642448         0.047670409         0.102024917	D1 (	-1.0/9505071	0.01920112	0.10/070003
Itih2         -1.673617683         0.011343841         0.107723281           Sfrs3         -1.672628055         0.008945402         0.107600372           Gm5512         -1.672067783         0.006677079         0.105745966           Rpa3         -1.667642448         0.047670409         0.120024917	Pdgtra	-1.677144119	0.01222553	0.107723281
Sfrs3         -1.672628055         0.008945402         0.107600372           Gm5512         -1.672067783         0.006677079         0.105745966           Rpa3         -1.667642448         0.047670409         0.120024917	Itih2	-1.673617683	0.011343841	0.107723281
Gm5512         -1.672067783         0.006677079         0.105745966           Rpa3         -1.667642448         0.047670409         0.120024917	Sfrs3	-1.672628055	0.008945402	0.107600372
Rpa3         -1.667642448         0.047670409         0.120024917           Continued on next page	Gm5512	-1.672067783	0.006677079	0.105745966
Continued on next page	Rpa3	-1.667642448	0.047670409	0.120024917
Continued on next bage	· ·			Continued on next page

Table 6.2: List of transcripts deregulated in *Fto*-deficient midbrain microarray analysis

Table 6.2 – continued from previous page

Table 6.2 – continued from previous page			
Assignment	fc	pv	qv
Chordc1	-1.665182152	0.000454042	0.105745966
Ddvav	-1 664505144	0.012050526	0.105522281
Dux3x	-1.004/05144	0.0130/9520	0.10//23201
Atp5n	-1.663740006	0.000977462	0.105745966
Hspa8	-1.659467069	0.021507654	0.10956964
Efempi	-1.659298373	0.020800948	0.109317531
Rmnd1	-1 657164324	0.016447801	0 107723281
Labas	1.03/104324	0.010447091	0.10//23201
Lphn2	-1.656440827	0.004199498	0.105745966
Hspa8	-1.646885209	0.020553272	0.109270814
Mettl <sub>5</sub>	-1.644569525	5.15E-05	0.051083022
Gm10726	-1 642027025	0.002220226	0 105745066
Biiii0/20	1.042037033	0.002339220	0.103/43900
Psma5	-1.637343101	0.018383415	0.107723281
Cstad	-1.629911163	0.007196357	0.107008823
Arpc5	-1.627382445	0.004144678	0.105745966
Tomm22	-1 626652150	0.04662022	0 110728072
10hull22	1.020033139	0.04002033	0.119/200/3
Kcnc2	-1.62426084	0.004395858	0.105745966
Psmd10	-1.622996625	0.021328229	0.10956964
Gba	-1.621913261	0.025599605	0.110565417
Nripa	-1 61672765	0.000640478	0.105745066
Nilp3	-1.010/2/05	0.000049470	0.105/45900
1810030N24R1k	-1.615846328	0.035022634	0.113799868
Gjb2	-1.615431974	0.004410946	0.105745966
2410017P09Rik	-1.611990602	0.047576823	0.119963923
Tteach	1 610580508	0.045022051	0.110506050
1(0390	-1.010/80598	0.045932051	0.119500979
Gm5521	-1.60743084	0.019470211	0.108210826
Adamts1	-1.607133751	0.039423927	0.116024248
1810020D17Rik	-1.605845764	0.039139568	0.115957022
Sprig	1 605 108000	0.002428255	0.105745066
Sp140	-1.605408009	0.002438355	0.105745966
Snord87	-1.604836881	0.014667822	0.107723281
Polr1d	-1.604607004	0.017318098	0.107723281
Dhrs7	-1 601621507	0.045150506	0 110126062
Dilloj	1.001021397	0.043130300	0.119120003
крід	-1.596947259	0.009028466	0.107600372
Chrnb3	-1.596744336	0.011044687	0.107723281
Anoz	-1.596626284	0.002484819	0.105745966
Mrplco	-1 506552506	0.011387585	0.1077222281
DC N D'I	-1.590552500	0.01120/303	0.10//23201
D630004N19R1k	-1.595505225	0.0121444	0.107723281
Hdac3		0.004199016	0.105745966
Rpl5	-1.592190912	0.007986224	0.107008823
Duana un OccaBile			0.44600.40.18
D430042O09KIK	-1.59081/189	0.039335141	0.116024246
Sept4	-1.587360708	0.007660099	0.107008823
Agxt2l1	-1.585242261	0.014482225	0.107723281
Gtphp8	-1 577634858	0.00610051	0 105745066
afragat=JooBile	1.577054050	0.00010991	0.100,74,9900
2610017109K1K	-1.577208437	0.022324734	0.10956964
Gabra5	-1.575977204	0.017252598	0.107723281
Gstm1	-1.573303134	0.001694706	0.105745966
Lphn2	-1 573200400	0.001258544	0 105745966
Crifter i	1.373299499	0.001330344	0.103/43900
Gm8304	-1.572914226	0.000231863	0.101410316
Rps12	-1.572521781	1.78E-05	0.025735818
Fgf13	-1.572114904	0.023355478	0.110058377
Parl	-1 570640850	0.006044262	0 106421422
	1.570040059	0.000944303	0.100431423
Lmo3	-1.567921503	0.002091215	0.105745966
Arpc3	-1.567736757	0.028249369	0.111732284
Gm5778	-1.566896623	0.022209946	0.10956964
4020455F22Rik	-1 =62107128	0.000205818	0.1077222281
4930455123111	-1.50310/138	0.009395818	0.10//23281
Txnl4b	-1.562930183	0.037845173	0.11559365
Bckdhb	-1.561767829	0.007945643	0.107008823
Gm447	-1.560180918	0.040030257	0.116437995
Gm12176	-1 550152802	0.042550462	0.11828=272
Company			
Gnpnati	-1.558170745	0.015155721	0.107723281
Ctbs	-1.556303393	0.010220326	0.107723281
Rnpep	-1.555954637	0.016161944	0.107723281
Hha-aa	-1 554010616	0.028424211	0.115781817
1104-42	-1.554919010	0.030424211	0.115/0101/
Atp11b	-1.5539535	0.001252108	0.105745966
Camta1	-1.552234652	0.017024474	0.107723281
Hist2h2be	-1.551556966	0.030689347	0.111930776
Kibiaa	-1 ==001=400	0.025260611	0.114141072
Ku1132	-1.550915409	0.035300011	0.1141419/2
D16H22S680E	-1.547836766	0.013802924	0.107723281
Rpl9	-1.547786699	0.011246319	0.107723281
Nkiras1	-1.54777597	0.02829242	0.111732284
Baaaa8aDozRik	-1 = 45536634	0.010600717	0.10820025
1230300D0/MIK	-1.54/730034	0.019009/17	0.10030935
Lepr	-1.547650811	0.023290941	0.110058377
Hist1h2bc	-1.547475605	0.027972056	0.111732284
Atp5h	-1.54715385	0.000460279	0.105745966
Ndufafa		0.018007514	0.107700081
Induïar2	-1.54001774	0.018397514	0.10//23281
Psma5	-1.545074782	0.02139651	0.10956964
Hba-a1	-1.545071212	0.036604766	0.114852466
Cones	-1 542540406	0.024204026	0 112722582
PC			
DC057170	-1.542560065	0.013751163	0.107723281
Dennd4a	-1.542314164	0.03968435	0.116339767
Rbbp8	-1.541124413	0.00696665	0.106431423
*	51 11 5	- ) 5	Continued on next n
			Communed on next page

Table 6.2 – continued from previous page

Finnt         -5.909/80/4         0.018/01/3         0.018/02/4           Jach         -5.909/80/4         0.018/02/4         0.018/02/4           Jach         -5.909/80/4         0.008/02/4         0.008/02/4           Jach         -5.909/80/4         0.008/02/4         0.009/20/4           LCC_13/02         -5.909/80/4         0.009/20/4         0.009/20/4           LCC_13/02         -5.909/80/4         0.009/20/4         0.009/20/4           LCC_13/02         -5.909/80/4         0.009/20/4         0.009/20/4           New         -5.937/93/1         0.009/20/4         0.009/20/4           Andread         -5.937/93/1         0.009/20/4         0.009/20/4           Andread         -5.937/93/1         0.009/20/4         0.009/20/4           Andread         -5.937/93/1         0.009/20/4         0.009/20/4           Stala         -5.937/93/1         0.009/20/4         0.009/20/4           Stala         -5.937/93/1         0.009/20/4         0.009/20/4           Stala         -5.937/93/1         0.009/20/4         0.009/20/4           Term         -5.937/93/1         0.009/20/4         0.009/20/4           Term         -5.937/93/1         0.009/20/4         0.009/20/4	Assignment	fc	pv	qv
inflat	Fmn1	-1.540636667	0.02809123	0.111732284
india4.5960935angarayay4.148546Appr4.3957471angarayay4.148546Appr4.3957471angabyy4.148546Appr4.3957471angabyy4.148546Charger4.3957811angarayay4.195246Nor4.3958519angabyy4.195246Nor4.3958519angabyy4.195246Dernda4.3959519angabyy4.195246Dernda4.3959519angabyy4.195246Conys4.3959519angabyy4.195246Conys4.3959519angabyy4.195246Conys4.3959519angabyy4.195246Conys4.3959519angabyy4.195246Conys4.3959519angabyy4.195246Conys4.3959519angabyy4.195246Conys4.3959519angabyy4.195246Conys4.3959519angabyy4.195246Conys4.3959519angabyy4.195246Conys4.3959519angabyy4.195246Conys4.3959519angabyy4.195246Conys4.3959519angabyy4.195246Conys4.3959519angabyy4.195246Conys4.3959519angabyy4.195246Conys4.3959519angabyy4.195247Conys4.3959519angabyy4.195247Conys4.3959519angabyy4.195249Conys4.3959519angabyy4.195249Conys4.3959519	Eef1b2	-1.539853748	0.034471601	0.113740124
Nature	Josd1	-1.538630345	0.047207309	0.119852203
Appr:	Ndufa9	-1.538584131	0.036587997	0.114852466
LC         1.505/359/1         0.002/359/2         0.002/359/2           Nor         -535/59/1         0.002/359/2         0.002/359/2           Corpsyl         -535/59/1         0.002/359/2         0.002/359/2           Corpsyl         -535/59/2         0.002/359/2         0.002/359/2           Skyla         -535/59/2         0.002/359/2         0.002/359/2           Skyla         -535/59/2         0.002/359/2         0.002/359/2           Skyla         -535/59/2         0.002/359/2         0.002/359/2           Corpsyl         -535/59/2         0.002/359/2         0.002/359/2	Aqp11	-1.537972812	0.000888799	0.105745966
DCgsysip.spigspåoxoseffrjoa.spigspåMetsspigspåoxysipa.spigspåMetsspigspåoxysipa.spigspåMetsspigspåoxysipa.spigspåMetsspigspåoxysipa.spigspåMetsspigspåa.spigspåa.spigspåMetsspigspåa.spigspåa.spigspåMetsspigspåa.spigspåa.spigspåSkysinspigspåa.spigspåa.spigspåSkysinspigspåa.spigspåa.spigspåTennabspigspåa.spigspåa.spigspåTennabspigspåa.spigspåa.spigspåTennabspigspåa.spigspåa.spigspåTennabspigspåa.spigspåa.spigspåTennabspigspåa.spigspåa.spigspåTennabspigspåa.spigspåa.spigspåTennabspigspåa.spigspåa.spigspåTennabspigspåa.spigspåa.spigspåTennabspigspåa.spigspåa.spigspåChianspigspåa.spigspåa.spigspåChianspigspåa.spigspåa.spigspåChianspigspåa.spigspåa.spigspåChianspigspåa.spigspåa.spigspåChianspigspåa.spigspåa.spigspåChianspigspåa.spigspåa.spigspåChianspigspåa.spigspåa.spigspåSpigspåspigspå <t< td=""><td>LOC433762</td><td>-1.536928446</td><td>0.002508739</td><td>0.105745966</td></t<>	LOC433762	-1.536928446	0.002508739	0.105745966
Normal	LOC433762	-1.536928446	0.002508739	0.105745966
Number	Nov	-1 =2=78=421	0.006100602	0.105745066
nmmisul	Moter	-1 525558240	0.002462	0.105745966
Internation	Donnd (a	1.535556349	0.003402	0.105/45900
Anthon         1.911119         0.0000007         0.000007           Comp 350         1.9339611         0.0015954         0.10170281           Fish         1.9339619         0.015954         0.10172964           Stylka         1.9339619         0.015954         0.10172964           Tame         1.9339754         0.0159545         0.1017298           Bife         1.93397544         0.0159547         0.1017298           Martin         1.93597549         0.0161616         0.1016730           Column         1.93597549         0.0161616         0.1016730           Martin         1.9359469         0.0026009         0.1019296           Martin         1.9359469         0.0026009         0.1019296           Nahrin         1.9359469         0.0026009         0.1019296           Nahrin         1.9359469         0.0026009         0.1019296           Nahrin         1.9359469         0.0026009         0.1019296           Nahrin         1.9329640         0.0026009         0.1019291           Nahrin         1.9329640         0.0026009         0.1019291           Statin         1.9329640         0.0026009         0.1019291           Passon         1.9329641	Definida	-1.534905905	0.00/340/58	0.10/008823
Ambgen         1-3333134         0.000199733         0.10021990           Changel         1-33301541         0.00019973         0.10021990           Siglas         1-33301541         0.00019977         0.10021996           Siglas         1-33005541         0.00019973         0.10021996           Siglas         1-33005541         0.00019973         0.10021996           Siglas         1-33005541         0.00121916         0.10071396           Markin         1-3505266         0.0021996         0.10071396           Markin         1-3505266         0.0021996         0.10071396           Markin         1-3505266         0.0021996         0.10075276           Markin         1-3505266         0.00219973         0.100564           Markin         1-3505266         0.00219973         0.100564           Markin         1-3505266         0.00219973         0.100564           Markin         1-3505266         0.00219973         0.100564           Liph         1-35052967         0.00529571         0.105954           Liph         1-3505296         0.002211979         0.1095964           Liph         1-3505296         0.002211979         0.1095964           Liph		-1.53411149	0.009000027	0.10/6003/2
Carsys <sup>3</sup> -1.53104.39         0.12057.09         0.11001.09           Style         -1.53104.59         0.017777.81         0.1071.596           Style         -1.53104.597         0.01297.78         0.1071.596           Style         0.1157.697         0.01297.78         0.1071.596           Style         0.1157.697         0.01297.798         0.01297.596           Marcha         -1.529.595.44         0.01297.596         0.1097.596.64           Consyl         -1.529.595.44         0.01297.596         0.1097.596.64           Consyl         -1.529.595.44         0.01297.596         0.1097.596.64           Consyl         -1.529.595.64         0.0029.595.64         0.1097.596.64           Consyl         -1.529.595.64         0.0029.595.64         0.1097.596.64           Consyl         -1.529.595.64         0.0029.595.64         0.1097.596.64           Consol         -1.529.595.66         0.0029.595.64         0.1197.596.64           Consol         -1.529.597.66         0.0029.597.64         0.1197.596.64           Consol         -1.529.597.66         0.0029.597.64         0.0029.596.64           Consol         -1.529.597.66         0.0029.597.64         0.0059.564.1           Consol         -1.52	Arngef6	-1.533353144	0.006350713	0.105745966
br.h         -1.5101659         0.01725951         0.10722381           Elign         -1.5101659         0.0172758         0.10722381           Elign         -1.5100659         0.0172758         0.10722381           Elign         -1.5100659         0.01722381         0.10722381           Machu         -1.5200514         0.0124666         0.10722381           Machu         -1.5200524         0.0124666         0.10722381           Machu         -1.5200524         0.0124666         0.1072266           Claan         -1.5200524         0.00246661         0.1072266           Nish         -1.5200524         0.00246661         0.1072266           Nish         -1.5200524         0.00246681         0.1072266           Nish         -1.5200527         0.0179266         0.1109564           Nish         -1.5200527         0.0179567         0.1095664           Nish         -1.5200527         0.0179567         0.1095664           Nish         -1.5200527         0.0195664         0.1179640           Tanku         -1.5166241         0.01239911         0.10792581           Tanku         -1.5166241         0.0129591         0.1095664           Nastanta         -1.5156	Gm3258	-1.533261034	0.024351585	0.110161209
SigSa         -1,510669         0.0077778         0.107758           Elaje         -1,500674         0.0014408         0.0077258           Tmembk         -1,500764         0.001458         0.1077258           Marchi         -1,500764         0.0114580         0.1077258           Marchi         -1,500764         0.021458         0.1077258           Marchi         -1,500764         0.0124599         0.1077258           Marchi         -1,500764         0.0124599         0.1077258           Nation         -1,500764         0.0125499         0.107258           Nation         -1,500764         0.0024697         0.1072564           Nation         -1,500764         0.0024697         0.107564           Nation         -1,500766         0.0024097         0.105954           Liph         -1,5107967         0.0159764         0.015974           Liph         -1,5107967         0.015954         0.015954           Liph         -1,510796         0.0159591         0.015954           Liph         -1,510776         0.0159591         0.015954           Liph         -1,510776         0.0159591         0.0159591           Tamen         -1,5107776         0.0159599	Fech	-1.531561536	0.015369054	0.107723281
Eige	Slc38a2	-1.531016679	0.001777778	0.105745966
Themioli         -1.5907590         0.01148/079         0.10773381           Marchi 1         -1.5907595         0.00448/66         0.0075385           Marchi 1         -1.5907595         0.00448/66         0.0075385           Clian         -1.5907595         0.00448/66         0.0075286           Clian         -1.5907595         0.01751399         0.1771289           Clian         -1.5907595         0.0185399         0.1771289           Marchi 1         -1.5907595         0.00259959         0.1771289           Marchi 2         -1.590759         0.00259959         0.179584           Japos 2         -1.590759         0.00250769         0.17984           Japos 2         -1.5905954         0.0025079         0.199594           Japos 2         -1.5958979         0.0035076         0.17984           Bhox 2         -1.5958979         0.0035076         0.17984           Bhox 3         -1.5979597         0.0035076         0.17984           Bhox 3         -1.5979597         0.0035076         0.179738           Bhox 3         -1.5979597         0.0035076         0.179738           Bhox 3         -1.5979597         0.0159997         0.179728           Bhox 3	Eif3e	-1.530376544	0.003841968	0.105745966
Tam	Tmem68	-1.530058344	0.011458463	0.107723281
Machin1.5931/9618o.oxq49/660.1.001/1203Clian1.5951/9610.041639910.17/1203Clian1.5951/9510.0216313990.0773381rowollykalka1.5951/9510.02020/070.0751/956Niho1.5821/9510.00260/070.0751/956Niho1.5821/9510.00260/070.0751/956Niho1.5821/9510.00260/070.0751/956Zipsyr1.5971/9510.00220/070.07959/951Zipsyr1.5971/9510.0021/9710.07959/951Zipsyr1.5971/9510.0021/9710.07959/951Zipsyr1.5971/9510.0021/9710.07959/951Zipsyr1.5971/9510.0021/9710.07959/951Zipsyr1.5971/9510.0021/9510.07972981Zipsyr1.5971/9510.0221/9510.07972981Zipsyr1.5971/9510.0221/9510.07972981Zipsyr1.5971/9510.0221/9510.07972981Zipsyr1.5971/9510.0221/9560.0772381Zipsyr1.5971/9510.0291/9510.07972381Zipsyr1.5979/9510.0291/9560.0772381Zipsyr1.5971/9510.0291/9560.0772381Zipsyr1.5971/9510.0291/9560.0772381Zipsyr1.5971/9510.0291/9560.0772381Zipsyr1.5971/9510.0291/9560.0772381Zipsyr1.5971/9510.0291/9560.0772381Zipsyr1.5971/9510.0	Tfam	-1.52977909	0.014987079	0.107723281
Cms.11         -1.595/03/64         0.0016/89/91         0.1072/38/6           Nuktra         -1.595/03/64         0.0126/39/92         0.1072/38/6           Nuktra         -1.595/03/64         0.0026/03/13         0.1072/38/6           Rhang         -1.594/23/03/64         0.0026/03/13         0.1075/38/6           Rhang         -1.594/23/03/14         0.0026/03/13         0.1075/38/6           Liph         -1.594/25/03/14         0.00221/97/2         0.0059/54           Liph         -1.594/25/03/14         0.00221/97/2         0.0059/54           Lipk         -1.594/25/03/14         0.00221/97/2         0.0059/54           Lipk         -1.594/25/03/14         0.00221/97/2         0.1059/54           Lipk         -1.594/25/03/14         0.00221/97/2         0.115/84/7           Roka         -1.594/54/14         0.00221/97/2         0.105/95/4           Roka         -1.594/54/14         0.00229/95/1         0.117/23/8           Roka         -1.594/54/14         0.00229/95/1         0.177/23/8           Roka         -1.594/54/14         0.00239/95/1         0.177/23/8           Roka         -1.594/54/14         0.00239/95/1         0.177/23/8           Roka         -1.591/54/14         0.0023	March11	-1.529369138	0.024346116	0.110161209
clas         -1.595/256         0.01291399         0.17712091           rponenyhrakik         -1.395/2566         0.0265/6591         0.0279/256           rponenyhrakik         -1.595/3566         0.0265/6591         0.0195/956           Nifb         -1.558/3566         0.0258/3591         0.1095/917           Nifb         -1.595/9566         0.0219/1591         0.0395/94           Zipaga         -1.5195/9576         0.00219/1591         0.0395/94           Ida         -1.5195/9576         0.00219/1591         0.1095/954           Ida         -1.5195/9576         0.00219/1591         0.1095/954           Ida         -1.5195/9577         0.00219/1591         0.1095/954           Ida         -1.5195/9577         0.00219/1591         0.1095/954           Ida         -1.5195/957         0.0195/9582         0.1195/851           Ida         -1.5195/957         0.0195/9582         0.1095/954           Immento         -1.5195/957         0.0195/9582         0.1097/9589           Immento         -1.5195/957         0.0195/958         0.077/9381           Immento         -1.5195/957         0.0195/958         0.077/9381           Immento         -1.5195/957         0.0195/958         0.0779/9	Gm5113	-1.529213668	0.004848662	0.105745966
Nakitri         1:55/2008         0.1072/2001           PromonyNLEM         1:25/20196         0.00266631         0.1072/2006           Rung         1:25/20196         0.00266631         0.1072/2006           Rung         1:25/20196         0.00266631         0.1072/2006           Rung         1:25/20166         0.0025/2019         0.1075/2016           Liph         1:25/0026668         0.00225/2019         0.1005/664           Data         1:25/0026668         0.00225/2019         0.1005/664           Lida         1:55/00279         0.0025/00279         0.1005/664           Data         1:55/00279         0.0025/0027         0.1119/848           Data         1:55/00279         0.0025/0027         0.1005/664           Data         1:55/00279         0.0025/0027         0.1119/848           Data         1:55/00279         0.0025/0027         0.1119/848           Data         1:55/00279         0.0025/0027         0.1119/848           Data         1:55/00279         0.0025/0027         0.1119/849           Data         1:55/00279         0.0025/0027         0.1119/849           Staces         1:55/00279         0.0025/0027         0.1119/9493           Staces	Ctlaza	-1.526925846	0.041629591	0.117112093
• Type         • Construction         • Construction           Non         • - Staty Stype         • Construction         • Construction           Nih         • - Staty Stype         • Construction         • Construction           Nih         • - Staty Stype         • Construction         • Construction           Zippes         • - Staty Stype         • Construction         • Construction           Zippes         • - Staty Stype         • Construction         • Construction           Idada         • - Staty Stype         • Construction         • Construction           System         • - Staty Stype         • Construction         • Construction           System         • - Staty Stype         • Construction         • Construction           System         • - Staty Stype         • Construction         • Construction         • Construction           System         • - Staty Stype         • Construction         • Construction         • Construction           System         • - Staty Stype         • Construction         • Construction         • Construction           System         • - Staty Stype         • Construction         • Construction         • Construction           System         • - Staty Stype         • Construction         • Construction         <	Nudtu	-1 526222686	0.012812200	0.107722281
phony name         131(2)50         00000000           Nils         132(2)50         00000000           Nils         132(2)50         01000000           Nils         132(2)50         01000000           Sign         131(2)10000         00000000           Janual         131(2)1000         00000000           Saca         131(2)10000         00000000           Janual         131(2)10000         00000000	1700010N12Rik	-1 524522000	0.002666821	0.107723201
amm	Rhma	-1 524228526	0.002400175	0.105745900
num         -1.5007/WT         0.00418/957         0.1105/94/7           Zipsys         -1.5109/566         0.002194133         0.1095/954           Ida         -1.5109/566         0.002194133         0.1095/954           Ida         -1.5109/566         0.002194133         0.1095/954           Bixoa         -1.5154/1746         0.002194133         0.1095/954           Sixoa         -1.5154/1747         0.002194133         0.1095/954           Bixoa         -1.5154/1747         0.002195/182         0.11852446           Pipparty         -1.5154/144         0.02129/181         0.1095/964           Fimmuy         -1.5154/144         0.02129/181         0.1077283           Stokes         -1.5154/144         0.02129/182         0.11712993           Tymb         -1.5154/144         0.02129/182         0.11712933           Tymb         -1.5154/144         0.02129/182         0.11712933           Stokes         -1.5154/144         0.02129/182         0.11712933           Tymb         -1.5154/144         0.02129/182         0.11712933           Stokes         -1.5154/144         0.0129/182         0.11712933           Stokes         -1.5154/144         0.0129/182         0.117121933	NEL	-1.524330520	0.002400175	0.105745900
Lipm         -1.5.907947         0.04213975         0.1059574           Zhyays         -1.5.9056608         0.02313913         0.1059594           Ida         -1.5.19056608         0.02313913         0.171284,8           Bhoa         -1.5.1905670         0.00559224         0.117284,8           Eboac         -1.5.1654973         0.02559224         0.115284,6           Eboac         -1.5.165497         0.02559224         0.1259594           Eboac         -1.5.165497         0.02559234         0.1259594           Eboac         -1.5.165497         0.023130185         0.0395944           Tmeminy         -1.5.165497         0.03926954         0.17723381           Sinkori         -1.5.195378         0.03926953         0.17973984           Sinkori         -1.5.1953954         0.041359492         0.171190493           Méã         -1.5.1953954         0.04135954         0.1372384           Sinkori         -1.5.1953954         0.04135954         0.171190493           Méã         -1.5.1953954         0.04135954         0.17723381           Sinkori         -1.5.935657         0.02735956         0.17723381           Chi         -1.5.935672         0.03568448         0.11723283		-1.522022831	0.025082835	0.110505417
Z/p395     15.1997/501     0.022119/74     0.3059/54       Ida     15.1917/501     0.022119/21     0.3059/54       Ida     15.1917/5967     0.026227/65     0.31797888.3       Shoat     15.1917/5967     0.02659/04     0.31959/54       Shoat     15.1917/5967     0.02659/24     0.31959/54       Shoat     15.1917/5967     0.02659/24     0.31959/54       Phparys     15.1916/912     0.02201570     0.03959/54       Tmeminy     15.1916/912     0.02201570     0.03959/54       Shoat     15.1916/912     0.02209/511     0.02299/51       Shoat     15.1916/912     0.02209/511     0.0229/513       Shoat     15.1916/912     0.02209/511     0.0229/513       Shoat     15.1917/518     0.0229/511     0.0219/516       Shoat     15.1916/512     0.0219/516     0.0171285       Stoat     15.1917/512     0.0219/516     0.0171285       Stoat     15.1917/512     0.0219/516     0.0179/515       Stoat     15.1917/512     0.0219/516     0.0179/515       Stoat     15.9917/512     0.0219/516     0.01917/515       Stoat     15.9917/512     0.0219/516     0.01917/515       Stoat     15.9917/512     0.0219/516     0.01917/516	Liph	-1.52070467	0.044438795	0.118749173
Tarkla         -1:5/1906/66/8         0.0.223/01/93         0.1.11/28/18           Ida         -1:5/1906/7         0.004/01/95         0.1.11/28/18           Phota         -1:5/1920/7         0.004/01/95         0.1.095/04           Shorts         -1:5/164/79         0.025/5522.4         0.145/544           Exosci         -1:5/164/79         0.025/5522.4         0.145/544           Demminy         -1:5/164/14         0.0221/39/18         0.025/5522.4           SixKost         -1:5/164/14         0.0221/39/18         0.025/5524           SixKost         -1:5/164/14         0.0221/39/18         0.017/120/31           SixKost         -1:5/165/14         0.0221/39/18         0.117/120/31           SixKost         -5:1/15/54/1         0.0242/39/56         0.117/120/31           SixKost         -5:1/15/54/1         0.0242/39/56         0.117/120/31           SixKost         -5:1/15/54/1         0.0242/39/56         0.117/120/31           SixKost         -5:1/15/54/1         0.0242/39/56         0.117/120/31           SixKost         -5:1/15/54/1         0.0272/55/66         0.117/120/31           SixKost         -5:1/15/52/27         0.02/15/54         0.1072/33/51           SixKost         -5:0/15/53/21 </td <td>Ztp595</td> <td>-1.519756301</td> <td>0.022119974</td> <td>0.10956964</td>	Ztp595	-1.519756301	0.022119974	0.10956964
Ida     1;3;18;396     0.08;22765     0.1377/88;4       Pbroa:     1.3;16;13;61     0.02(5):37     0.1070/88;3       \$9;3;3;3;16;18k     1.3;16;13;1     0.02(5):37     0.14;8;14;64       Pprars:     1.3;16;13;1     0.02(5):37     0.14;8;14;64       Piprars:     1.5;16;14;1     0.02(5):37     0.15;9;54       SixKon     1.5;16;14;1     0.02(5):57     0.13;723;8;1       Tumorni 9     1.5;16;14;1     0.02(5):57     0.13;723;8;1       SixKon     1.5;35;17     0.03(2):57:1     0.13;723;8;1       Tubb     1.5;35;17     0.03(2):67;13     0.13;723;8;1       SixKon     1.5;375;16     0.01(2):85:6     0.17;723;8;1       Cirk     1.5;375;17     0.03(2):65;1     0.17;723;8;1       Cirk     1.5;375;17     0.03(2):65;1     0.17;723;8;1       Cirk     1.5;375;17     0.03(2):65;1     0.17;723;8;1       OppryPNRik     1.5;972;10;10     0.037;13;6     0.107;13;6       OppryPNRik     1.5;973;10     0.03(2):65;1     0.107;13;6       OppryPNRik     1.5;973;10     0.03(2):65;1     0.107;13;6       Nirat     1.5;973;10     0.03(2):65;1     0.107;13;6       Nirat     1.5;973;10     0.03(2):65;1     0.107;13;16       Nirat     1.5;953;10	Tarsl2	-1.519696608	0.021504193	0.10956964
Broac         -1.517730/1         0.006401397         0.1009504           Syncy MM (MK)         -1.516546779         0.036559224         0.11095064           Exosci         -1.516546779         0.039559244         0.11095064           Themma 9         -1.5165481         0.023330181         0.10995064           Sixkossi         -1.5154444         0.023330181         0.10975281           Sixkossi         -1.51374177         0.039859751         0.109752851           Sixkossi         -1.5130641         0.01398062         0.117113093           Sixkossi         -1.5130591         0.01398052         0.117113093           Sixkossi         -1.5130591         0.01398052         0.10772381           McRa         -1.5130591         0.01398052         0.10772381           McRa         -1.510297153         0.013488418         0.117113093           Sixkossi         -1.510297153         0.013488418         0.11722381           McRa         -1.500524133         0.016716185         0.10772381           MrRa         -1.5005244         0.007310803         0.100751996           MrRa         -1.50056919         0.00281873         0.100751996           MrRa         -1.500569139         0.00281936	Id2	-1.518433086	0.029227683	0.11178848
spag.sphupBik         -1.516/92/91         0.0216/31/97         0.1148/534/64           Piparya         -1.516/44/14         0.02201579/9         0.1198/534/64           Sinkona         -1.515/44/14         0.0220/351/11         0.1097/64/64           Sinkona         -1.515/44/14         0.01220/311         0.1097/23/21           Sinkona         -1.515/44/14         0.01220/311         0.1097/23/21           Sinkona         -1.515/34/14         0.012/30/51         0.1097/23/21           Sinkona         -1.515/34/14         0.012/30/51         0.1097/23/21           Sinkona         -1.513/2006/4         0.0013/85/31         0.1097/23/21           Sinkona         -1.513/2006/4         0.0013/85/31         0.1197/23/21           Sinkona         -1.513/2007/2         0.0013/85/31         0.1097/23/21           Chi         -1.5002/23/13         0.002/16/85         0.1097/23/21           Pinka         -1.5003/24/24         0.002/16/84         0.1097/23/81           Oldephy         -1.5005/93/14         0.002/93/96         0.1097/23/81           Oldephy         -1.5005/93/14         0.002/93/96         0.1097/23/96           Oldephy         -1.5005/93/14         0.002/93/96         0.1007/93/96           Oldephy <td>Fbx02</td> <td>-1.517759637</td> <td>0.008420158</td> <td>0.107008823</td>	Fbx02	-1.517759637	0.008420158	0.107008823
Exosec.         -1.546546779         0.0365592.4.         0.13852466           Therm 9         -1.5464314         0.02135791         0.1095664           Sindeas         -1.5134444         0.021325131         0.10723281           Sindea         -1.51347748         0.02135791         0.1072351           Sindea         -1.51374177         0.00355751         0.1072353           Tphtb         -1.51376117         0.00315693         0.111712093           Side         -1.51376412         0.00315693         0.111712093           Side         -1.51376512         0.02138859         0.10723251           Ch         -1.510329715         0.03186418         0.117712093           GradysBorRik         -1.510329715         0.0318859         0.10727281           GradysBorRik         -1.500297413         0.01671615         0.10727281           GradysBorRik         -1.500386141         0.10973966         0.10973966           Tarpez         -1.50851939         0.02428674         0.10973966           Tarpez         -1.5085197         0.005054         0.10773281           Danda         -1.5005681         0.0024887         0.10773281           Danda         -1.5003668         0.0025187         0.10773281 <td>5830433M19Rik</td> <td>-1.516732501</td> <td>0.021631357</td> <td>0.10956964</td>	5830433M19Rik	-1.516732501	0.021631357	0.10956964
Pparse         -1.516/93141         0.0201579         0.10996/4           Sinkoss         -1.515/6444         0.012259311         0.109752381           Sinkoss         -1.515/6444         0.012259311         0.10772381           Sinkoss         -1.515/75147         0.005/85751         0.10772381           Sinkoss         -1.515/200684         0.001/8503         0.117912893           Sinkoss         -1.515/200684         0.001/8503         0.117912893           Sinkoss         -1.515/200684         0.001/8503         0.117912893           Sinkoss         -1.515/200684         0.001/8503         0.117912893           Mcfa         -1.515/20072         0.0021/8503         0.10772281           Cfh         -1.510202231         0.002954455         0.10772281           Denduda         -1.5003072         0.00295445         0.10772956           Thappe         -1.5003072         0.00286874         0.10975966           Thappe         -1.5003072         0.00286874         0.10975966           Nrin         -1.5003072         0.00286874         0.10975966           Nrin         -1.50306974         0.00286974         0.10975966           Nrin         -1.50305972         0.00285961         0.1077728	Exosc1	-1.516546779	0.036559224	0.114852466
Terminy         -15/60/28         0.0233/2181         0.0209/64           Sixdoxi         -15/54/644         0.012259311         0.1097/2381           Sixdoxi         -15/54/27908         0.0235751         0.1097/2381           Tprbb         -15/13/2717         0.00953751         0.1097/2381           Sixdoxi         -15/13/2717         0.00953751         0.1097/2381           Sixdoxi         -15/13/281         0.00953751         0.1097/2381           Sixdoxi         -15/13/281         0.00953751         0.1097/2381           Sixdoxi         -15/03/291         0.0095455         0.119/14/03           Kfa         -15/03/291         0.0095455         0.1097/2381           Gfb         -15/03/291         0.0095455         0.1097/2381           49/3497/NoRIK         -15/03/291         0.002485/24         0.10097/2485           Demda/a         -15/05/0592         0.002485/24         0.10097/2485           Tappez         -15/05/0597         0.0265/054         0.10097/2486           Nrma         -15/05/057         0.117/2391         0.1097/24966           Nrma         -15/05/057         0.114/254442         0.0016721           Dihgr         -15/05/056         0.002485/59         0.1097/2381<	Ppp2r5c	-1.516403124	0.022015579	0.10956964
SixKosi         -1.5554/44         000239311         0.0327938           SixKosi         -1.5544/44         001239311         0.0327938           SixKosi         -1.55427938         00320052         0.1372285           SixKosi         -1.553200584         0.04159692         0.17112093           SixKosi         -1.5530599         0.00138853         0.1119193           Mcfa         -1.5530599         0.01288899         0.01723281           Mcfa         -1.5530591         0.01288893         0.01772381           Mcfa         -1.5530591         0.01288893         0.01772381           GrapsBlop/Bikk         -1.55004231         0.009984855         0.01973948           Demdat         -1.5903584         0.0097144         0.10773281           Demdat         -1.5903584         0.0097144         0.10974948           Sixx         -1.5903584         0.0029748         0.10773281           Sixx         -1.5905954         0.00297498         0.10773281           Sixx         -1.5905957         0.00580263         0.10773281           Sixx         -1.5905977         0.00850451         0.10773281           Krip         -1.5903697         0.0057249         0.10974946           P	Tmem10	-1 5160528	0.021226181	0 10056064
anom         1054P444         00122951         0017952           Sincia         -151376117         0.00383751         0.10773281           Tprkb         -151395149         0.00383751         0.10774566           Sila         -151395149         0.00383751         0.10774566           Attention         -151005769         0.00915603         0.11319491           Mcfa         -151005775         0.034986418         0.13722955           Cfh         -1510039715         0.034986418         0.103974396           Vajjup7/No1Rik         -1590972413         0.00716155         0.10773281           Denndq         -1590972413         0.00716155         0.10791286           Denndq         -1590972413         0.007124537         0.10391413           Denndq         -159097341         0.007924956         0.10391413           Trappez         -15009534         0.002488574         0.10391413           Denndq         -159059387         0.00502498         0.10497442           Ublcp1         -150569387         0.00524948         0.103974956           Ublcp1         -150569387         0.016251217         0.10793381           Brond         -150059368         0.0024859811         0.01991435      <	Six60s1	-1 =1=46444	0.012250211	0.107722281
Anta         1-3347/360         0.034 X052         0.137/4293           Tprkb         1-337677         0.0353751         0.137/4293           Sig	Shoosi	1.5140444	0.012299311	0.1107/23201
IprAb       -1,5137917       0.003935731       0.105745969         Si4       -1,513053K4       0.014556422       0.11191493         2210012G02K1K       -1,513053K4       0.01435869       0.01772381         6720435607K1K       -1,51005971       0.01486819       0.01772381         6720435607K1K       -1,5002331       0.00958155       0.10772381         673147       -1,50023614       0.005745966       0.10772381         673147       -1,50023614       0.007710435       0.10772381         673147       -1,50023614       0.007710435       0.10772381         178070       -1,50025647       0.003704574       0.107974966         178070       -1,50050584       0.00370494       0.10774396         178070       -1,50050584       0.00370494       0.107749566         178070       -1,50050584       0.00451841       0.10774956         178070       -1,50050584       0.00450254       0.10774946         178071       -1,50036937       0.003602748       0.11475442         150169997       0.003627485       0.11475442       0.10772381         1010471       -1,50036937       0.10772381       0.10772381         1010471       1,50016733       0.00763956	5hca	-1.514277908	0.034200092	0.113/22583
Sl4       -1-5132005ki       0-117112093         Z210013C02Rkik       -1-513005ka       0-01772381         McTa       -1-510302231       0.00393455       0.10772381         Cfh       -1-510032231       0.00393455       0.10773381         Cfh       -1-5003757       0.00393455       0.10773281         Demd4       -1-50936474       0.007124353       0.10773281         Demd4       -1-50912677       0.00301104       0.105745966         Tarppcz       -556651393       0.00391854       0.109745966         Nm1       -1596513055       0.00318541       0.109745966         Alp5h       -1-50912677       0.00301054       0.109745966         Nm1       -159613085       0.00318541       0.109745966         Alp5h       -1-50912697       0.00301651247       0.10774584         Dblp1       -1-50912697       0.003024655       0.107745966         Alp5h       -1-501381108       0.004545959       0.10772381         Bbm3       -1-501381108       0.004545959       0.10772381         Dblp4       1-50012681       0.00457529       0.10772381         Bbm3       1-50012681       0.00475292       0.10772381         Dblp5054       0.007723	Тргкв	-1.51378117	0.003835751	0.105745966
2210012GodRk         -1;51903549         0.03013803         0.111914933           Mcfa         -1;51903540         0.01328809         0.01752351           Cfh         -1;510039715         0.034086148         0.11572253           Cfh         -1;510039715         0.0395455         0.107574565           Demd4a         -1;509286474         0.00712433         0.1059745966           Demd4a         -1;509286474         0.00724353         0.1059745966           Demd4a         -1;509286474         0.00291865         0.1059745966           Nimi         -1,5095393         0.00281854         0.100291433           Nimi         -1,5095395         0.003026144         0.109745966           Nimi         -1,50950387         0.003026144         0.109753081           Nimi         -1,50950387         0.003026145         0.109745966           Nimi         -1,50950387         0.00723481         0.109745966           Nimi         -1,50950387         0.00752381         0.109745966           Pickxi         -1,50050869         0.00757350         0.1175244           Borg         -1,5003668         0.003675895         0.10772381           Dinkc         1,500129907         0.0285951         0.10772381     <	St4	-1.513200684	0.041596492	0.117112093
Mfz         -15113691         0.01388909         0.10773281           Graugsför/Rik         -151032715         0.03406418         0.11372255           Ch         -1.51032715         0.03406418         0.11372255           Graugsför/Rik         -1.5002231         0.00398455         0.10773281           Mfza         -1.5002541         0.00710433         0.105743966           Denndat         -1.5002564         0.00248657         0.105743966           Tarppez         -1.5063554         0.00248657         0.105743966           Nrn         -1.50936919         0.0248657         0.105743966           AlpSh         -1.50936918         0.00249641         0.105743966           Nrn         -1.50936918         0.00249641         0.105743966           AlpSh         -1.50136108         0.00249641         0.10773281           Ublep1         -1.50136108         0.00248959         0.105743966           Drahc         -1.50136518         0.00248955         0.105743966           Cpb1         -1.50136108         0.00248959         0.105743966           Drahc         -1.50136681         0.00245491         0.10773281           Rbm3         -1.50136910         0.00245949         0.10773281	2210012G02Rik	-1.513053849	0.030136803	0.111919493
6/2342680781k         -15/0259715         0.03406418         0.113722851           Cfh         -15/002231         0.005984555         0.107742966           4933407N1R1kk         -15/0924911         0.007716485         0.107742966           Plka         -15/09246174         0.0071104333         0.105743966           Dennd4a         -15/09145072         0.00301054         0.105743966           Tappez         -15/0659584         0.00301059         0.107749866           Nrna         -15/0543956         0.003810867         0.107543966           Nrna         -15/0543958         0.003810867         0.107543966           Apph         -1.5/0543958         0.004810841         0.107543966           Nrna         -1.5/0545957         0.03607496         0.114754442           Bccip         -1.5/0545957         0.03607496         0.114754442           Bcdip         -1.5/0545961         0.00244655         0.016723281           Prokx         -1.5/0032668         0.003673969         0.114724442           Drahog         1.5/0032665         0.016773207         0.00773281           Prokx         1.5/0032668         0.016797496         0.11492405           Drahog         1.5/0145961         0.0167974966	Mcf2	-1.51130691	0.014388809	0.107723281
Ch         -1.510032231         0.00954555         0.109754506           P1ka         -1.509386474         0.007120453         0.109754966           P1ka         -1.509386793         0.02386574         0.103974193           Dennda         -1.509386793         0.02386574         0.1039741936           Styx         -1.50954939         0.02386574         0.1039745966           Nrm1         -1.505431085         0.004819641         0.109745966           Nrm1         -1.50545937         0.00302454         0.109745966           Lblp1         -1.50545937         0.00302543         0.109743966           Bcrip         -1.50054937         0.00392543         0.109743966           Dblp1         -1.50054937         0.00392634         0.10973284           Bcrip         -1.50012668         0.00244655         0.109743966           Prdx1         -1.50012668         0.004546990         0.10773284           Dnahc3         1.50045132         0.016975170         0.10773284           Sty2         1.50045132         0.0169751926         0.11711203           Dright652e         1.50145132         0.019751926         0.1171203           Dright652e         1.50145163         0.007713926         0.11771203	6720456B07Rik	-1.510259715	0.034086418	0.113722583
493347NonRik         -1.90924413         0.007f12453         0.10579194           Plka         -1.909126072         0.007112453         0.10571956           Trappca         -1.50851939         0.02486574         0.105745966           Nrn1         -5.9055935         0.00819541         0.105745966           Nrn1         -5.9055935         0.00819641         0.105745966           Alp5h         -1.50545937         0.00802234         0.1075745966           Alp5h         -1.505459187         0.00526396         0.114754442           BcCp         -1.50268219         0.016551117         0.107573081           Brbm3         -1.501981108         0.0024685         0.103745966           Prdx1         -50193907         0.008598911         0.109732381           Brbm3         -1.50145108         0.00454959         0.107732381           Drahc3         1.50025086         0.107733281         0.007733281           Cpb1         1.500245946         0.01071133         0.10773381           Ntsdc         1.50245945         0.00711396         0.10773381           Drabc1d652e         1.50045945         0.007713926         0.10773381           Ntsdc         1.50245981         0.00211592         0.10773381	Cfh	-1.510092231	0.005958455	0.105745966
Plka         -1.9938(47,4         0.007120453         0.106791498           Dennd4a         -1.59126072         0.00301014         0.105745966           Tarpcz         -1.50651939         0.0248657,4         0.10294143           Slyx         -1.5050554         0.003745966         0.107545966           Nrnt         -1.505125027         0.008302634         0.107545966           Alp5h         -1.505269379         0.005627498         0.114754442           Bcip         -1.502689319         0.016251217         0.1075435966           Bcip         -1.502689319         0.028895110         0.107545966           Bchm3         -1.5018108         0.00444655         0.107545966           Dnahc3         1.50017923         0.036851604         0.114939658           Cpb1         1.50024656         0.016737370         0.10773381           Shya         1.50014932         0.01675370         0.10773381           Ntsdc1         1.50149132         0.01675856         0.10773381           Ntsdc1         1.50149132         0.01675979         0.11712030           Hift         1.50245921         0.10773281         0.007713962         0.10773381           Ntsdc1         1.502359819         0.007113962	4933407N01Rik	-1.509729413	0.016716185	0.107723281
Demula         -1.5912672         0.003010194         0.103743966           Trappca         -1.5065551939         0.024886374         0.103743966           Nrn         -5.50635543         0.00301863         0.103743966           Mph         -1.505431085         0.008302634         0.10773256           Alp3h         -1.505459187         0.00523298         0.114754442           Bccip         -1.505459187         0.00244653         0.107732561           Bray         -1.50345108         0.00244653         0.107732561           Prdx1         -1.5030568         0.00244653         0.107732861           Dnahcs3         -1.5030565         0.016737207         0.10773281           Cpb1         1.50045914         0.00244653         0.10773281           Sty2         1.50045914         0.016737207         0.10773281           Sty2         1.50045914         0.016737207         0.10773281           Sty2         1.50045914         0.016737207         0.10773281           Sty2         1.50045914         0.00471592         0.10773281           Sty2         1.50045914         0.00471592         0.10773281           Sty2         1.5014591         0.0074719562         0.107723281	Plk2	-1.509286474	0.007120453	0.106791948
Trappez         -1.508651939         0.02488674         0.110391413           Styx         -1.50085584         0.002901863         0.105745966           Nrmt         -1.505431085         0.008302634         0.105745966           Alp3h         -1.505431085         0.008302634         0.107008823           Ublcp1         -1.50549309         0.095027498         0.114754442           Bkm3         -1.501981108         0.0024685         0.105745366           Prdx1         -1.50039907         0.02859811         0.10723281           Dnahcg         1.50016733         0.00653107         0.107723281           Dnahcg         1.50026156         0.01673707         0.107723281           Styz         1.50034940         0.0101733         0.107723281           Dnahcg         1.50045940         0.016737207         0.107723281           DigErd652e         1.501804132         0.04196956         0.10773281           DigErd652e         1.501804122         0.04196956         0.10773281           DigErd652e         1.50180412         0.00271592         0.10773281           Styz         1.50245910         0.00271592         0.10773281           Styz         1.503459491         0.02715926         0.11773284 </td <td>Dennd4a</td> <td>-1.509126072</td> <td>0.003010194</td> <td>0.105745966</td>	Dennd4a	-1.509126072	0.003010194	0.105745966
Styx     -1.5609354,1     0.003901863     0.105743966       Nrnt     -1.95132037     0.0082634     0.105743966       Mpph     -1.59153027     0.0082634     0.10774381       Bccip     -1.5085927     0.036027498     0.114754142       Bccip     -1.5085927     0.036027498     0.114754142       Bccip     -1.500369279     0.0024655     0.105743966       Pdxta     -1.50032668     0.00424655     0.105743966       Dnahc3     1.50015733     0.03693164     0.11493655       Cpb1     1.50025156     0.016737207     0.10773381       Ntsdc1     1.50015733     0.03693164     0.11493655       Othoryz381     0.00773381     0.00773381       Ntsdc1     1.50015731     0.0265955     0.10773381       Ntsdc1     1.50015732     0.04196526     0.117112093       Htfmt     1.5024581     0.004715492     0.10773381       D1g5trd652e     1.50174926     0.10773281     0.11732284       Gm6319     1.502759492     0.10773381     0.11732284       Gm641     1.59037633     0.0271505     0.11732284       Gm6429     1.59037633     0.02715305     0.11732284       Gm6491     1.59049414     0.016539445     0.10773381       Anxato <td>Тгаррса</td> <td>-1.508651939</td> <td>0.024886374</td> <td>0.110291413</td>	Тгаррса	-1.508651939	0.024886374	0.110291413
Nmi         -1.50431085         0.004819841         0.105745966           Atp5h         -1.505415027         0.008302634         0.107008823           Lblkpi         -1.50569387         0.016251217         0.107008823           Bccip         -1.502689219         0.016251217         0.10773381           Bkm3         -1.5019907         0.00244685         0.103745966           Prdxt         -1.50032668         0.00244685         0.1037435966           Dnahc3         1.50015723         0.03683164         0.11492658           Cpb1         1.50025156         0.016737207         0.00773281           Dnahc3         0.10773281         0.01773281         0.01773281           Sty2         1.500454946         0.01011183         0.10773281           DisBrd652e         1.501841122         0.04169536         0.117112093           Hift         1.50236891         0.004715492         0.105743966           Gm6219         1.50245471         0.0270279         0.1173284           Gm6219         1.50257819         0.00711962         0.106791494           Igsf1         1.50245984         0.03643638         0.1173284           Gm6219         1.50245984         0.03643638         0.1173284	Styx	-1.506095584	0.002901863	0.105745966
Anax         1.5933203         0.004979,04.1         0.10574390           Abpsh         1.59515027         0.0630264         0.17078381           Ublop1         1.59569987         0.05627498         0.11475444           Bccip         -1.502689219         0.016251217         0.10773381           Bhm3         -1.5003668         0.0024985         0.003549566           Prdx1         -1.5003668         0.004249899         0.105745966           Dnahc5         1.50016723         0.036583164         0.114929658           Cpb1         1.50026156         0.016737207         0.10773381           Ntsdc1         1.500459446         0.01499526         0.10773381           DryErtd652e         1.50143668         0.006769855         0.010773381           DryErtd652e         1.50143068         0.0027990         0.11732284           Gm6219         1.50242711         0.020719362         0.106791948           Igsf1         1.502779492         0.0109487         0.10773381           Introb         1.502359819         0.0271505         0.11752284           Gm6219         1.50245844         0.03643658         0.11773284           Gm6219         1.504568718         0.02755261         0.1175781817 </td <td>Nrn1</td> <td>-1 505421085</td> <td>0.004810841</td> <td>0.105745066</td>	Nrn1	-1 505421085	0.004810841	0.105745066
Artipsi         1-595(12502)         0.00502344         0.10700023           Becip         1-595(69397)         0.05622498         0.114754442           Becip         1-502689219         0.01651217         0.10773281           Rbm3         1-50109907         0.02859811         0.109349143           Ephx4         1-50109907         0.02859811         0.109349143           Dnahc3         1.50016723         0.036831604         0.114920658           Cpb1         1.50045166         0.016737207         0.107723281           Sty2         1.50045166         0.016737207         0.107723281           Nt5dc1         1.50143668         0.01466526         0.117712093           Hrifnt         1.50246281         0.002715492         0.007723281           Nt5dc1         1.50242731         0.027302579         0.11773284           Gm6219         1.502479492         0.01094927         0.10773281           1110018H23Rik         1.5036601         0.02267987         0.10773281           1110018H23Rik         1.504499194         0.02627987         0.10773281           1110018H23Rik         1.50494124         0.005749396         0.11773284           Gm9891         1.5044499194         0.02657555         0.1	Atash	1.505491009	0.008202624	0.107008822
Outp1         -1.505/093/97         0.03002/493         0.114/954442           Becip         -1.5028/89219         0.016251217         0.10773381           Rbm3         -1.5010981108         0.0024/685         0.105743966           Prdx1         -1.50109907         0.020859811         0.109732966           Dnahc3         1.50016723         0.036831604         0.114929658           Cpb1         1.50026156         0.016737207         0.10773381           Nt5dc1         1.5001494946         0.01011183         0.10773381           Nt5dc1         1.501494368         0.018676895         0.10773381           Nt5dc1         1.501494368         0.018676895         0.107733281           Nt5dc1         1.502362891         0.004715492         0.10773281           DrigFtrdf5ze         1.502442731         0.027302579         0.11773284           Gm6219         1.50279492         0.010904827         0.1009743981           Igsf1         1.50376935         0.01173284         0.0105745966           Gm6219         1.50245784         0.0275305         0.1173284           Gm6219         1.50449394         0.016539445         0.10773381           Arxa10         1.503769383         0.0275305         0.111	Thlend	-1.505125027	0.000302034	0.10/000023
bccp         -1.50289219         0.01052127         0.10773281           Rbm3         -1.50193907         0.0024/685         0.103745966           Prdx1         -1.50032668         0.004349999         0.103745966           Dnahc3         1.50016723         0.03681604         0.114929658           Cpb1         1.50025615         0.016737207         0.107733281           Sky2         1.500454946         0.01011183         0.107733281           Nt5dc1         1.500454946         0.01011183         0.107733281           Sky2         1.500454946         0.01011183         0.107733281           Nt5dc1         1.50149568         0.0167526         0.117112093           Hifnt         1.502412731         0.02732579         0.117112093           Gmd219         1.502412731         0.02732579         0.11712093           Igsf1         1.502412731         0.0272579         0.1171203           Igsf1         1.502473942         0.10974964         0.10773381           Igsf1         1.50247394         0.0094827         0.10773381           Igsf1         1.50249794         0.10954564         0.11732284           Gmd219         1.50425784         0.02755561         0.111732284		-1.505089387	0.03002/498	0.114754442
kbm3         -1.501981108         0.0024895         0.105745966           Prdx1         -1.50199907         0.20859811         0.105745966           Ephx4         -1.50032668         0.004548999         0.105745966           Dnahc5         1.50016723         0.036831604         0.114929658           Cpb1         1.500250156         0.0167737207         0.107723281           Ssty2         1.50045668         0.01011183         0.107723281           D19Ertd652e         1.50149568         0.01695956         0.107723281           D19Ertd652e         1.501804132         0.041969526         0.107723281           Gm6219         1.50242731         0.027302579         0.11713203           Hint         1.502375819         0.004715492         0.10079348           Gm6219         1.50253519         0.002710362         0.10079348           Itio018H23Rik         1.5025791         0.11732284         0.002712381           1110018H23Rik         1.5025751         0.111732284         0.007723281           1110018H23Rik         1.504269134         0.02752505         0.111732284           Olfrigg         1.504245914         0.02752505         0.111732284           Olfrigg         1.504459142         0.007573966 <td>BCCIP</td> <td>-1.502689219</td> <td>0.016251217</td> <td>0.107723281</td>	BCCIP	-1.502689219	0.016251217	0.107723281
rrtxt         -1.50039907         0.02859811         0.109349143           Ephx4         -1.50032668         0.004548999         0.105745966           Dnahc3         1.50016723         0.036831604         0.114929658           Cpb1         1.50045946         0.01183         0.107723281           Sky2         1.50045946         0.01187         0.107723281           D1yErtd652e         1.501804132         0.041969526         0.1177112093           H1fnt         1.502356891         0.007119362         0.105745966           Gm6219         1.502355819         0.007119362         0.107723281           Igsf1         1.5024779492         0.007119362         0.107723281           Intol8H23Rik         1.50235819         0.007119362         0.107723281           Intol8H23Rik         1.5023769383         0.02715305         0.107723281           Intol8H23Rik         1.503766491         0.02627987         0.10956964           Anxato         1.503769383         0.02715305         0.11173284           Gm9891         1.50439714         0.005749366         0.117723281           Gm9891         1.504597365         0.0216539445         0.107723281           Gm7112         1.504597365         0.002715305	KDM3	-1.501981108	0.00244685	0.105745966
Ephx4         -1.50032668         0.004543999         0.105745966           Dnahc3         1.50016723         0.036831604         0.114929658           Cpb1         1.500226156         0.016737207         0.107723281           Ssty2         1.500454946         0.01011183         0.107723281           Nt5dc1         1.50149658         0.041969526         0.11712093           D19Ertd652e         1.50149618         0.004715492         0.105745966           Gm9961         1.502424731         0.027302579         0.11732284           Gm6219         1.502553819         0.001904827         0.106791348           Igsf1         1.50279492         0.010904827         0.107723281           Anxato         1.503769383         0.02715305         0.11732284           Gm9931         1.504255884         0.03653945         0.107723281           Gm9831         1.50425584         0.03653945         0.11732284           Olfr157         1.50449914         0.016539455         0.11773281           Tgm4         1.50449914         0.005740396         0.105745966           Olfr157         1.50495755         0.21615993         0.105745966           Tbx         1.50687525         0.021615993         0.105765464 </td <td>Prdx1</td> <td>-1.501099907</td> <td>0.020859811</td> <td>0.109349143</td>	Prdx1	-1.501099907	0.020859811	0.109349143
Dnahcy         1.50016733         0.036831604         0.114929658           Cpb1         1.500261156         0.01011183         0.107723281           Nt5dc1         1.500449466         0.01011183         0.107723281           D19ErtId552e         1.50149368         0.041969526         0.117712093           H1fnt         1.502428911         0.02730279         0.11792284           Gm6219         1.502442731         0.02730279         0.11792284           Gm6219         1.502779492         0.01094827         0.107723281           1110018H23Rik         1.502796983         0.022627987         0.107723284           Gm9891         1.502379983         0.022627987         0.10723284           Gm9891         1.502379983         0.022627987         0.10723284           Gm9891         1.5045584         0.038643638         0.1173284           Gm9891         1.50456718         0.0275551         0.111732284           Olfr157         1.504944204         0.005743966         0.105745966           Thza         1.50651322         0.039012757         0.115781817           Gm7112         1.50675265         0.016159393         0.10954966           Vmn2r22         1.508753028         0.008314445         0.	Ephx4	-1.50032668	0.004548999	0.105745966
Cpb1         1.500226156         0.016737207         0.107723281           Sty2         1.500454946         0.011183         0.107723281           Nt5dcr         1.501496368         0.018676895         0.107723281           DigErtId652e         1.50184132         0.041969526         0.117112033           Hifnt         1.50242731         0.0027302579         0.11732284           Gm6219         1.502759492         0.10094827         0.107723281           IntoristRig         1.502779492         0.01094827         0.107723281           IntoristRig         1.502779492         0.01094827         0.107723281           IntoristRig         1.502779492         0.01094827         0.107723281           IntoristRig         1.502759493         0.022627987         0.10956964           Anxato         1.503769383         0.02715305         0.111732284           Gm9891         1.504499194         0.016539445         0.107723281           Acsa3         1.504568718         0.02755261         0.111732284           Olfr177         1.504949194         0.005740396         0.109745966           Tk2         1.50675265         0.0215993         0.109545966           Olfr177         1.506875265         0.02215993	Dnahc3	1.50016723	0.036831604	0.114929658
Ssty2         1.500454946         0.01011183         0.107723281           Nt5dc1         1.501436568         0.018676895         0.107723281           D19Ertd652e         1.501804132         0.0041969526         0.107713284           Gmog61         1.50242891         0.004715492         0.105745966           Gm6219         1.502753819         0.007119362         0.106791948           Igsf1         1.502366401         0.022627987         0.1095664           Anxato         1.50366401         0.022627987         0.1095664           Gmog81         1.503769383         0.02715305         0.11732284           Gm9891         1.504255884         0.038643638         0.115781817           Tgm4         1.504366718         0.02755261         0.11732284           Olfr157         1.504946204         0.03740396         0.107723281           Olfr157         1.504496194         0.016539445         0.107723281           Olfr157         1.504966718         0.02755261         0.11732284           Olfr157         1.506875265         0.021615993         0.105745966           Thz         1.506875265         0.021615993         0.105745966           Ofm122         1.508753028         0.008314445         0.	Cpb1	1.500226156	0.016737207	0.107723281
Nt5dc1         1.501436368         0.018676895         0.107723281           DigErtd652e         1.501804132         0.041969526         0.117112093           Hifnt         1.502362891         0.004715492         0.105745966           Gm9961         1.5024242731         0.027302579         0.11173284           Gm6210         1.50253819         0.007119362         0.106743281           Intori8H23Rik         1.502376933         0.022627987         0.10956964           Anxato         1.503769383         0.022715305         0.11732284           Gm6291         1.504499194         0.016539445         0.107723281           Timori8H23Rik         1.50499194         0.016539445         0.107723281           Gm9891         1.504499194         0.016539445         0.107723281           Tgm4         1.504949194         0.016539445         0.107723281           Olfrify7         1.504949140         0.005740396         0.10773284           Olfrify7         1.50494804         0.005740396         0.107545966           Olfrify7         1.506875265         0.021615993         0.105745966           Thx2         1.5068753028         0.002312487         0.105745966           Vmn222         1.508753028         0.025	Ssty2	1.500454946	0.01011183	0.107723281
DigErtd652e         1.501804132         0.041969526         0.117112093           Hifnt         1.502562891         0.004715492         0.105745966           Gm9961         1.502442731         0.027302579         0.111732284           Gm6219         1.502579492         0.010904827         0.109759281           1110018H23Rik         1.50279492         0.010904827         0.10956964           Anxato         1.503769383         0.02715305         0.111732284           Gm9891         1.50459584         0.038643638         0.115781817           Tgm4         1.504499194         0.016539445         0.107723281           Acss3         1.50456718         0.02755261         0.111732284           Ollfr157         1.50456718         0.02755261         0.111732284           Ollfr157         1.504941204         0.005749396         0.105745966           Tlx2         1.50651322         0.039012757         0.115781817           Gm7112         1.50857265         0.021615993         0.1095745966           Vmar222         1.508753028         0.008314445         0.105745966           Vmar24         1.50875025         0.02302487         0.105745966           Vmar25         1.508951741         0.026642406	Nt5dc1	1.501436368	0.018676895	0.107723281
Hifnt         1.502362891         0.004715492         0.105745966           Gm9961         1.502442731         0.027302579         0.111732284           Gm6219         1.502553819         0.007119362         0.106791948           Igsf1         1.502779492         0.010904827         0.107723281           1110018H23Rik         1.503366401         0.022627987         0.1095694           Anxa10         1.503769383         0.02715305         0.111732284           Gm9591         1.50425584         0.038643638         0.115781817           Tgm4         1.5043584         0.038643638         0.11732284           Olfr157         1.504568718         0.0275261         0.11732284           Olfr157         1.504944204         0.005740396         0.105745966           Tlx2         1.50685122         0.039012757         0.115781817           Gm7112         1.50685265         0.02151993         0.1095745966           Vmm2r22         1.5085205         0.0212487         0.105745966           Vmm2r23         1.5087505         0.002312487         0.105745966           Gmr414         1.509317859         0.002312487         0.105745966           Vmm2r22         1.508951741         0.026642406         0.1	D19Ertd652e	1.501804132	0.041969526	0.117112093
Gmg961         1.502442731         0.027302579         0.111732284           Gm6219         1.502452731         0.027302579         0.107723281           Inton18H23Rik         1.502779492         0.010904827         0.107723281           1110018H23Rik         1.503769383         0.02715305         0.111732284           Gm9801         1.503769383         0.02715305         0.111732284           Gm9801         1.504491914         0.01539445         0.107723281           Arxato         1.50491914         0.015539445         0.107723281           Acss3         1.504568718         0.02755261         0.111732284           Olfr157         1.504944204         0.005740396         0.105745966           Tlx2         1.50651322         0.039012757         0.115781817           Gm7112         1.50875265         0.0215293         0.10956964           Gper         1.50875026         0.002312487         0.105745966           Vmm2r22         1.50875028         0.008314445         0.10708823           Gm10883         1.50345953         0.025058454         0.11072882           Gnpda1         1.50345955         0.037375221         0.115780202           Lok         1.510346953         0.025084544 <t< td=""><td>H1fnt</td><td>1.502362891</td><td>0.004715492</td><td>0.105745966</td></t<>	H1fnt	1.502362891	0.004715492	0.105745966
Gm6219         1.502553819         0.007119362         0.106791948           Igsf1         1.502553819         0.007119362         0.106791948           Igsf1         1.50279492         0.010904827         0.107723281           1110018H23Rik         1.503769383         0.02715305         0.111732284           Gm9801         1.504255884         0.038643638         0.117732281           Gm9801         1.504255884         0.02755261         0.117732281           Acss3         1.504568718         0.02755261         0.117732284           Olfr157         1.50494204         0.005740396         0.105745966           Tlx2         1.506875265         0.021615993         0.10956964           Gm7112         1.506875265         0.021615993         0.105745966           Tlx2         1.508675265         0.021615993         0.10956964           Gper         1.508575028         0.002312487         0.105745966           Vmn2r22         1.50875028         0.002312487         0.107008823           Gmpda1         1.509317859         0.02505454         0.11072282           Gnpda1         1.50346953         0.025058454         0.110291413           Gvin1         1.510489055         0.037375221         0.1	Gm9961	1.502442731	0.027302579	0.111732284
Interpret         Interpret         Interpret           Igsfi         1.502779492         0.010904827         0.107723281           1110018H23Rik         1.503769383         0.022627987         0.10956964           Anxato         1.503769383         0.02715305         0.111732284           Gm9891         1.504255884         0.038643638         0.11773281           Tgm4         1.504499194         0.016539445         0.107723281           Acss3         1.504568718         0.02755261         0.11732284           Olfr157         1.50494204         0.005749396         0.105743966           Tlx2         1.50651322         0.039012757         0.115781817           Gm7112         1.50687565         0.02151993         0.10956964           Gper         1.50840679         0.002312487         0.105745966           Vmn2r22         1.508753028         0.008314445         0.107008823           Gmpda1         1.509317859         0.035025006         0.113799868           Lck         1.510346953         0.02508454         0.110291413           Gvin1         1.510483055         0.037375221         0.15180202           LOC100041256         1.51085627         0.018154611         0.10723281 <td>Gm6219</td> <td>1.502553819</td> <td>0.007119362</td> <td>0.106791948</td>	Gm6219	1.502553819	0.007119362	0.106791948
The second sec	løsfi	1.502779492	0.010904827	0.107723281
Anxato         1.59539424         0.0220/997         0.1095994           Anxato         1.503769383         0.02715305         0.111732284           Gmg891         1.504255884         0.038643638         0.115781817           Tgm4         1.504499194         0.016539445         0.107723281           Acss3         1.504568718         0.0275261         0.111732284           Olfr157         1.504944204         0.005740396         0.105745966           Tlx2         1.50685265         0.021615993         0.1095745966           Gper         1.50855265         0.021615993         0.1095745966           Gper         1.50857265         0.002312487         0.1095745966           Vmm2r22         1.50875028         0.00331445         0.107008823           Gm10883         1.509317859         0.035025006         0.113799868           Lck         1.510346953         0.02508454         0.110291413           Gvin1         1.510483055         0.037375221         0.15180202           LOC100041256         1.51085627         0.018154611         0.10773281	1110018H22Rik	1 502266401	0.022627087	0 10056064
Instato         1.503/05/05         0.02/15305         0.111/32204           Gm9891         1.50425584         0.038643638         0.115781817           Tgm4         1.504499194         0.01539445         0.107723281           Acss3         1.50456718         0.02755261         0.111732284           Olfr157         1.504944204         0.005740396         0.105745966           Tlx2         1.50651322         0.039012757         0.115781817           Gm7112         1.50857265         0.02165993         0.10956964           Gper         1.50875028         0.008314445         0.10708823           Gm10883         1.50891741         0.026642406         0.11107282           Gnpda1         1.50346953         0.035025006         0.113799868           Lck         1.510346953         0.025058454         0.110291413           Gvin1         1.510483055         0.037375221         0.1518202           LOC100041256         1.51085627         0.037375221         0.15180202	Anyato	1 =02760282	0.02715205	0 111722284
Onsola         1-50425004         0.030043050         0.115701017           Tgm4         1.504499194         0.016539445         0.107723281           Acss3         1.504568718         0.02755261         0.11732284           Olfr157         1.50494204         0.005740396         0.105745966           Tlx2         1.50651322         0.039012757         0.115781817           Gm7112         1.506875265         0.021615993         0.105745966           Vmn2r22         1.508575028         0.008314445         0.105745966           Gmt0883         1.508951741         0.026642406         0.111072282           Gnpda1         1.5034953         0.035025006         0.113799868           Lck         1.510346953         0.025058454         0.110221413           Gvin1         1.510483055         0.037375221         0.1518202           LOC100041256         1.51085627         0.018154611         0.10723281	Gmo8o1	1 504255884	0.02/13303	0.1117/32204
1 giriq       1.504499194       0.010539445       0.107723281         Acss3       1.504568718       0.02755261       0.111732284         Olfr157       1.50494204       0.005740396       0.105745966         Tlx2       1.50657322       0.039012757       0.115781817         Gm7112       1.506875265       0.0231615993       0.10956964         Gper       1.50875028       0.003312487       0.105745966         Vmn2r22       1.508753028       0.003314445       0.107008823         Gmpda1       1.509317859       0.035025006       0.113799868         Lck       1.510346953       0.02508454       0.110291413         Gvin1       1.510483055       0.037375221       0.1518202         LOC100041256       1.51085627       0.018154611       0.10772381	Ciiig091	1.304255004	0.030043030	0.115/0101/
Acss3         1.504508718         0.02755261         0.111732284           Olfr157         1.50494204         0.005749396         0.105745966           Tlx2         1.50651322         0.039012757         0.115781817           Gm7112         1.50687565         0.02312487         0.10956964           Gper         1.508753028         0.003312487         0.107745966           Vmn2r22         1.508753028         0.00331445         0.107008823           Gmpda1         1.509317859         0.035025006         0.113799868           Lck         1.510346953         0.025058454         0.110291413           Gvin1         1.510483055         0.037375221         0.15180202           LOC100041256         1.51085627         0.018154611         0.10702881	1 gm4	1.504499194	0.016539445	0.10//23281
Ultris7         1.504944204         0.005740396         0.105745966           Tlx2         1.50651322         0.039012757         0.115781817           Gm7112         1.506855265         0.021615993         0.10956964           Gper         1.50875055         0.002312487         0.105745966           Vmnzr22         1.50875028         0.008314445         0.107008823           Gm10883         1.508951741         0.026642406         0.111072282           Gnpda1         1.50346953         0.025058454         0.110291413           Gvin1         1.510483055         0.037375221         0.115180202           LOC 100041256         1.51085627         0.018154611         0.10702881	Acss3	1.504568718	0.02755261	0.111732284
Thz         1.50651322         0.039012757         0.115781817           Gm7112         1.506875265         0.02165993         0.10956964           Gper         1.508240679         0.002312487         0.105745966           Vmn2r22         1.508753028         0.008314445         0.107008823           Gm10883         1.509317859         0.035025006         0.111072282           Gnpda1         1.50347653         0.025058454         0.110291413           Gvin1         1.510483055         0.037375221         0.115180202           LOC 100041256         1.510856527         0.018154611         0.10702881	Oltr157	1.504944204	0.005740396	0.105745966
Gm7112         1.506875265         0.021615993         0.10956964           Gper         1.508240679         0.002312487         0.105745966           Vmn2r22         1.508753028         0.008314445         0.107008823           Gm10883         1.508951741         0.026642406         0.111072282           Gnpda1         1.509317859         0.035025006         0.113799868           Lck         1.510346953         0.025058454         0.110291413           Gvin1         1.510483055         0.037375221         0.15180202           LOC100041256         1.510856277         0.018154611         0.107723281	Tlx2	1.50651322	0.039012757	0.115781817
Gper         1.508240679         0.002312487         0.105745966           Vmn2r22         1.508753028         0.008314445         0.107008823           Gm10883         1.508951741         0.026642406         0.111072282           Gnpda1         1.509317859         0.035025006         0.113799868           Lck         1.510346953         0.025058454         0.110291413           Gvin1         1.510483055         0.037375221         0.15180202           LOC100041256         1.510856277         0.018154611         0.10772381	Gm7112	1.506875265	0.021615993	0.10956964
Vmn2r22         1.508753028         0.008314445         0.107008823           Gm10883         1.508951741         0.026642406         0.111072282           Gnpda1         1.509317859         0.035025006         0.113799868           Lck         1.510346953         0.025058454         0.110291413           Gvin1         1.510483055         0.037375221         0.115180202           LOC100041256         1.510856527         0.018154611         0.107723281	Gper	1.508240679	0.002312487	0.105745966
Gm10883         1.508951741         0.026642406         0.11072282           Gnpda1         1.509317859         0.035025006         0.113799868           Lck         1.510346953         0.025058454         0.110291413           Gvin1         1.510483055         0.037375221         0.115180202           LOC100041256         1.510856527         0.018154611         0.107723281	Vmn2r22	1.508753028	0.008314445	0.107008823
Gnpda1         1.509317859         0.035025006         0.113799868           Lck         1.510346953         0.025058454         0.110291413           Gvin1         1.510483055         0.037375221         0.115180202           LOC100041256         1.510856527         0.018154611         0.107723281	Gm10883	1.508951741	0.026642406	0.111072282
Lck         1.510346953         0.025058454         0.110291413           Gvin1         1.510483055         0.037375221         0.115180202           LOC100041256         1.510856527         0.018154611         0.107723281	Gnpda1	1.509317859	0.035025006	0.113799868
Gvin1         1.510483055         0.037375221         0.115180202           LOC100041256         1.510856527         0.018154611         0.107723281	Lck	1.510346953	0.025058454	0.110291413
LOC100041256         1.510856527         0.018154611         0.107723281	Gvin1	1.510483055	0.037375221	0.115180202
Continued on part asso	LOC100041256	1.510856527	0.018154611	0.107723281
		J-~~J-		Continued on next page

Table 6.2 – continued from previo	ous page		
Assignment	fc	pv	qv
Scd4	1.510929836	0.000260222	0.101410316
LOC382133	1.511638673	0.004771573	0.105745966
Gm8780	1.511701542	0.023846022	0.110058377
Thefir	1 511054002	0.040741112	0.116858776
F 1	1.5119/4002	0.040/41112	0.110050770
Fsd2	1.512267477	0.049386388	0.120564663
Wfdc15b	1.513141249	0.011827764	0.107723281
Pla2g2d	1.513392989	0.019476121	0.108210826
Svcp1	1.51/127/7	0.008983301	0.107600372
Olfrigo	1 515082828	0.008104267	0.107008833
011129	1.515082828	0.000194207	0.10/000823
Aldh3b2	1.516157889	0.010035598	0.107723281
Olfr156	1.51652926	0.012222092	0.107723281
Iqcf1	1.516662415	0.034733848	0.113740124
Gm6280	1 517577206	0.008084406	0.107008823
Eame	1.91/9//290	0.000004400	0.407000023
Fami8ia	1.518029682	0.013977435	0.107723281
Txlnb	1.519233195	0.021743322	0.10956964
Gsc	1.519872181	0.016979061	0.107723281
Casp1	1.521273975	0.015807825	0.107723281
Cappio	1 524465222	0.015156888	0.107722281
Capillo	1.524405323	0.015170888	0.10//23281
1ry4	1.525525892	0.020950188	0.109360201
Clca6	1.525783218	0.009220906	0.107600372
Bace2	1.525973597	0.042447478	0.117395681
Gmouos	1 526206745	0.00701645	0.10662028=
Catro	1.920390/45	0.00/01045	0.1000.30203
35ty2	1.527801027	0.00668459	0.105745900
Neb	1.527843388	0.00117393	0.105745966
Gm7455	1.528171719	0.008054475	0.107008823
Olfr875	1.528397709	0.034141174	0.113722583
Tafasta	1.920397709	0.034141174	0.1113/22303
	1.520574200	0.0304132/	0.111930//0
Colioai	1.529217201	0.031673294	0.112100718
Gm9198	1.529471616	0.021076947	0.1095063
Gm10863	1.529959362	0.008695036	0.107600372
100625002	1 52042212	0.040105502	0.116562227
E0C035992	1.53043312	0.040195503	0.11050322/
BC028471	1.530998992	0.010155286	0.107723281
Phldb3	1.531193559	0.018349155	0.107723281
Myo18b	1.531409381	0.029182837	0.11178848
Mrgpra6	1.532276512	0.04921693	0.120446832
Tradcala	1 522225600	0.0052522.00	0.107008922
11pu5213	1.533225009	0.007353349	0.10/000823
1128b	1.533572813	0.04819322	0.120254373
Cd96	1.533664942	0.01476872	0.107723281
Serpine3	1.533909464	0.008654149	0.107600372
Eva	1 53466454	0.004240565	0.105745966
1500025HotPik	1 525 4661 06	0.044621054	0.1188-0184
170002511011KIK	1.535400100	0.044031074	0.118653184
Mia1	1.536016095	0.035992784	0.114754442
Il2orb	1.53627519	0.035961668	0.114754442
Asb10	1.537034982	0.010671635	0.107723281
Gm2524	1 528420615	0.007346535	0.107008823
Vario		0.007,540,555	0.107000025
V 1119	1.530449051	0.003/81981	0.105/45966
Ssty2	1.53974346	0.007896418	0.107008823
Vmn2r9	1.542043361	0.009675699	0.107723281
Prtna	1.542228642	0.009293127	0.107723281
Olfricon	1.542522280	0.007008767	0.111700084
0111034	1.543722309	0.027238705	0.111732284
r tger2	1.545078352	4.99E-05	0.051083022
Fam183b	1.545717494	0.025976152	0.110694341
Ssty2	1.546006802	0.012650682	0.107723281
LOC100134980	1.547725905	0.00238/13/	0.105745966
Gm10008	1 = 478=4647	0.005245201	0.105745066
Cm (% )		0.005245391	0.103/43900
G114814	1.548816972	0.028922704	0.11178848
1700007I08Rik	1.549028119	0.012227636	0.107723281
Trim8	1.549973267	0.012401341	0.107723281
Ooep	1.550252626	0.013686233	0.107723281
Dmkn	1 5505 42782	0.028105405	0.111722284
Colum	1.550542703	0.020195490	0.111/32204
Ssty2	1.550961993	0.006116264	0.105745966
Gm10751	1.551008579	0.044212592	0.118683725
Olfr350	1.552848051	0.031172925	0.111930776
Dub2a	1.552000046	0.010372072	0.107723281
Defba	1 == 2888= -	0.00000000000	0.105745066
	1.553000074	0.0057/45/1	0.105745900
Hormadi	1.554815433	0.006273066	0.105745966
Zfp42	1.55628901	0.006131402	0.105745966
Gm10787	1.556447233	0.006364826	0.105745966
Oit3	1.557458081	0.047006735	0.119837811
Arzoorthus Pil	1 == 9-6==6=	0.047096733	0.1108-2202
	1.550305105	0.04/230035	0.119052203
Oltr113	1.559031416	0.017323599	0.107723281
Gm10421	1.559161098	0.000534002	0.105745966
Prrg4	1.561471964	0.003614507	0.105745966
Gm414	1 =6=8=4020	0.00402007	0.105745066
011414 A	1.505054323	0.00492997	0.105/45900
Acrv1	1.567512195	0.045219369	0.119147006
Dao	1.56791788	0.003992695	0.105745966
Itln1	1.568530229	0.003557167	0.105745966
Cyp2w1	1.571512049	0.046244957	0.119506979
71	J/ J+/	1.	Continued on new eres
			Continued on next bag

Table 6.2 – continued from previous page

Fpl	Assignment	fc	pv	qv
inc;ispacialispacialispacialincerting:space:space:spaceincerting:space:space:spaceintering:space:space	Fgl1	1.572122169	0.0084568	0.107111315
Lenk	Lrrc25	1.57302689	0.008288377	0.107008823
construction         construction         construction           Call         1.559541491         construction         construction           Call         1.559541491         construction         construction           Call         1.559541491         construction         construction           Call         1.559541491         construction         construction           Call         1.55954591         construction         construction           Call         1.55954591         construction         construction           Call         1.55954592         construction         construction           Call         1.55954592         construction         construction           Call         1.55954592         construction         construction         construction           Call         1.55954593         construction         construction         construction           Call         1.55954593         construction         construction         construction           Call         1.55954593         construction         construction         construction           Construction         1.55954593         construction         construction         construction           Construction         1.55954593         construction	Leeth	1 573270472	0.022872066	0 110058277
Construction         Construction         Construction           Cal         1.5559293         0.0000000         0.0000000           Cal         1.5550293         0.0000000         0.0000000           Diltring         1.5550293         0.0000000         0.0000000           Badi         1.55502936         0.0000000         0.000000           Diversion         1.55502936         0.0000000         0.000000           Construction         1.55502936         0.000000         0.000000           Construction         1.55502936         0.000000         0.000000           Construction         1.55502937         0.0000000         0.0000000           Construction         1.55502937         0.0000000         0.0000000         0.0000000           Construction         1.55502937         0.0000000         0.0000000         0.0000000         0.0000000           Construction         1.55502937         0.00000000         0.0000000         0.0000000         0.0000000         0.0000000         0.0000000         0.0000000         0.0000000         0.0000000         0.0000000         0.0000000         0.00000000         0.00000000         0.0000000         0.00000000         0.00000000         0.000000000         0.00000000000         0.00000000	1700066B10Pik	1 == 188=108	0.029072900	0.11179848
Cambragin         2.99942421         0.00974231         0.0097423           Cambragin         2.999494         0.009742         0.009749           David         2.999494         0.009741         0.009749           David         2.9994944         0.019979         0.009741         0.1199778           David         2.97994949         0.0097941         0.1199778         0.019978           David         2.97994949         0.0097941         0.1199778         0.019978           David         2.97994949         0.0097941         0.1199778         0.019978           Camorys         2.9799494         0.00979423         0.019979         0.019979           Shipp         2.9999494         0.0199791         0.019979         0.019979           Shipp         2.999949         0.0199791         0.0199791         0.0199791         0.0199791           Tanya         2.999949         0.0199791         0.0199791         0.0199791         0.0199791           Tanya         2.9995944         0.0199791         0.02995944         0.0199791         0.02995944           Camoragin         2.9995944         0.0199791         0.02995944         0.0199791         0.02995944           Camoragin         2.9995944 <td>1/00066019KIK</td> <td>1.5/4005190</td> <td>0.0200529/4</td> <td>0.111/0040</td>	1/00066019KIK	1.5/4005190	0.0200529/4	0.111/0040
Cal         4.9758.392         0.0958.292         0.0958.292           Officing         4.9759.2956         0.0974.654         0.0974.654           Dask         4.9779.9566         0.0974.654         0.0139.756           Dask         4.9799.9566         0.0974.654         0.0139.756           Dask         4.9799.9566         0.009.856         0.0197.166           Dask         4.9799.9566         0.0197.556         0.0197.166           Dask         4.9799.9566         0.0197.556         0.1197.579           Dask         0.9799.9566         0.0197.557         0.0197.556           Dask         0.9799.9567         0.0197.558         0.1197.579           Dask         0.9799.9567         0.0197.958         0.1197.579           Dask         0.9799.9567         0.0197.958         0.0197.938           Dask         0.9599.958         0.0059.958         0.0197.938           Offrag         0.9597.959         0.0197.938         0.0197.938           Spela         0.9597.959         0.0197.926         0.0197.938           Offrag         0.9597.959         0.0197.956         0.0197.938           Offrag         0.9597.956         0.0197.956         0.0197.956           Spel	Gm16432	1.575642242	0.008976243	0.107600372
Off:r.io%	Gal	1.575813355	0.005823011	0.105745966
Here Duald1.575/05/000.0007/95/10.01190/70*Duald1.5770/05/00.0109/70*Duald1.5770/05/00.0109/70*Duald1.5770/05/00.0007/95/10.01190/70*Duald1.5770/05/00.0007/95/10.01190/70*Duald1.5770/05/00.0007/95/10.01190/70*Offrage1.5950/97/00.0007/95/960.01190/95/0Offrage1.5950/97/00.0007/95/960.0077/95/96Duald1.5950/97/00.0007/95/960.0077/95/96Duald1.5950/97/00.0007/95/960.0077/95/96Duald1.5950/97/00.0007/95/960.0077/95/96Duald1.5950/97/00.0007/95/960.0077/95/96Duald1.5950/97/00.0007/95/960.0007/95/96Duald1.5950/97/00.0007/95/960.0007/95/96Duald1.5950/97/00.0007/95/960.0007/95/96Duald1.5950/97/00.0007/95/960.0007/95/96Duald1.5950/97/00.0007/95/960.0007/95/96Duald1.5950/97/00.0007/95/960.0007/95/96Duald1.5950/97/00.0007/95/960.0007/95/96Duald1.5950/97/00.0007/95/960.0007/95/96Duald1.5950/97/00.0007/95/960.0007/95/96Duald1.5950/97/00.0007/95/960.0007/95/96Duald1.5950/97/00.0007/95/960.0007/95/96Duald1.5950/97/00.0007/95/960.0007/95/96Duald1.5950/97/0<	Olfr1165	1.576042748	0.0219427	0.10956964
Dubil1.57798%0.00798%10.017978%Cmurys1.57896%0.0198%00.017978%Cmurys1.57896%0.04461290.0129876Chitay2.79806%0.04461290.0129876Chitay2.798076%0.0129876%0.0129876Chitay2.798076%0.0129876%0.0129876Chitay2.798076%0.0129876%0.0129384Chitay2.959107%0.0129876%0.0129384Chitay2.959107%0.020987740.01793384Chitay2.959107%0.02097840.0129384Chitay2.959107%0.02097840.0129384Chitay2.959107%0.012929410.01292941Chitay2.959107%0.012929410.01292941Chitay2.959107%0.012929410.01292941Chitay2.959107%0.012929410.01292941Chitay2.959107%0.012929410.01292941Chitay2.959107%0.012929410.01292941Chitay2.959107%0.012929410.01292941Chitay2.959107%0.012929410.01292941Chitay2.959107%0.012929410.01292941Chitay2.959107%0.012929410.01292941Chitay2.959107%0.012929410.01292941Chitay2.959107%0.012929410.01292941Chitay2.959107%0.012929410.01292941Chitay2.959107%0.012929410.0129297Chitay2.9595070.012929410.	Hsn2	1.57665827	0.000877596	0.105745966
Dudi         1.275986         0.092874         0.159976           Canceys         1.2599286         0.0052861         0.0072384           Canceys         1.2599286         0.005287         0.0052861         0.0072384           LDCconsigneys         1.569177         0.005297         0.005297         0.005297           Subjer         1.569177         0.005297         0.0052986         0.0072384           Canceys         1.5695949         0.0052984         0.0057288         0.0052986           Canceys         1.5955947         0.0052984         0.0057288         0.0052986           Canceys         1.5955947         0.0052984         0.0057288         0.0052986           Canceys         1.5955948         0.0052984         0.0057298         0.0052987           Canceys         1.5955948         0.0055954         0.0057298         0.0057298           Canceys         1.5955954         0.005959         0.0077298         0.005979           Canceys         1.5955954         0.005959         0.0077298         0.0077298           Canceys         1.5955957         0.005959         0.0077298         0.0077298           Canceys         1.5955957         0.0059597         0.0077298         0.00772	Duxbl	1.577798896	0.030748514	0.111030776
Conserved         1.2.9.9.8000         0.0.9.9.801         0.1.19.9.9.01           Conserved         1.5.9.9.9.900         0.0.4.9.9.9.9         0.1.19.9.9.01           Conserved         1.5.9.9.9.9.000         0.0.4.9.9.9.9.000         0.0.4.9.9.9.9.000           Solg         1.5.9.9.9.9.000         0.0.4.9.9.9.9.000         0.0.1.9.9.9.9.000           Solg         1.5.9.9.9.9.000         0.0.0.9.9.9.9.000         0.0.1.9.9.9.9.000           Solg         1.5.9.9.9.9.9.000         0.0.0.9.9.9.9.000         0.0.1.9.9.9.9.000           Solg         1.5.9.9.9.9.9.000         0.0.0.9.9.9.9.000         0.0.1.9.9.9.9.9.000           Solg         1.5.9.9.9.9.9.000         0.0.0.9.9.9.0.000         0.0.1.9.9.9.0.000           Conserved         1.5.9.9.9.9.9.000         0.0.0.9.9.9.0.000         0.0.1.9.9.9.9.9.0.000           Conserved         1.5.9.9.9.9.9.000         0.0.0.9.9.9.0.000         0.0.1.9.9.9.0.000           Conserved         1.5.9.9.9.9.9.000         0.0.0.9.9.9.0.000         0.0.1.9.9.9.0.000           Conserved         1.5.9.9.9.9.9.000         0.0.0.9.9.9.0.000         0.0.1.9.9.9.0.000           Conserved         1.5.9.9.9.9.9.000         0.0.0.9.9.9.0.000         0.0.0.9.9.9.0.000           Phil         1.5.9.9.9.9.000         0.0.0.9.9.9.0.000         0.0.0.9.9.9.0.000	Duvh	1.577790090	0.000740514	0.111020556
Controlsysty         19.3999990         0.0079801         0.1072910           LPCasary/19         19.3999990         0.00891631         0.1072910           LPCasary/19         19.3999990         0.00891631         0.1072910           LPCasary/19         19.3997991         0.00891631         0.10729160           Cess         19.3997921         0.0092666         0.1092666           Cess         19.3997921         0.0092666         0.1092666           Cess         19.3997921         0.0092666         0.1092666           Special         1.59379498         0.0192666         0.1092666           Special         1.59379498         0.0192666         0.1092666           Special         1.59379498         0.0192564         0.1092666           Control         1.59379497         0.01329261         0.1092666           Control         1.5937957         0.01329261         0.1092666           Control         1.5937957         0.01329261         0.1092666           Control         1.5937957         0.01421743         0.1092666           Control         1.5937957         0.01421743         0.1092666           Control         1.59387957         0.01421743         0.1092666	Buxbi	1.577790890	0.030/40514	0.111930770
Kripsy?         1.999908         0.054898         0.1092806           LSC.Physpoo         1.999008         0.0029533         0.1092806           LSC.Physpoo         0.0029533         0.1092806           Construct         1.9910979         0.0029533         0.1092806           Construct         1.9910975         0.0029573         0.1092806           Construct         1.9910975         0.0029729         0.1092966           Construct         1.9910975         0.0029729         0.1092966           Construct         1.9980980         0.0029729         0.1179281           Construct         1.9980980         0.0029729         0.1179281           Construct         1.9980980         0.00197983         0.01792981           Construct         1.9980980         0.0131982         0.0179281           Construct         1.9980980         0.0131982         0.0179281           Construct         1.99829981         0.0131982         0.0179281           Construct         1.99829981         0.0131982         0.0179281           Construct         1.99829981         0.0179281         0.0179281           Construct         1.99829981         0.0179281         0.0179281           Construct <td>Gm10755</td> <td>1.578936699</td> <td>0.01878801</td> <td>0.107723281</td>	Gm10755	1.578936699	0.01878801	0.107723281
Olfration         6.59900000         0.0440129         0.18859184           Coltaoutagings         1.59000000         0.0420129         0.18859184           Shipy         1.59000000         0.04207490         0.11444510           Cons         1.59707597         0.07206464         0.007207581           Dispositionality         1.59705959         0.002070783         0.10720510           Dispositionality         1.5980590         0.002070783         0.10720510           Speki         1.5980590         0.00207093         0.10720510           Consums         1.5980590         0.00205924         0.10972051           Consums         1.5980590         0.00205921         0.10722451           Olfraid         1.5980590         0.002059121         0.10722451           Olfraid         1.59905954         0.002059121         0.10722451           Olfraid         1.59905951         0.002059121         0.10722451           Olfraid         1.59905951         0.002059121         0.10792751           Olfraid         1.59905951         0.00205951         0.11092756           Olfraid         1.5990597         0.11992756         0.01191392         0.11992756           Olfraid         1.5990597         0.11	Krtap4-7	1.579505908	0.00640548	0.105745966
IOC:000(9)0     1.500(9)2     0.000(9)2     0.100(9)20       Ship?     1.500(7)2     0.000(2)20     0.100(9)20       Cest     1.500(7)2     0.000(2)20     0.100(9)20       Cest     1.500(7)2     0.100(9)20     0.100(9)20       Cest     1.500(7)2     0.100(9)20     0.100(9)20       Cest     1.500(7)2     0.100(9)20     0.100(9)20       Cest     1.500(7)2     0.100(9)20     0.100(9)20       StepPin     1.500(7)2     0.000(9)20     0.100(9)20       Cestatting     1.500(9)20     0.000(9)20     0.100	Olfr1410	1.579900096	0.044601259	0.118853184
Ship         1.59/37/3         0.5375/49         0.114/65/3           Cena         5.59/37/2         0.0564/77/4         0.1075/32           Texta 2         5.58/89/6         0.0564/77/4         0.1075/32           Olfosis         1.59/37/64         0.0564/77/4         0.1159/32           Olfosis         1.59/37/64         0.03/37/24         0.1159/32           Capies         1.59/37/64         0.03/37/24         0.1159/32           Capies         1.59/37/64         0.03/37/24         0.1179/36           Capies         1.59/07/64         0.03/37/24         0.07/36/34           Capies         1.59/07/64         0.03/37/24         0.07/36/34           Concord         1.59/07/64         0.03/37/24         0.03/37/24           Concord         1.59/07/64         0.03/37/24         0.03/37/24           Concord         1.59/07/64         0.03/37/24         0.03/37/24           Concord         1.59/07/64         0.03/37/24         0.03/37/24           Concord         1.59/37/26         0.03/37/24         0.03/37/24           Concord         1.59/37/26         0.03/37/24         0.03/37/24           Concord         1.59/37/26         0.03/37/24         0.03/37/24	LOC100046350	1.580049767	0.002956233	0.105745966
css         1.9179797         0.0279580         0.1079298           css_1         1.9509174         0.00051358         0.1079596           css_2         1.9509174         0.00051358         0.1079596           Spiral         1.9509174         0.00051358         0.10792586           Spiral         1.9509179         0.00051358         0.10792586           Ceacaminy         1.94091896         0.00051378         0.10792586           Ceacaminy         1.94091896         0.0015197         0.10792586           Diffuig         1.94091897         0.0015197         0.10792586           Diffuig         1.94091897         0.0015197         0.10792586           Diffuig         1.9409197         0.00255118         0.10792586           Diffuig         1.9409197         0.00255118         0.10792786           Diffuig         1.9409197         0.00255118         0.10792786           Diffuig         1.60091497         0.00255118         0.10792786           Diffuig         1.60091497         0.00255118         0.10792586           Diffuig         1.60091497         0.00255518         0.10792586           Diffuig         1.60091497         0.00255568         0.11592682	Snhg	1.581715359	0.035756495	0.114628526
1         0.900000000000000000000000000000000000	Cost	1 581939387	0.017480860	0.107722281
Lat.y2         1.59.0792         0.00043492         0.1079259           Approx2.504000         1.59.05590         0.000543492         0.1079258           Option         1.59.05590         0.0015909         0.1779258           Cascarray         1.59.05590         0.0015929         0.1779258           Cascarray         1.59.05591         0.0015929         0.1779238           Cascarray         1.59.05595         0.0015929         0.1779238           Temm876         1.59.055951         0.00129763         0.1779238           Offrage         1.59.055951         0.00129763         0.1779238           DOCcomport         1.59.055951         0.00129763         0.1779238           DOCcomport         1.59.055951         0.00297671         0.1579578           DOCcomport         1.59.055951         0.00297671         0.1579578           DOCcomport         1.600147675         0.0017979         0.1779288           DOCcomport         1.600147675         0.0017979         0.0779288           DOCcomport         1.600147675         0.0017979         0.0779288           DOCcomport         1.600147675         0.0779288         0.0779288           DOCcomport         1.600147675         0.0779288         0	Terrer		0.017409009	0.10//23201
490:393:00000         1.59574983         0.00054392         0.159754984           Spirts         1.59574983         0.000579329         0.00773281           Spirts         1.59574993         0.00057937         0.00773281           Company         1.5957499         0.00057947         0.00773281           Company         1.5957499         0.00357047         0.00773281           Tamestob         1.59594954         0.00357047         0.00773381           Tamestob         1.59594957         0.0231755         0.00773381           Ottomay         1.60414795         0.04417443         0.01997384           Ottomay         1.60414795         0.04417443         0.01997384           Ottomay         1.60414795         0.04417443         0.01997384           Ottomay         1.60414795         0.0417443         0.01997384           Ottomay         1.60414976         0.039744047         0.0773381           Ottomay         1.60414976         0.039744047         0.0773381           Ottomay         1.60414976         0.039744047         0.0773381           Ottomay         1.60491492         0.039744047         0.03773381           Ottomay         1.60991449         0.03974948         0.03773381	lex19.2	1.581901752	0.009247774	0.107693259
Offreys         1.55/55/49         0.03307048         0.11392239           CypReh         1.58/55/49         0.008/57/88         0.1172338           CypReh         1.58/55/49         0.008/57/88         0.1172338           Consumu         1.59/55/41         0.03/306/07         0.077338           Consumu         1.59/55/41         0.03/306/07         0.077338           Offreys         0.01/27/55         0.077338         0.077338           Offreys         0.01/27/55         0.077338         0.01/27/53           Offreys         0.01/27/55         0.01/27/53         0.01/27/53           Offreys         0.01/17/54         0.01/27/54         0.01/27/54           Offreys         0.01/17/54         0.01/27/54         0.01/27/54           Offreys         0.01/17/54         0.01/27/54         0.01/27/54           Offreys         0.01/17/54         0.01/27/54         0.01/27/54           Offreys         0.01/17/54         0.01/27/34         0.01/27/34           Offreys         0.01/17/54         0.01/27/34         0.01/27/34           Offreys         0.01/16/54         0.01/27/34         0.01/27/34           Offreys         0.01/16/54         0.01/27/34         0.01/27/34 <t< td=""><td>4930539E08Rik</td><td>1.582888901</td><td>0.000634382</td><td>0.105745966</td></t<>	4930539E08Rik	1.582888901	0.000634382	0.105745966
Speta         1.958/97/9         0.008/370/97         0.177/3281           Creatminy         1.958/97/9         0.008/370/97         0.177/3281           Creatminy         1.998/95/86         0.003/97/97         0.177/3281           Differing         1.999/95/86         0.003/97/97         0.177/3381           Differing         1.999/95/87         0.003/97/95         0.077/3381           Differing         1.999/95/87         0.003/97/95         0.077/3381           DOCtocouptory         1.998/55/95         0.003/97/95         0.011/97/95           DOCtocouptory         1.6001/97/95         0.04/17/443         0.199/95/97           DOCtocouptory         1.6001/97/95         0.04/17/443         0.199/95/97           DOCtocouptory         1.6001/97/95         0.04/17/443         0.199/95/97           DOCtocouptory         1.6001/97/96         0.007/92/97         0.077/92/97           DOCtocouptory         1.6001/97/96         0.007/92/97         0.077/92/97           DOCtocouptory         1.6001/97         0.007/92/97         0.077/92/97           DOCtocouptory         1.6001/97         0.007/92/97         0.007/92/97           Doctocouptory         1.6001/97         0.007/92/97         0.007/92/97         0.007/92/97     <	Olfr983	1.583748588	0.033070248	0.112932239
CypBn'         1.898/89/2         0.0032904/         0.1171228/           Caseaniny         1.5989/81/6         0.0031292/4         0.107238/           Campaya         1.5991/81/6         0.0031292/4         0.107238/           TmemBb         1.5971/91/81         0.0131292         0.107238/           Campaya         1.5991/91/91         0.0112192         0.107238/           Chinago         1.5991/91/91         0.0112192         0.107238/           Chinago         1.5991/91/91         0.0112192         0.111990/91           Chinago         1.6012/91/91         0.0112192         0.111990/91           Chinago         1.6012/91/91         0.011990/91         0.111990/91           Chinago         1.60012/91/91         0.011990/91         0.111990/91           Chinago         0.011990/91         0.111990/91         0.111990/91           Chinago         0.011990/91         0.111990/91         0.011990/91           Chinago         0.011990/91         0.011990/91         0.011990/91           Chinago         0.011990/91         0.011990/91         0.011990/91           Chinago         0.011990/91         0.011990/91         0.011990/91           Chinago         0.011991/91         0.011990/91	Spef2	1.585854047	0.010807988	0.107723281
Consump         1.593/5566         0.0005/5727         0.1970/5831           Philds         1.593/5566         0.0005/5727         0.1970/5831           Philds         1.597/5564         0.01570/5813         0.1970/5831           Offrag         1.597/5564         0.01572/581         0.10772381           Offrag         1.598/55751         0.0227351         0.1075/541           Offrag         1.608/575         0.0241275         0.1105/646           IOCConcuput)         1.608/575         0.04417/43         0.1105/646           IOCConcuput)         1.608/575         0.04417/43         0.1105/646           IOCConcuput)         1.608/562         0.032759         0.1113/9776           Emilis         1.608/562         0.0327595         0.1113/9776           Emilis         1.608/566         0.0327595         0.1113/9776           Emilis         1.608/566         0.0327595         0.1113/9776           Cala         1.608/566         0.0327595         0.1113/9776           Ageococo/BRik         1.618/93/665         0.0327595         0.11772381           Ageococo/BRik         1.618/93/673         0.0327595         0.10772381           Ageococo/BRik         1.618/93/673         0.0327595 <td< td=""><td>Cvp8b1</td><td>1.58817879</td><td>0.028230097</td><td>0.111732284</td></td<>	Cvp8b1	1.58817879	0.028230097	0.111732284
Compute         Supplication         Constraint           Thembibi         1.59712554         0.01207027         0.102722384           Thembibi         1.59705744         0.01207027         0.002722384           Myha         1.59905975         0.01231530         0.012722384           DCI:concurrent         1.59955975         0.00255712         0.10529784           DCI:concurrent         1.59955975         0.00255712         0.10529784           DCI:concurrent         1.60042975         0.00157123         0.11595479           DCI:concurrent         1.60042975         0.00157133         0.11595479           DCI:concurrent         1.60049765         0.01197133         0.11595479           DCI:concurrent         1.60049765         0.01197133         0.11595479           DCI:concurrent         1.60049765         0.01197133         0.11972384           DCI:concurrent         1.60049765         0.01297239         0.11772384           Drinh         1.61039919         0.00295918         0.10792481           Clifati         1.610399192         0.00295929         0.10972496           Drinha         1.613549617         0.00297532         0.11772384           Offrafa         1.62329569         0.10972496	Ceacamio	1 50200150	0.004252044	0 105745066
Cuingquip         1.59/21/21         0.10/0002/21/21           Timentbô         1.59/21/21         0.10/722/21           Offragi         0.59/25/24         0.01/722/21           Offragi         1.59/25/24         0.01/722/21           Myha         1.59/25/25         0.04/21/21         0.10/722/21           DC/Cooquiry         1.600/475         0.04/01/21         0.10/92/21           DC/Cooquiry         1.600/475         0.01/11         0.10/92/21           DC/Cooquiry         1.600/475         0.01/11         0.10/92/21           DC/Cooquiry         1.600/97/21         0.01/92/21         0.01/92/21           DC/Cooquiry         1.600/97/21         0.01/92/21         0.01/92/21           DC/Cooquiry         1.601/97/21	Creation	1.99209199	0.004332944	0.103/43900
Internation         1.597(13):584         0.033(2007)         0.10772.381           Offerty 0         1.597(5):594         0.013(2205)         0.11070.2481           Offerty 0         1.598(57):51         0.023(225)         0.11070.2481           DCCocquery         1.600.4575         0.04[47]:43         0.1199(597)           DCCocquery         1.600.4575         0.04[47]:43         0.1199(597)           DCCocquery         1.600.4575         0.04[47]:43         0.1199(597)           DCCocquery         1.600.4575         0.04[47]:43         0.1199(57)           EmBSc         1.600.4507         0.039(8)5         0.1179(57)           Cols         1.600.4507         0.039(8)5         0.1179(57)           Cols         1.600.4506         0.0407(56)         0.1179(57)           Cols         1.600.4506         0.0407(56)         0.1179(52)           AgoocaCol6081k         1.610.379(50)         0.0179(52)         0.10772.281           AgoocaCol6081k         1.610.379(50)         0.0179(596)         0.1079(596)           Offragk         1.610.379(56)         0.0179(596)         0.1079(596)           Offragk         1.610.379(596)         0.0139(525)         0.1097(596)           Offragk         1.6207(593)	Di 1 11 -	1.594052000	0.00015/32/	0.10/000023
Imem8b         1.59705941         0.0137320         0.10772381           Olffrag         1.5970597         0.0131330         0.10772381           Myhla         1.5985795         0.02413753         0.1008/db/db           LOCtooxquay         1.6985795         0.046177413         0.13956979           LOCtooxquay         1.6004765         0.046177413         0.13956979           LOCtooxquay         1.6004765         0.00151302         0.10772381           LOCtooxquay         1.6004766         0.00795153         0.10792381           Cda8         1.6004766         0.00795183         0.10792381           Cda8         1.6004766         0.00795183         0.10792381           Cda8         1.6004766         0.00795183         0.10792381           Cda8         1.6193697         0.01379509         0.10792381           Olffafi         1.6193697         0.01379509         0.10792381           Defba6         1.61939129         0.0026937         0.10972381           Defba6         1.6293690         0.0037559         0.10972481           Defba6         1.6293691         0.0027537         0.10974946           LCC         1.6004968         0.00375597         0.10974946	Phidb3	1.597312584	0.013206027	0.107723281
Offraging         1.59978697         00.1151302         0.1075424           IACC:concupy1         1.59875751         0.00257124         0.1054444           IACC:concupy1         1.600143755         0.04447443         0.1193076           IACC:concupy2         1.600143755         0.04447443         0.1193076           IACC:concupy2         1.600143755         0.04447443         0.1193076           IACC:concupy2         1.600143755         0.0391595         0.11193076           IACC:concupy2         1.600143755         0.0391595         0.11193076           Cold         1.600143755         0.0391595         0.01119322         0.0173381           Cold         1.61094947         0.01357918         0.01973381         0.01973381           Apport201681K         1.61394955         0.0279456         0.0173381         0.01973456           Datalics         1.61549584         0.0025765         0.01974566         0.00254566           Offragin         1.61549584         0.0025678         0.01974566         0.00254566           Offragin         1.62958195         0.00215734         0.01974566         0.00254566           Offragin         1.62958195         0.00215734         0.01974566         0.00214466	Tmem86b	1.597655844	0.013972651	0.107723281
Mybix         1988/5395         0.02(12)55         0.105/04/40           IOC:0000(207)         1.6001/575         0.04(4)1/41         0.1950/594           IOC:000(207)         1.6001/575         0.04(4)1/41         0.1950/594           IOC:000(207)         1.6001/575         0.04(4)1/41         0.1950/594           IOC:000(207)         1.6001/575         0.04(4)1/413         0.1950/594           IOC:000(207)         1.6001/575         0.04(4)1/413         0.1970/384           Clask         1.6001/575         0.01/4/1002         0.11/12/284           Clask         1.6001/575         0.01/4/1002         0.11/12/284           Clask         1.6001/575         0.01/4/1002         0.01/12/284           Olfraft         1.6110/9709         0.01/12/285         0.01/12/284           Olfraft         1.6110/9709         0.01/12/285         0.01/12/286           Olfraft         1.6110/9709         0.01/12/285         0.01/12/286           Olfraft         1.6110/9709         0.01/12/286         0.01/12/286           Olfraft         1.6110/9709         0.00/9704         0.01/9704           Olfraft         1.6110/9709         0.00/9704         0.01/9704           Olfraft         1.62/97018         0.00/9704	Olfr149	1.597906877	0.011513302	0.107723281
LÓC:0004001         1.998527951         0.00395742         0.19397844           LOC:0044207         1.600142795         0.44447443         0.119396979           LOC:0044207         1.600142795         0.44447443         0.119396979           LOC:0044207         0.1007521281         0.1193976           LOC:004407         0.107721281         0.107721281           Cd28         1.6059642         0.04075518         0.107721281           Cd28         1.6059642         0.04075518         0.107721281           Cd28         1.6059642         0.04075518         0.107721281           Cd28         1.61031953         0.01551952         0.117123281           Offråf         1.614995951         0.0075958         0.107723381           DeBabc         1.615745789         0.00256957         0.13723966           Clrsg         1.60595842         0.0025786         0.13724566           Lecy         1.605745988         0.00795354         0.10795383           Olfrafé         1.652745988         0.0073534         0.12594566           Dubb         1.658749312         0.02320131         0.13594363           Olfrafé         1.652745986         0.00332435         0.127594366           Dubb <t< td=""><td>Mybl2</td><td>1.598253958</td><td>0.024121558</td><td>0.110084646</td></t<>	Mybl2	1.598253958	0.024121558	0.110084646
LOC:nov[277]         1.6012755         0.04417443         0.11596679           LOC:nov[277]         1.6012755         0.04417443         0.11596679           LOC:nov[277]         1.6012755         0.04417443         0.11596679           LOC:nov[277]         1.6012755         0.04417443         0.11595679           LOC:nov[277]         1.6012755         0.017140427         0.0772381           Cals         1.66096462         0.0175513         0.0772381           Aspont/OKRK         1.6159256         0.0175138         0.0772381           Aspont/OKRK         1.61592561         0.027568-0         0.117284           Dhabr         1.61592691         0.002568-0         0.117284           Dhabr         1.61592691         0.002568-0         0.10754306           Offraf         1.61592692         0.0025633         0.01754306           Dhabr         1.63598466         0.0075534         0.10754306           Offraf         1.6235685         0.0025678         0.10754306           Stropa Art Rk         1.6426509         0.00306578         0.1385406           Stropa Art Rk         1.6426509         0.0390578         0.13924956           Duxbl         1.658519551         0.0390578         0.1392413 <td>LOC100040031</td> <td>1.598257651</td> <td>0.020556124</td> <td>0.109270814</td>	LOC100040031	1.598257651	0.020556124	0.109270814
Loc. Novi 1979         Output/1413         Output/1413         Output/1413           DCC Look 1977         1.60 12975         0.03 195 0677         0.11 195 0677           LOC Took 1977         1.60 12975         0.03 191 060         0.11 195 077           LOC Took 1977         1.60 12975         0.03 191 060         0.11 191 177           Class         1.60 960 062         0.04 075 1318         0.10773381           Class         1.60 050 062         0.01 15 1912         0.1773381           Off 14         1.61 103 1963         0.01 15 1912         0.1773381           Off 14         1.61 195 1963         0.01 15 1912         0.1773381           Off 14         1.61 195 1963         0.02 15 1912         0.1773381           Off 14         1.61 195 1963         0.02 195 196         0.02 195 196           Off 14         1.65 195 196         0.02 295 196         0.02 195 196           Off 14         1.65 195 196         0.02 295 197         0.12 195 196           Locy C         1.65 195 196         0.02 295 197         0.12 195 196           Locy C         1.65 195 196         0.02 295 196         0.12 195 196           Locy C         1.65 195 197         0.02 295 196         0.12 195 196           Locy C	LOC100041207	1 6001 45565	0.046417442	0.110506050
Loc. Local Jan?         Local JgPs         Ox/44/743         Ox/199679           LOC Grypp         Local JgPs         Ox/199776         Ox/199679           Fam Byc         Locay JgPs         Ox/1740047         Ox/1792181           Clas         Locay JgPs         Ox/1740047         Ox/1792181           Gayood DORBIK         Locay JgPs         Ox/1740047         Ox/1792181           Gayood DORBIK         Locay JgPs         Ox/1792181         Ox/0722381           Apport 2016BiK         Locay JgPs         Ox/1792181         Ox/0722381           Olfragh         Locay JgPs         Ox/0722381         Ox/0722381           Dahos         Lory JgPs         Ox/0723990         Ox/0722381           Dahos         Lory JgPs         Ox/0723962         Ox/0722381           Dahos         Locy JgPs         Ox/072990         Ox/072990         Ox/072990           Dolfragh         Locay JgPs         Ox/072990         Ox/072990         Ox/072990           Dolfragh         Locay JgPs         Ox/072990         Ox/072990         Ox/072990           Dolfragh         Locay JgPs         Ox/072990         Ox/072990         Ox/072990           Sigragh (TBK         Locay JgPs         Ox/072990         Ox/072990         Ox/	100004120/	1.000145/05	0.04041/443	0.1195009/9
LCL 6/1920         1.4024933         0.03918/59         0.11972281           Cl2B         1.40529644/7         0.017404/7         0.10772381           Cl2B         1.4052964         0.0467953         0.1189661           Gaydon/DSRKK         1.605297565         0.017573181         0.10772381           Plof         1.6119350         0.01619052         0.11972384           Algon2DSrBKK         1.6119350         0.0157596         0.11972381           Olfraft         1.6119567         0.0157596         0.11972381           Dahlad         1.611956799         0.00249031         0.109749966           Dahlad         1.61195612         0.00249053         0.109749966           Strants         1.6025698         0.00219534         0.109749966           Strants         1.6025698         0.00219534         0.109749966           Strants         1.6025698         0.00219534         0.109749966           Davbl         1.60256912         0.02306578         0.11834143           Davbl         1.60256912         0.02306578         0.11024413           Davbl         1.602576912         0.02795830         0.109749966           Davbl         1.605719548         0.00795850         0.109749966	100100041207	1.000145765	0.040417443	0.119506979
Fam3p2c         1.669964497         0.037740047         0.11782681           6.49660.100881k         1.669736650         0.03753118         0.10773281           6.49660.100881k         1.61391569         0.03753118         0.10773281           6.49660.100881k         1.61391592         0.01773281         0.10773281           6.49660.100881k         1.61391951         0.02756759         0.10773281           0.01641         1.61391952         0.00249037         0.10773281           0.016426         1.6033162         0.00225063         0.10773281           0.016441         1.60393162         0.00225063         0.10774966           0.016441         1.60393162         0.00225063         0.10794966           0.016441         1.66295688         0.00123438         0.10794966           0.016441         1.66295693         0.00225063         0.10794966           0.016411         1.66295693         0.00239478         0.11828686         0.01794966           0.016411         1.66295693         0.00239478         0.11828686         0.01794966           0.016411         1.66295693         0.00239478         0.11974966         0.000974966           0.016411         1.66295693         0.0024956         0.10794966	LOC674930	1.60248035	0.03091859	0.111930776
Cd28         i.6de0pid028         0.04p6/5969         0.015/5969           Opend CMSRki         i.6de0pid028         0.016/1962         0.10772381           Pief A         i.61193563         0.0116/1962         0.10772381           Olfrafs         i.61199547         0.0357666         0.10772381           Olfrafs         i.61199547         0.0357666         0.10772381           Dublacy         i.61599547         0.00357666         0.10772381           Olfrafs         i.61599547         0.00357666         0.10772381           Olfrafs         i.6259572         0.00279368         0.109749966           Olfrafs         i.620564966         0.00295969         0.109749966           Slovai3         i.620564966         0.00295969         0.109749966           Slovai3         i.62056496         0.007958063         0.109749966           Slovai3         i.6205693         0.0029583         0.109749966           Dush         i.626519532         0.00339581         0.109749966           Dush         i.626519632         0.0029583         0.109749966           Dush         i.62651975         0.00339251         0.109749966           Dush         i.62651972         0.00339256         0.109749966	Fam83c	1.605964497	0.017140047	0.107723281
643600C08Bk         1.608712665         0.01573318         0.1073281           Phoft         1.6113923         0.1073284         0.111173284           A930012O16Bk         1.611492165         0.007591.82         0.10708823           Olltyå1         1.65156527         0.007591.82         0.10708823           Dahler         1.65156527         0.00255069         0.10723281           Dehba         1.637362790         0.00225073         0.10725566           Dehba         1.637362790         0.00225073         0.10725566           Clery         1.63073628         0.00225073         0.10725566           Silvari3         1.63086866         0.00795394         0.10725666           Silvari3         1.630736788         0.10735968         0.10735966           310032(Collk         1.64736588         0.0073248         0.10735966           310032(Collk         1.64736588         0.0073534         0.10745966           Daubl         1.6317473         0.0285059         0.10745966           Daubl         1.6317473         0.0286376         0.10745966           Daubl         1.63159707         0.007474         0.10275966           Clory         1.65159707         0.0075755         0.10773581 </td <td>Ccl28</td> <td>1.606090662</td> <td>0.040676563</td> <td>0.11680661</td>	Ccl28	1.606090662	0.040676563	0.11680661
Perf         1.61193692         0.0159392         0.1792881           Aggoot20468Lk         1.611942485         0.02768529         0.17972881           Dhahc3         1.61369547         0.0375766         0.0772381           Dhahc3         1.61369547         0.0375766         0.0772381           Dhahc3         1.61369547         0.0357566         0.0772381           Dhahc3         1.613695496         0.00295097         0.10274566           Olff4gh         1.619591526         0.00295097         0.10274566           Olff4gh         1.62958496         0.007984099         0.107945831           Slopara         1.62958595         0.03708578         0.13254666           Stopara         1.62956931         0.03294595         0.107945831           Stopara         1.6375588         0.03294595         0.107945845           Stopara         1.63756913         0.03294595         0.107945845           Stopara         1.63756913         0.03294595         0.107945845           Duabl         1.63756961         0.03294566         0.107945966           Corr         1.63756969         0.00293744         0.102745966           Corr         1.664597967         0.10274566         0.10772381	6430601O08Rik	1.608712665	0.015753118	0.107723281
Typest         1.00173303         000170392         00171201           Aggonz 2016kik         1.611439363         000759182         0.10704883           Olfrafs         1.614393647         000355966         0.10772381           Defba5         1.617362797         0.00355967         0.105743966           Defba5         1.60333622         0.002356937         0.105743966           Lecyc         1.60393462         0.002356937         0.105743966           Signat         1.62958696         0.00235595         0.105743966           Signat         1.6295899         0.00331334         0.10574966           Signat         1.6295688         0.00334285         0.10794883           Datab         1.628119582         0.002985305         0.12849689           Datab         1.628119582         0.02978505         0.1299466           Datab         1.628119582         0.02978505         0.12994131           Cm8944         1.63211952         0.02978124         0.12974966           Dynthz         1.63914779         0.06627674         0.129749566           LOC36094         1.6437688         0.00732851         0.1073281           Dynthz         1.669797024         0.002467468         0.10773281	Profi	1 611022602	0.011612052	0.107720281
Agyonizyrinokik         1.61142185         0.02720529         0.11712244           Dinahcis         1.613429561         0.02720529         0.10772381           Dinahcis         1.61349547         0.0335766         0.10773281           Dinahcis         1.61349547         0.0335766         0.10773281           Olffaghi         1.613495156         0.002400433         0.10574566           Olffaghi         1.62235859         0.0027098409         0.107724966           Silografi         1.62355869         0.007998409         0.10724966           Magfio         1.62355869         0.007998409         0.10724966           stiopza&Artikik         1.6245698         0.00723418         0.10724966           stiopza&Artikik         1.6245698         0.00723418         0.10724966           Duabi         1.63876913         0.03208131         0.10394133           Gm89ag         1.63350861         0.00783066         0.10724966           Duabi         1.63876913         0.00281066         0.10772381           Dirabi         1.64395076         0.0029329         0.10394926           Dirabi         1.64395076         0.00293455         0.10274366           Dirabi         1.64395076         0.00293476         <	A second (Bil)	1.011033093	0.011013032	0.10//23201
Ollrafsi         1.61495961         0.00790832         0.107008833           Dahabcy         1.617762799         0.00296907         0.105742966           Debba6         1.617762799         0.00225963         0.105745966           Derbyk         1.60235622         0.002225963         0.105745966           Stepart 3         1.602568496         0.007915354         0.105745966           Stepart 3         1.60256859         0.00310354         0.105745966           Stopart 4         1.62256059         0.00310354         0.105745966           Stopart 5         0.13549669         0.105745966         0.105745966           Daubd         1.63519582         0.007915394         0.13602453           Daubd         1.63574958         0.007915394         0.10706883           Daubd         1.63574972         0.00781539         0.10360495           Daubd         1.639141779         0.006207674         0.105745966           DVMbb2         1.639141779         0.006332581         0.1079745966           LOC360094         1.643574594         0.00274946         0.105745966           DVMbb2         1.66377074         0.00247496         0.105745966           CC7         1.66571704         0.00247496         0	A930012O16KIK	1.611942185	0.027626529	0.111732284
Dnahc3         1.6154pc8,47         0.01357696         0.01722181           Dohb26         0.617974299         0.000400433         0.105745966           DiFt4g8         1.619591526         0.002425063         0.105745966           Locyc         1.62032622         0.00255053         0.105745966           Sk[rat13         1.62054866         0.007945905         0.105745966           Sciop38A11Rik         1.62325059         0.00350578         0.113694869           2310034G01Rik         1.623745988         0.00732438         0.1075745966           Dubbl         1.6331932         0.02501131         0.11059413           Camb394         1.63350833         0.025021131         0.10032413           Camb394         1.63350833         0.02502174         0.12020897           Bglap1         1.63350833         0.00784396         0.007754381           CC38094         1.6375054         0.00974826         0.019774966           ICC38094         1.6378535         0.002167486         0.00974830           IPae         1.64859756         0.00397486         0.109774381           IPae         1.64959756         0.00397485         0.109745966           Cryc         1.668591704         0.000397485         0.10	Olfr481	1.614950561	0.00759182	0.107008823
Dehzá         1.617740279         0.00295977         0.105745966           Olffaglis         1.62013262         0.00225063         0.105745966           Lecyc         1.62013262         0.00225063         0.10770883           Meglís         1.62258059         0.00798499         0.1070883           Jatory LGNIRk         1.62276588         0.00725348         0.113848689           Jatory LGNIRk         1.628769382         0.00725349         0.10708833           Dubbl         1.638719582         0.007953995         0.11369405           Dubbl         1.638769312         0.025021131         0.10908833           Dubbl         1.63876935         0.002620754         0.105745966           Combspd         1.63976976         0.00620754         0.105745966           LOC36094         1.63976976         0.00620754         0.10773581           LOC36094         1.66177853         0.01021646         0.107745966           LOC300945         1.66177853         0.010274596         0.00745966           LOC3004929         1.665870976         0.0084197         0.10773581           LOC3004928         1.67280711         0.005719743         0.107745966           LOC3004929         1.675894976         0.00641975	Dnahc3	1.615405847	0.01357696	0.107723281
Olfragå         1.61959152         0.00420013         0.10574956           Skra13         1.620568406         0.00225053         0.10574956           Skra13         1.620568406         0.00225053         0.10574956           Skra13         1.620568406         0.00235057         0.10574956           Skra14         1.6225693         0.00319657         0.11524668           SalossA11Rk         1.62256833         0.00795595         0.10740883           Daubh         1.68819382         0.00795595         0.10740883           Daubh         1.688789312         0.023346059         0.103749566           Carsopaq         1.63341732         0.027574         0.105749566           LOC36094         1.63341732         0.00745395         0.105749566           LOC36094         1.63934173         0.0027574         0.105749566           LOC36094         1.64959476         0.00319785         0.105749566           LOC36094         1.664897696         0.003974142         0.105749566           Carr         1.665717024         0.003497486         0.105749566           LOC10004932         1.665971970         0.00354197         0.10754566           LOC20004932         1.669598496         0.005374735         0	Defb26	1.617362799	0.002965037	0.105745966
Legr         1.42032802         0.00228003         0.107745966           Slcyata         1.620568496         0.007964009         0.10774596           Megfé         1.62258059         0.00303574         0.15754596           atioga&AtaRik         1.64295005         0.0308575         0.12848689           atioga&Chikk         1.628705883         0.00123243         0.107545966           Dubbl         1.688119512         0.002302131         0.10304833           Blaph         1.63236833         0.00254236         0.10754596           Comb94         1.632369312         0.002502131         0.10324433           Blaph         1.63334772         0.04287974         0.102745966           LOC38094         1.63258066         0.00883266         0.10772381           LOC38094         1.648987969         0.00391742         0.107545966           LOC30040239         1.66587094         0.0034748         0.107545966           LOC30040239         1.66587094         0.0031765         0.107545966           LOC30004039         1.665870976         0.0044748         0.107545966           LOC30004039         1.665870976         0.0031765         0.107545966           Carr         1.664893796         0.0031765	Olfr448	1.619591526	0.004400433	0.105745966
Bicyari         1.620568496         0.00796029         0.10704853           Megfé         1.620568496         0.00795554         0.107245966           Scioga8,11Rik         1.64225699         0.00308576         0.11248666           Dubb         1.68276988         0.007295395         0.107908833           Dubb         1.6828789312         0.007985095         0.107908833           Cm8994         1.6828789312         0.025021131         0.110291413           Cm8994         1.693341792         0.002502131         0.10204957           Bjalp1         1.693941779         0.000852866         0.1077459566           LOC38094         1.64376873         0.01021646         0.10773281           Tes22         1.64957967         0.000397442         0.105745966           LOC3004023         1.665719764         0.000397442         0.105745966           Cc77         1.65771974         0.00267415         0.105745966           LOC10004023         1.6688799         0.00397447         0.105745966           LOC2004923         1.679289701         0.00397474         0.105745966           Corr         1.679289701         0.003974173         0.105745966           Corr         1.679289701         0.105745966	Leese	1 620332622	0.002225063	0 105745966
adv_drij       1.6.2036940       0.00794209       0.107048023         Megtié       1.6.2255059       0.003015554       0.103743906         2.610528A11R1k       1.624561095       0.00304575       0.103743906         Duxbl       1.628119582       0.007985305       0.10704823         Duxbl       1.628119582       0.007985305       0.10704823         Cm8994       1.63350493       0.033946059       0.113692285         Krtaps-3       1.6333147732       0.04781024       0.102743966         LOC36094       1.64356496       0.003052856       0.109745966         LOC36094       1.64356496       0.008532851       0.100745966         LOC36094       1.64350496       0.003971442       0.109745966         LOC300923       1.665970976       0.0084197       0.109745966         Cc77       1.665710767       0.00397453       0.109745966         Cdrocycapa       1.666970976       0.00391742       0.109745966         Cdrocycapa       1.669870976       0.0084197       0.109745966         Cdrocycapa       1.669870976       0.0034678       0.109745966         Cdrocycapa       1.669870976       0.00534975       0.109745966         Cdrabre       1.679349368       <	Sloraza	1 620568 406	0.007222,000	0.107098933
Indegro         1.6.223603         0.00310354         0.01304394           Seriogz&A1:Rik         1.6.2436003         0.031008575         0.11324(868)           2310034G01Rik         1.628769312         0.007985925         0.10204833           Ilaarh         1.628769312         0.025021131         0.110291413           Gm6394         1.63314732         0.0478104         0.10202807           Krlap 5-3         1.63314732         0.0478104         0.10202807           Bglap1         1.639344732         0.007845966         0.109745966           Tex22         1.64759768         0.0003915281         0.107545966           Dynlfb2         1.66479653         0.0021646         0.10775381           Dynlfb2         1.66570976         0.00391424         0.105745966           Ccr7         1.66570976         0.00391498         0.107545966           Cdr0x00329         1.66570976         0.003919785         0.105745966           Cdr0x003190481         1.679343083         0.003914984         0.107545966           Gm6795         1.679349156         0.02657473         0.105745966           Gm6795         1.67934936         0.02657487         0.11792284           Gm649         1.69689038         0.02657487	Sic/al3	1.020508490	0.007980409	0.10/008823
2610528A11K1k       1.62450095       0.03794595       0.13848689         2310034Cn1R1k       1.62725588       0.0012343       0.103745966         Duxbl       1.628769312       0.020201131       0.110291413         Cm8594       1.63316933       0.033946959       0.13569285         Ktup5-3       1.633141732       0.04781024       0.102745966         LOC380994       1.63354932       0.005287674       0.103745966         LOC380994       1.64736785       0.00381268       0.103745966         LOC380994       1.64736785       0.003297444       0.109745966         LOC380994       1.6677853       0.01021646       0.10773381         H2-M10.2       1.66478957       0.00397144       0.109745966         Ccr7       1.665717024       0.00391745       0.109745966         Cdr7       1.665719704       0.0039175       0.109745966         Cdr7       1.665719704       0.0039175       0.109745966         Cdr7       1.66749583       0.00189628       0.109745966         Cdr7       1.667495935       0.01974133       0.109745966         Cdr7       1.6674934586       0.00574743       0.109745966         Gm6295       1.679291366       0.00574973 <td< td=""><td>Megf6</td><td>1.622258059</td><td>0.003015354</td><td>0.105745966</td></td<>	Megf6	1.622258059	0.003015354	0.105745966
310034G018kk         1.6295888         0.001232438         0.105745966           Duxbl         1.628769312         0.0025021131         0.110291413           Illaorb         1.638769312         0.0025021131         0.110291413           Gm8594         1.639341732         0.04761024         0.1200687           Bglap1         1.639341732         0.04761024         0.105745966           LOC350994         1.64958768         0.0088266         0.10773281           Dynlba         1.66177653         0.002375281         0.107743966           Ccr7         1.665717024         0.00247646         0.105745966           LOC100040239         1.66597054         0.003971412         0.10773281           H2*M10.2         1.66597054         0.00397545         0.107745966           LOC100040239         1.66597054         0.00397545         0.107745966           LOC100040239         1.6597056         0.00377413         0.105745966           Megf6         1.67934956         0.003774396         0.105745966           Gm1968         1.66749397         0.1173284         0.10773281           Gm1968         1.67934953         0.01574596         0.10773281           Gm1966         1.67945953         0.01574596	2610528A11Rik	1.624561095	0.033008578	0.112848689
Dubl         1.62811952         0.007985305         0.107008823           llaorb         1.628796312         0.025021131         0.110291413           Gm894         1.623306833         0.03940659         0.11369285           Krtap5-3         1.633341773         0.006207674         0.105745966           Bglap1         1.633941779         0.006207674         0.105745966           LCQ38094         1.64356286         0.105745966         0.10773281           Texza         1.64879768         0.00033784         0.10705883           Dynlrba         1.664779653         0.002467466         0.105745966           Ccr7         1.66571024         0.002467486         0.105745966           LOC10000329         1.665870976         0.00319785         0.105745966           LOC10000329         1.672480701         0.00319785         0.105745966           Gm6ry5         1.672491033         0.00189628         0.105745966           Gmary6         1.66989037         0.005319785         0.105745966           Gmary6         1.67249103         0.005319785         0.105745966           Gmary6         1.67249103         0.005319785         0.105745966           Gmary6         1.672490436         0.005319785         <	2310034G01Rik	1.627265888	0.001232438	0.105745966
Ibarb         1.628789312         0.025021131         0.110291413           Gm8994         1.63236833         0.03394059         0.11690285           Krtap5-3         1.633341729         0.0066207674         0.12020897           JBglap1         1.633341729         0.00682366         0.105745966           LOC380994         1.64786768         0.00883251         0.10708823           Dynlhbz         1.661797853         0.010216646         0.10773381           Dynlhbz         1.665717024         0.002467486         0.105745966           CC7         1.665717024         0.002467486         0.105745966           LOC100040329         1.665870976         0.00841497         0.107008823           LOC100040329         1.665870976         0.0033465         0.105745966           LOC100040329         1.665870976         0.0033465         0.105745966           LOC100040329         1.665870976         0.0035319785         0.105745966           Gm6y6         1.67280901         0.005319785         0.105745966           Gm795         1.67280933         0.005757487         0.1173284           Gm1968         1.6968938         0.002757387         0.1173284           Gm1964         1.720152731         0.005795953 <td>Duxbl</td> <td>1.628119582</td> <td>0.007985305</td> <td>0.107008823</td>	Duxbl	1.628119582	0.007985305	0.107008823
Gm894         1.63236833         0.03346059         0.11369285           Krtaps-3         1.633341732         0.04781024         0.12020897           Bglap1         1.633941779         0.066307674         0.105743506           LOC380994         1.64356296         0.000882866         0.105743506           LOC380994         1.64376873         0.00216646         0.10773381           H2-Mito.2         1.664839769         0.003971442         0.105745966           Ccr         1.65579076         0.00841497         0.107008823           H2-Mito.2         1.665870976         0.00841497         0.107048833           Hpse         1.6771086794         0.0039465         0.105745966           Card         1.672939166         0.00574596         0.105745966           Gmbry5         1.673432083         0.001886628         0.105745966           Gabre         1.673432083         0.00189648         0.105745966           Gabre         1.673432083         0.00189645         0.10773381           A130066N16Rik         1.70149655         0.01773381         0.11732284           Gm6193         1.72145951         0.015743596         0.10773381           A130066N16Rik         1.70149655         0.01973381         <	Il2orb	1.628789312	0.025021131	0.110291413
Carsopy       Cosystep:059       Cosystep:059       Cosystep:059         Bglap1       1.633341732       Cost20697       Cost20697         Bglap1       1.633341732       Cost20697       Cost20697         LOC380904       1.643562866       Cost20697       Cost20697         LOC380904       1.643562866       Cost2745966       Cost2745966         Dynhbz       1.664789768       Cost206746       Cost2745966         Car7       1.665971024       Cost267486       Cost2745966         LOC1cood9239       1.665970976       Cost267486       Cost2745966         LOC1cood9239       1.665970976       Cost267487       Cost2745966         LOC1cood9239       1.665970976       Cost274785       Cost2745966         Car7       1.67280901       Cost29747       Cost2745966         Car6795       1.6728091366       Cost27477       Cost745966         Garbee       1.67834536       Cost27477       Cost745966         Garbee       1.67834536       Cost27487       Cost745966         Garbee       1.69869138       Cost27487       Cost74595         Garbee       1.69869138       Cost27487       Cost74595         Garbee       1.69869138       Cost298595       Cost	Gm8004	1 622260822	0.022046050	0.112600285
Krtap-3         1.93341732         0.0470104         0.1200897           Bglap1         1.639341779         0.06627674         0.105745966           LOC380994         1.647562866         0.105745966         0.105745966           Dynlhb2         1.64768753         0.000833581         0.10708823           H2-M10.2         1.668776853         0.0003071412         0.105745966           Ccr7         1.665717024         0.002467486         0.105745966           Ccr7         1.6658709076         0.00844197         0.107008823           Hpse         1.6712809701         0.003519785         0.105745966           Carb         1.672809701         0.005319785         0.105745966           Gabre         1.67343085         0.00574713         0.105745966           Gabre         1.673432083         0.00188628         0.105745966           Gabre         1.673432083         0.002567487         0.111732284           Gantof6         1.6861739         0.015743966         0.002752831           A130066N16Rik         1.701487635         0.01651768         0.107723281           A130066N16Rik         1.7018753         0.015745996         0.10273295           LOC100039614         1.7489753         0.010773281	Kalaan a	1.032300033	0.033940039	0.113099203
lsgap1         1.639341779         0.006207974         0.105743966           LOCS80994         1.6437563866         0.005745966         0.107708823           Dynhb2         1.64789768         0.00337281         0.107708823           Dynhb2         1.664739769         0.003971412         0.10773281           Ccr7         1.665717024         0.002467486         0.105743966           LOCStooug329         1.665870976         0.0084197         0.105743966           LOCCtooug329         1.665870976         0.0030465         0.105743966           Meg16         1.672809701         0.0033475         0.105743966           Gmfv95         1.673432083         0.00784966         0.005743966           Gabre         1.674332083         0.00784966         0.00773281           Gmtv68         1.861739         0.015634537         0.10773281           Enkur         1.69689038         0.016821788         0.10773281           Enkur         1.69689038         0.01682179         0.11173224           Gmtv648         1.701487655         0.0347515         0.11293722           Clmoop514806         1.69743966         0.00773281         0.00773281           Gmtv648         1.701487655         0.0348705         0.	Krtap5-3	1.633341732	0.04781024	0.12020897
LOC,36094         1.643562896         0.000832866         0.103745966           Tex22         1.64776653         0.003335281         0.10708823           JPulh2         1.667776853         0.003971442         0.103745966           Car7         1.665717024         0.0024674966         0.103745966           LOC10004929         1.665870976         0.003465         0.105745966           LOC10004929         1.665870976         0.005317975         0.105745966           Cmf795         1.67280901         0.005317975         0.105745966           Gmf975         1.673432083         0.001889628         0.103745966           Gabre         1.673432083         0.01681788         0.107733281           Gm1968         1.6861739         0.015634537         0.107733281           A130066N16Rik         1.701487635         0.017933156         0.107733281           A130066N16Rik         1.701487635         0.017939156         0.107733161           Gmf648         1.72015731         0.0032687015         0.10723281           Gmf648         1.72018731         0.023687015         0.10723281           Gmf649         1.77018512         0.04823396         0.10773381           Gmf649         1.770221635         0.04823396<	Bglap1	1.639341779	0.006207674	0.105745966
Texa2         1.64789768         0.008335281         0.107008833           Dynlb2         1.661776853         0.010216646         0.10773281           H2-Mio.2         1.66587197024         0.0003971442         0.105745966           Ccr7         1.665870976         0.00341497         0.107008833           Hpse         1.671086794         0.0033465         0.105745966           LOC10004929         1.67086794         0.003319755         0.105745966           Gm6795         1.672991366         0.006377413         0.105745966           Gm6795         1.672991366         0.006377433         0.105745966           Gabre         1.673432083         0.00188628         0.105745966           Ganto68         1.66809038         0.016541758         0.10773281           Gm1068         1.6681739         0.01554557         0.10773281           Gm648         1.701487635         0.03248075         0.1372283           Gm648         1.720152731         0.00789533         0.105745966           Bhmt         1.728966601         0.03246975         0.13253972           Olfra6         1.7352435         0.04893396         0.10773381           Gm10748         1.70021635         0.04893396         0.10773381 <td>LOC380994</td> <td>1.643562896</td> <td>0.000882866</td> <td>0.105745966</td>	LOC380994	1.643562896	0.000882866	0.105745966
Dynliba         1.661776853         0.010216646         0.107723281           Ha-Mio.a         1.664839769         0.003471442         0.105745966           Ccr7         1.665717024         0.002467486         0.105745966           LOC100040329         1.665870976         0.00844197         0.107008823           Hpse         1.671086794         0.0033455         0.105745966           Megf6         1.672809701         0.005319785         0.105745966           Gabre         1.675432083         0.00189628         0.105745966           Gabre         1.675432083         0.0015945745         0.11732284           Gmiy68         1.66689038         0.015634537         0.107723281           Enkur         1.66689038         0.016821788         0.107723281           Gméd61         1.701487655         0.017938156         0.107723281           Gméd48         1.701487635         0.017938156         0.107723281           Gméd48         1.701487637         0.02348705         0.110258377           D/Drace         1.73843458         0.01890394         0.10772381           Gméd48         1.70128731         0.02348705         0.110958377           D/Drace         1.73843458         0.01890394         0.	Tex22	1.64789768	0.008335281	0.107008823
H2-M10.2         1.664393769         0.00397142         0.105743966           Ccry         1.665870976         0.00347486         0.105743966           LOC100040329         1.665870976         0.0033465         0.105743966           Megf6         1.672809701         0.0033465         0.105743966           Megf6         1.672809701         0.005319785         0.105743966           Gabre         1.673432083         0.001889628         0.105743966           Gabre         1.673432083         0.0027657487         0.11732284           Gm1968         1.6861739         0.015634537         0.107723281           Enkur         1.696890338         0.01534537         0.107723281           A130066N16Rik         1.701487635         0.013411594         0.113722583           Gm648         1.720152731         0.005798953         0.105745966           Bhmt         1.728966601         0.003284076         0.11059372           Olfrade         1.753284358         0.01890795         0.11259372           Olfrade         1.753284358         0.01890794         0.105745966           Bhmt         1.72866601         0.00328975         0.11259372           Olfrade         1.753284358         0.018907934         0	Dynlrb2	1.661776853	0.010216646	0.107723281
Ctry         1.057/17024         0.0024f7486         0.105745966           LOC 100040329         1.665870976         0.0024f7486         0.105745966           Megf6         1.672809701         0.0005319785         0.105745966           Gmf0795         1.6728091366         0.006377413         0.105745966           Gabre         1.673432083         0.001889628         0.105745966           E330013P04Rik         1.67884586         0.027657487         0.111732284           Gmi696         1.6681739         0.01581788         0.107723281           Enkur         1.668690388         0.016821788         0.107723281           A130066N16Rik         1.701487635         0.03111594         0.113722583           Gm6219         1.72152731         0.00598953         0.105743966           Bhmt         1.728546661         0.032687015         0.113723281           LOC100039614         1.74475497         0.02324076         0.10058377           Olfrade         1.770221635         0.048923396         0.105743986           Gmi0748         1.770221635         0.048923396         0.105743981           Gmi0748         1.77158512         0.0468957091         0.110578373           Olfrafo         1.780550474         0.0	H2-M10.2	1.664839769	0.003971442	0.105745966
Cx,         Dots/1/024         Dots/1/024         Dots/1/024         Dots/1/024           LOC100040329         1.655870976         0.00841197         0.109708823           Hpse         1.671086794         0.0033465         0.105745966           Megf6         1.672809701         0.005319785         0.105745966           Gmi6795         1.672931366         0.00188628         0.105745966           E330013P04Rik         1.676384586         0.00574596         0.107723281           Gmi498         1.696809338         0.016821788         0.107723281           Enkur         1.696809338         0.015949575         0.113722583           Gm6219         1.718095225         0.017938156         0.107723281           Gm644         1.720152731         0.0032687015         0.112593722           Olfrazó         1.73284358         0.01890394         0.107723281           Olfrazó         1.73284358         0.01890394         0.107723281           Olfrazó         1.720152731         0.002867015         0.112593722           Olfrazó         1.73284358         0.01890394         0.10772381           Olfrazó         1.770128512         0.04685142         0.10772381           Olfrazó         1.77012815         <	Corz.	1 66=717024	0.002467486	0.105745066
Loc.100049329         1.06570970         0.00841197         0.107008823           Hpse         1.671086794         0.0030465         0.105745966           Megt6         1.672809701         0.005319785         0.105745966           Gm6795         1.672991366         0.001889628         0.105745966           Gabre         1.67384586         0.027657487         0.107723281           Gm1968         1.66840338         0.01889628         0.107723281           Enkur         1.669690338         0.016821788         0.107723281           Gm6219         1.718095225         0.017915156         0.107723281           Gm6448         1.720152731         0.00578953         0.105745966           Bhmt         1.728966601         0.02968953         0.107723281           COC00039614         1.74475497         0.02324076         0.110795377           Olfrade         1.753284358         0.01890334         0.107723281           Gm10748         1.77021635         0.004833396         0.105745966           Phypeli         1.771158512         0.04893396         0.107723281           Gm10748         1.77021635         0.004833396         0.107723281           Olfrafo         1.79916525         0.008284509         <		1.003/1/024	0.00240/400	0.103/43900
Inpse         1.671086794         0.00303465         0.105745966           Megf6         1.672809701         0.005319785         0.105745966           Gahre         1.673432083         0.005377413         0.105745966           Gabre         1.673432083         0.001889628         0.105745966           E330013P04Rik         1.678384586         0.027657487         0.111732284           Gm1968         1.6861739         0.015634537         0.107723281           Enkur         1.696890338         0.03411594         0.113722533           Gm6219         1.718095225         0.01793156         0.10773281           Gm648         1.720152731         0.005798953         0.105745966           Bhmt         1.728966601         0.0324076         0.110058377           Olfr26         1.75384358         0.0399494         0.10773281           Gm10748         1.770221635         0.04893396         0.10773281           Gm17748         1.770221635         0.04823396         0.10773281           Gm17748         1.77015812         0.04895142         0.119723073           Olfr475         1.780550474         0.042857091         0.10976823           Pppde1         1.779158512         0.046895142         0.11970	100100040329	1.0050/09/0	0.0004419/	0.10/000023
Megt6         1.672809701         0.005319785         0.105745966           Gmb7y5         1.672891366         0.006377413         0.105745966           Gabre         1.673432083         0.001889628         0.105745966           F330013P04Rik         1.67384586         0.02755747         0.107723281           Gm1968         1.6861739         0.01634537         0.107723281           Fnkur         1.696890338         0.016821788         0.107723281           A130066N16Rik         1.701487635         0.034111594         0.113722583           Gm6219         1.718095225         0.017938156         0.107723281           Gm6648         1.720152731         0.005278953         0.107243281           Gm6649         1.720152731         0.0032687015         0.112593722           LOC100039614         1.744475497         0.02324076         0.110058377           Olfr26         1.770221635         0.00483396         0.107743281           Gm10748         1.770128512         0.00483396         0.107745566           Ppde1         1.77195512         0.004823396         0.107745966           Ppde3         1.7799916525         0.0042857091         0.11926073           Olfr495         1.799916525         0.00428457	нрѕе	1.671086794	0.00303465	0.105745966
Gm6795         1.672991366         0.006377413         0.105745966           Gabre         1.673432083         0.001886628         0.105745966           E330013P04Rik         1.67834586         0.027657487         0.111732284           Gm1968         1.6861739         0.016821788         0.107723281           Enkur         1.696890338         0.016821788         0.107723281           A130066N16Rik         1.701487635         0.034111594         0.113722583           Gm6428         1.720152731         0.005798953         0.105743966           Bhmt         1.72866601         0.032687015         0.11259372           Olfr26         1.73284358         0.01899934         0.107723281           Gm6448         1.7014475497         0.02324076         0.110058377           Olfr26         1.73284358         0.01899034         0.107723281           Gm10748         1.770221635         0.004823396         0.107723281           Gm1748         1.770221635         0.004823396         0.107723281           Olfr26         1.780550474         0.045857091         0.119728073           Olfr495         0.10890734         0.119705073         0.119705073           Olfr495         1.804184234         0.001400764	Megf6	1.672809701	0.005319785	0.105745966
Gabre         1.673432083         0.001889628         0.105745966           E330013P04Rik         1.678384586         0.027657487         0.111732284           Gm1968         1.6861739         0.015634537         0.107723281           Enkur         1.696890338         0.016821788         0.107723281           A130066N16Rik         1.701487635         0.034111594         0.11722283           Gm6219         1.718095225         0.01793156         0.107723281           Gm6648         1.720152731         0.005798953         0.105745966           Bhmt         1.728966601         0.032687015         0.112593722           LOC100039614         1.744475497         0.02324076         0.110593377           Olfr26         1.753284358         0.01890394         0.107723281           Gm10748         1.770221635         0.00483396         0.105745966           Ppde1         1.77158512         0.046895142         0.107723281           Olfr495         1.790550474         0.045857091         0.119708073           Olfr495         1.79991525         0.068284509         0.107008823           Hsd11b1         1.804184234         0.02714435         0.111702249           Bclp2         1.804184234         0.02714435 </td <td>Gm6795</td> <td>1.672991366</td> <td>0.006377413</td> <td>0.105745966</td>	Gm6795	1.672991366	0.006377413	0.105745966
E330013P04Rik         1.678384586         0.027657487         0.11732284           Gm1968         1.6861739         0.015634537         0.107723281           Enkur         1.696890338         0.016821788         0.107723281           A130066N16Rik         1.701487635         0.034111594         0.113722583           Gm6219         1.718095225         0.017938156         0.107723281           Gm6648         1.720152731         0.005798953         0.105745966           Bhmt         1.72866601         0.032687015         0.112593722           LOC 100039614         1.744475497         0.02324076         0.10058377           Olfr26         1.753284358         0.018990394         0.107723281           Gm10748         1.770221635         0.004823396         0.105745966           Pipde1         1.771158512         0.048857901         0.11920873           Olfr26         1.780550474         0.045857091         0.11920873           Olfr495         1.780550474         0.04885509         0.10708823           Hsd11b1         1.804184234         0.041100764         0.117072249           Bclp2         1.804184234         0.02714435         0.11773284           Olfr328         1.807843759         0.015964933	Gabre	1.673432083	0.001889628	0.105745966
Lyber         Lyber         Lyber         Lyber         Lyber           Gm1968         1.6861739         0.015634537         0.107723281           Arjoofe0         1.696890338         0.016821788         0.107723281           A130066N16Rik         1.70148/635         0.034111594         0.113722583           Gm6219         1.718095225         0.017938156         0.107723281           Gm6648         1.720152731         0.005798953         0.105745966           Bhmt         1.728966601         0.032687015         0.112593722           LOC 100039614         1.744475497         0.02324076         0.100723281           Gm10748         1.770221635         0.04893396         0.107723281           Gm10748         1.770221635         0.048895142         0.110928073           Olfr495         1.780550474         0.045857091         0.119728073           Olfr495         1.799916525         0.00824509         0.107008823           Hsd11b1         1.804184234         0.041100764         0.11732284           Olfr328         1.807843759         0.015964933         0.107723281           Gm10534         1.820952555         0.014456206         0.107723281           Klkh11         1.852735156         0	E330013P04Rik	1.678384586	0.027657487	0.111732284
Chingto         1.001739         0.01594337         0.107723281           Enkur         1.696890338         0.016821788         0.107723281           A130066N16Rik         1.701487635         0.034111594         0.113722583           Gm6219         1.718095225         0.017938156         0.107723281           Gm6648         1.720152731         0.005798953         0.105745966           Bhmt         1.728966601         0.032687015         0.112593722           LOC100039614         1.744475497         0.02324076         0.100723281           Gm10748         1.770221635         0.018990394         0.107723281           Gm10748         1.770221635         0.004823396         0.105745966           Pppde1         1.771158512         0.046895142         0.119728073           Olfr495         1.780550474         0.042857091         0.119728073           Olfr495         1.799916525         0.00824509         0.107008823           Hsd11b1         1.804184234         0.041100764         0.117072249           Bclp2         1.804184234         0.02714435         0.107723281           Olfr328         1.807843759         0.015964933         0.107723281           Gm10534         1.820952555         0.01445620	Cm1068	1 6861720	0.015624527	0.107722281
LINUT         1.09890338         0.010821788         0.107723281           A130066N16Rik         1.701487635         0.03411194         0.113722583           Gm6219         1.718095225         0.017938156         0.107723281           Gm6648         1.720152731         0.005798953         0.105745966           Bhmt         1.728966601         0.032687015         0.112593722           LOC100039614         1.744475497         0.02324076         0.105745966           Olfr26         1.753284358         0.018990394         0.107723281           Gm10748         1.77012635         0.004833966         0.105745966           Pppde1         1.771158512         0.048857091         0.11926073           Olfr495         1.790550474         0.045857091         0.119506979           Cpa6         1.79991525         0.062824509         0.107008823           Hsd11b1         1.804184234         0.041100764         0.117072249           Bclp2         1.804184234         0.02714435         0.11773284           Olfr328         1.807843759         0.015964933         0.107723281           Gm10534         1.820952555         0.014456206         0.107723281           Gm105324         1.852735156         0.016132265 <td>Enlarge</td> <td>1.0001/39</td> <td>0.015034537</td> <td>0.10//23201</td>	Enlarge	1.0001/39	0.015034537	0.10//23201
A130066N16Rik       1.701487635       0.034111594       0.113722583         Gm6219       1.718095225       0.017938156       0.107723281         Gm6648       1.720152731       0.0057989533       0.105745966         Bhmt       1.728966601       0.032687015       0.112593722         LOC100039614       1.744475497       0.02324076       0.110058377         Olfr26       1.753284358       0.018990394       0.107723281         Gm10748       1.770221635       0.004823396       0.105745966         Pppde1       1.77115512       0.04855791       0.11928073         Olfr495       1.780550474       0.045857091       0.119708823         Phst       1.780550474       0.04282509       0.10708833         Hsd11b1       1.804184234       0.041100764       0.117072249         Bclp2       1.804184234       0.02714435       0.11732284         Olfr328       1.807843759       0.015964933       0.107723281         Gm10534       1.82095255       0.01456206       0.107723281         Klkb11       1.852735156       0.016132265       0.107723281	Enkur	1.096890338	0.016821788	0.107723281
Gm6219         1.718095225         0.017938156         0.107723281           Gm6648         1.720152731         0.005798953         0.105745966           Bhmt         1.728966601         0.032687015         0.112593722           LOC 100039614         1.744475497         0.02324076         0.107723281           Gm10748         1.753284358         0.018990394         0.107723281           Gm10748         1.77125512         0.048895142         0.10773281           Olfr495         1.77155512         0.048895142         0.119728073           Olfr495         1.780550474         0.045857091         0.119708073           Olfr495         1.799916525         0.008284509         0.107008823           Hsd11b1         1.804184234         0.041100764         0.11792249           Bclp2         1.804184234         0.02714435         0.107723281           Olfr328         1.807843759         0.015964933         0.107723281           Gm10534         1.820952555         0.014456206         0.107723281           Klk1b11         1.852735156         0.014456206         0.107723281	A130066N16Rik	1.701487635	0.034111594	0.113722583
Gm6648         1.720152731         0.005798953         0.105745966           Bhmt         1.728966601         0.032687015         0.112593722           LOC100039614         1.744475497         0.02324076         0.110058377           Olfr26         1.753284358         0.01890394         0.107723281           Gm10748         1.770221635         0.004823396         0.105745966           Pppde1         1.771158512         0.046895142         0.119728073           Olfr495         1.780550474         0.048557091         0.119708079           Cpa6         1.79991525         0.00824509         0.10708823           Hsd11b1         1.804184234         0.041100764         0.11792249           Bclpz         1.804184234         0.02714435         0.11732284           Olfr328         1.807843759         0.015964933         0.107723281           Gm10534         1.820952555         0.014456206         0.107723281           Klk1b11         1.852735156         0.016132265         0.10723281	Gm6219	1.718095225	0.017938156	0.107723281
Bhmt         1.728966611         0.032687015         0.112593722           LOC 100039614         1.744475497         0.02324076         0.11058377           Olfr26         1.753284358         0.018990394         0.107723281           Gm10748         1.770221635         0.004823396         0.105745966           Pppde1         1.771158512         0.046895142         0.11928073           Olfr495         1.780550474         0.045857091         0.119506979           Cpa6         1.799915525         0.008284509         0.10708823           Hsd11b1         1.804184234         0.041100764         0.117072249           Bclp2         1.804184234         0.02714435         0.11732284           Olfr328         1.807843759         0.015964933         0.107723281           Gm10534         1.820952555         0.01456206         0.107723281           Klk1b11         1.852735156         0.016132265         0.10723281	Gm6648	1.720152731	0.005798953	0.105745966
LOC100039614         1.744475497         0.02324076         0.110058377           Olfr26         1.753284358         0.018990394         0.107723281           Gm10748         1.770221635         0.004823396         0.105745966           Pppde1         1.771158512         0.046895142         0.11928073           Olfr495         1.780550474         0.045857091         0.119506979           Cpa6         1.799916525         0.00824509         0.10702249           Bclp2         1.804184234         0.041100764         0.11732284           Olfr328         1.807843759         0.015964933         0.107723281           Gm10534         1.820952555         0.014456206         0.107723281           Klk1b11         1.852735156         0.016132265         0.107723281	Bhmt	1.728966601	0.032687015	0.112593722
1.744479497         0.00292070         0.11005977           Olfr26         1.753284358         0.018990394         0.107723281           Gm10748         1.770221635         0.004823396         0.105745966           Ppde1         1.771158512         0.048895142         0.119728073           Olfr495         1.780550474         0.045857091         0.119506979           Cpa6         1.799916525         0.00824509         0.107008823           Hsd11b1         1.804184234         0.041100764         0.11732284           Olfr328         1.807843759         0.015964933         0.107723281           Gm10534         1.820952555         0.014456206         0.107723281           Klk1b11         1.852735156         0.016132265         0.10773281	LOC100030614	1 744475407	0.02224076	0 110058277
Onizo         1.753204355         0.018909394         0.107723281           Gm10748         1.770221635         0.004823396         0.1077432673           Pppde1         1.771158512         0.046895142         0.119728073           Olfr495         1.780550474         0.045857091         0.119506979           Cpa6         1.799916525         0.00824509         0.107008823           Hsd11b1         1.804184234         0.041100764         0.117072249           Bclpz         1.804184234         0.02714435         0.107723281           Olfr328         1.807843759         0.015964933         0.107723281           Gm10534         1.820952555         0.014456206         0.107723281           Klk1b11         1.852735156         0.016132265         0.10723281	016406	/+++/->+>/	0.023240/0	0.1100.003//
Gm10748         1.770221635         0.004823396         0.105745966           Pppde1         1.771158512         0.046895142         0.11928073           Olfr495         1.780550474         0.045857091         0.119506979           Cpa6         1.799916525         0.008284509         0.107008823           Hsd11b1         1.804184234         0.041100764         0.117072249           Bclp2         1.804184234         0.02714435         0.11732284           Olfr328         1.807843759         0.015964933         0.107723281           Gm10534         1.820952555         0.01456206         0.107723281           Klk1b11         1.852735156         0.016132265         0.10723281	011720	1.753284358	0.018990394	0.10//23281
Pppde1         1.771158512         0.046895142         0.119728073           Olfr495         1.780550474         0.045857091         0.119506979           Cpa6         1.799916525         0.008284509         0.107008823           Hsd11b1         1.804184234         0.041100764         0.11732249           Bclp2         1.807184234         0.02714435         0.11732284           Olfr328         1.807843759         0.015964933         0.107723281           Gm10534         1.820952555         0.014456206         0.107723281           Klk1b1         1.852735156         0.016132265         0.107723281	Gm10748	1.770221635	0.004823396	0.105745966
Olfr495         1.780550474         0.045857091         0.119506979           Cpa6         1.799916525         0.008284509         0.107008823           Hsd1tb1         1.804184234         0.041100764         0.117072249           Bclp2         1.804184234         0.02714435         0.11732284           Olfr328         1.807843759         0.015964933         0.107723281           Gm10534         1.820952555         0.014456206         0.107723281           Klk1b11         1.852735156         0.016132265         0.10723281	Pppde1	1.771158512	0.046895142	0.119728073
Cpa6         1.799916525         0.008284509         0.107008823           Hsd11b1         1.804184234         0.041100764         0.117072249           Bclp2         1.804184234         0.02714435         0.11732284           Olfr328         1.807843759         0.015964933         0.107723281           Gm10534         1.820952555         0.014456206         0.107723281           Klk1b11         1.852735156         0.016132265         0.107723281	Olfr495	1.780550474	0.045857091	0.119506979
Hsd11b1         1.804184234         0.041100764         0.117072249           Bclp2         1.804184234         0.02714435         0.11732284           Olfr328         1.807843759         0.015964933         0.107723281           Gm10534         1.820952555         0.014456266         0.107723281           Klk1b11         1.852735156         0.016132265         0.107723281	Сраб	1.799916525	0.008284509	0.107008823
Instruct         Instruct	Hedithi	1 804184224	0.041100764	0 117072240
Dup2         1.004104254         0.02714435         0.111732264           Olfr328         1.807843759         0.015964933         0.107723281           Gm10534         1.820952555         0.014456206         0.107723281           Klk1b11         1.852735156         0.016132265         0.107723281	Relpa	1 804184234	0.02714425	0.111500084
Olir328         1.807843759         0.015964933         0.107723281           Gm10534         1.820952555         0.014456206         0.107723281           Klk1b11         1.852735156         0.016132265         0.107723281		1.004104234	0.02/14435	0.111732204
Gm10534         1.820952555         0.014456206         0.107723281           Klk1b11         1.852735156         0.016132265         0.107723281	Olfr328	1.807843759	0.015964933	0.107723281
Klk1b11         1.852735156         0.016132265         0.107723281           Continued on next page	Gm10534	1.820952555	0.014456206	0.107723281
Continued on next page	Klk1b11	1.852735156	0.016132265	0.107723281
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Table 6.2 – continued from previous page

Assignment	fc	pv	qv	
Gm5841	1.879101939	0.042109656	0.117171004	
Ccl12	1.907720741	0.032423673	0.112503534	
Spef2	1.969400687	0.002857891	0.105745966	
Tnnt2	1.991460227	0.000830242	0.105745966	
A730020M07Rik	2.011906602	0.001976607	0.105745966	
Spef2	2.035570704	0.007990949	0.107008823	
Spef2	2.074111329	0.04059774	0.116749128	
Ccl17	2.318518653	0.019034701	0.107723281	
Olfr161	2.354123487	0.009348122	0.107723281	
Dbh	2.39085505	0.008901351	0.107600372	
Tdgf1	2.774036301	0.000560319	0.105745966	

Transcript Symbol	Transcript Name	Location
0610037L13Rik		CDS
1110012J17Rik		5'UTR
1110014N23Rik	protein fat-free homolog	CDS
1110032F04Rik	hypothetical protein LOC68725 precursor	CDS
1110034B05Rik		5′UTR
1110051M20Rik	hypothetical protein LOC228356	CDS
1200018I18Rik	NJPolicical protein 20 e220330	2/UTR
1500010J10Kik	hypothetical protein LOC66222	2/UTP
	hypothetical protein LOC66323	3 UIK
1700001O22Rik		CDS
1700017B05Rik	hypothetical protein LOC74211	3'UTR
1700020L24Rik	hypothetical protein LOC66330	CDS
1700030J22Rik	hypothetical protein LOC69528	3'UTR
1700037H04Rik	hypothetical protein LOC67326	3'UTR
1700106N22Rik	hypothetical protein LOC73582	5'UTR
1810011H11Rik	hypothetical protein LOC60060	2'UTR
1810007HTTPik	hypothetical protein LOC67704	CDS
101003/11/Kik	hypothetical protein LOCG-00	CDS
1810043G02Kik	nypotnetical protein LOC67884	CDS
2010109K11Rik	hypothetical protein LOC72123	CDS
2210018M11Rik	protein EMSY	3'UTR
2310021P13Rik	hypothetical protein LOC268721	5'UTR
2310022B05Rik	hypothetical protein LOC69551	CDS
2310022B05Rik	hypothetical protein LOC69551	3'UTR
2310061I04Rik	hypothetical protein LOC69662	3'UTR
2410001C21Rik	hypothetical protein LOC66404	-/UTR
2410001C21KIK	hypothetical protein 10000404	SOL
2010002I17KIK	transmembrane protein 103	
2610002M06Rik	charged multivesicular body protein 1b-2	5'UTR
2610015P09Rik		CDS
2700078E11Rik	hypothetical protein LOC78832 isoform 3	CDS
4632415K11Rik	hypothetical protein LOC74347	CDS
4020420K17Rik	hypothetical protein LOC652025	='UTR
4930420R1/Rik	hypothetical protein LOC7420	CDS
4930452B06KIK	hypothetical protein EOC/4430	CD3
4930539E08R1k	hypothetical protein LOC207819	3'UTR
4932411E22Rik	hypothetical protein LOC214604	CDS
4932412H11Rik	hypothetical protein LOC242838	5'UTR
4933413G19Rik	hypothetical protein LOC71149	3'UTR
5330417C22Rik	hypothetical protein LOC229722	CDS
5420411K18Rik		2/UTR
6220F4FA04Rik	mire domain-containing protein Crarf8e homolog	CDS
		(UTD)
6430548M08K1K	hypothetical protein LOC234797 isoform c	5'UIK
9130011E15Rik	hypothetical protein LOC71617	CDS
9430016H08Rik	hypothetical protein LOC68115 precursor	5'UTR
9430038I01Rik	hypothetical protein LOC77252	3'UTR
9930111J21Rik1	interferon-inducible GTPase family member	3'UTR
A830018L16Rik	hypothetical protein LOC320492 isoform 4	5'UTR
A820002124Rik	hypothetical protein LOC207021	5'UTR
Aamp	angio-associated migratory cell protein isoform	2/LTR
A and	anglo-associated migratory cell protein isoform	-/UTD
Aamp	angio-associated migratory cell protein isoform	5 UIK
Aars	alanyl-tRNA synthetase, cytoplasmic	CDS
Abcb8	ATP-binding cassette sub-family B member 8,	CDS
Abhd2	abhydrolase domain-containing protein 2	3'UTR
Ablim2	actin-binding LIM protein 2 isoform 6	3'UTR
Abr	active breakpoint cluster region-related protein	5'UTR
Abtb2	ankyrin repeat and BTB/POZ domain-containing	5'UTR
Acads	short-chain specific acyl-CoA dehydrogenase	CDS
Acadyl	very long-chain specific acyl-CoA debydrogenase	CDS
Acana	art CAD with coiled coil ANK report and DLI	-/ITP
A shale	art-GAT with concercon, AINK repeat and FFI	-/ITP
ACDOB	acyi-CoA-binding domain-containing protein 6	5 U I K
Accn4	amiloride-sensitive cation channel 4	5 UTR
Acot2	acyl-coenzyme A thioesterase 2, mitochondrial	CDS
Acrbp	acrosin-binding protein isoform 2	CDS
Actb	actin, cytoplasmic 1	5'UTR
Actn4	alpha-actinin-4	5'UTR
Actra	actin-related protein 2	e'HTR
A stee	actin related protein 2	-/ITD
Actr3	actin-related protein 3	5 UTK
Actr3b	actin-related protein 3B	5 UTK
Actr8	actin-related protein 8	5'UTR
Adam23	disintegrin and metalloproteinase	5'UTR
Adamtslı	ADAMTS-like protein 1	CDS
Adcyap1r1	pituitary adenylate cyclase-activating	CDS
Addı	alpha-adducin isoform 2	CDS
Addi	alpha-adducin isoform a	2/LITE
A 11-	apra-auducht isotorin 2	-/UTD
Add2	Deta-adducin	3 U I K
Adra1a	alpha-1A adrenergic receptor	CDS
Adra1a	alpha-1A adrenergic receptor	5'UTR
Adra2a	alpha-2A adrenergic receptor	CDS
Adra2b	alpha-2B adrenergic receptor	CDS

Table 6.3: Transcripts hypermethylated in *Fto*-deficient mice

Table 6.3 - continued from	previous page	
Transcript Symbol	Transcript Name	Methylation site
Adrb3	beta-3 adrenergic receptor	CDS
Aebp2	zinc finger protein AEBP2 isoform 1	CDS
Aff1	AF4/FMR2 family member 1 isoform 1	3'UTR
Aff3	AF4/FMR2 family member 3	3'UTR
Agap2	arf-GAP with GTPase, ANK repeat and PH	5'UTR
Agbl5	cytosolic carboxypeptidase-like protein 5	CDS
Agpat9	glycerol-3-phosphate acyltransferase 3	5'UTR
Ahctf1	protein ELYS	5'UTR
Ahr	aryl hydrocarbon receptor	CDS
AI593442	hypothetical protein LOC330941 isoform 2	5'UTR
Ak3	GTP:AMP phosphotransferase, mitochondrial	CDS
Ak5	adenylate kinase isoenzyme 5	3'UTR
Akap12	A-kinase anchor protein 12	3'UTR
Akap13	A kinase (PRKA) anchor protein 13	3'UTR
Akna	AT-hook-containing transcription factor	CDS
Akt2	RAC-beta serine/threonine-protein kinase	3'UTR
Aldh16a1	aldehyde dehydrogenase family 16 member A1	CDS
Aldh7a1	alpha-aminoadipic semialdehyde dehydrogenase	3'UTR
Alg2	alpha-1,3-mannosyltransferase ALG2	CDS
Alk	ALK tyrosine kinase receptor precursor	CDS
Alkbh3	alpha-ketoglutarate-dependent dioxygenase alkB	CDS
Alkbh5	probable alpha-ketoglutarate-dependent	5'UIK
Amigo1	amphoterin-induced protein 1 isoform 1	5'UIR
Ampd2	AMP deaminase 2	3'U I'K
Angpuz	angiopoletin-related protein 2 precursor	5 UIK
Ank	progressive ankylosis protein	5°UTK
AnK2	ankyrin-2 isoform 3	
Ankrd13b	ankyrin repeat domain-containing protein 13B	3'UIK
Ankrd13d	ankyrin repeat domain-containing protein 13D	5 UIK
Ankra56	ankyrin repeat domain-containing protein 56	5 UTK
Anksi	ankyrin repeat and SAM domain-containing protein	CD5
Anoo	anoctamin-6	5 UIK
Anp32e	acidic leucine-rich nuclear phosphoprotein 32	3 UIK
Auc2	AP a complex subunit beta a	3 UTK
Aphai	amyloid beta (A) precursor protein binding	-/UTR
Ароаг	adapameteus nalumesis seli protein bilang,	-///TP
Apc	adenomatous polyposis con protein	5 UIK
Aplia	amulaid like protein a	-/11TP
App	amyloid-like protein	-/1172
Arani	art CAP with Rho-CAP domain ANK repeat and PH	2/UTR
Arcn1	coatomer subunit delta	='UTR
Arfo	ADP-ribosylation factor 2	= UTR
Arfganz	ADP-ribosylation factor GTPase-activating	2/UTR
Arhgap26	rho GTPase-activating protein 26	CDS
Arhgap33	rho GTPase-activating protein 33	CDS
Arhgap44	81	3'UTR
Arhgef11	rho guanine nucleotide exchange factor 11	CDS
Arhgef17	rho guanine nucleotide exchange factor 17	5'UTR
Arhgef18	rho guanine nucleotide exchange factor 18	CDS
Arhgef2	rho guanine nucleotide exchange factor 2	CDS
Arhgef33	rho guanine nucleotide exchange factor 33	CDS
Arhgef37	rho guanine nucleotide exchange factor 37	3′UTR
Arid1a	AT-rich interactive domain-containing protein	3'UTR
Arl6ip6	ADP-ribosylation factor-like protein	5'UTR
Armc7	armadillo repeat-containing protein 7	CDS
Arpc1a	actin-related protein 2/3 complex subunit 1A	5'UTR
Arsk	arylsulfatase K	3'UTR
Arvcf	armadillo repeat protein deleted in	CDS
Arx	homeobox protein ARX	CDS
Arx	homeobox protein ARX	3'UTR
Asb3	ankyrin repeat and SOCS box protein 3	5'UTR
Ascc2	activating signal cointegrator 1 complex subunit	3'UTR
Asclı	achaete-scute homolog 1	5'UTR
Atf5		CDS
Atg2b	autophagy-related protein 2 homolog B	3'UTR
Atg3	ubiquitin-like-conjugating enzyme ATG3	5'UTR
Atg9a	autophagy-related protein 9A	3'UTR
Atg9b	autophagy-related protein 9B	3'UTR
Atnı	atrophin-1	CDS
Atoh8	protein atonal homolog 8	CDS
Atp10b	probable phospholipid-transporting ATPase VB	CDS
Atp13a2	probable cation-transporting ATPase 13A2 isoform	CDS
Atp1a3	sodium/potassium-transporting ATPase subunit	3'UTR
Atp1a3	sodium/potassium-transporting ATPase subunit	5'UTR
Atp2a2		5'UTR
Atp5d	ATP synthase subunit delta, mitochondrial	CDS
Atp5d	ATP synthase subunit delta, mitochondrial	5'UTR

Table 6.3 – continued from	previous	page
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Cacng4voltage-dependent calcium channel gamma-4CDSCadpscalcium-dependent secretion activator 1 isoform5'UTRCalyneuron-specific vesicular protein calcyon3'UTRCamta2calmodulin-binding transcription activator 2CDSCamta2calmodulin-binding transcription activator 23'UTRCand2cullin-associated NEDD8-dissociated protein 2CDSCaprin2caprin-53'UTRCapzbF-actin-capping protein subunit beta isoform a3'UTRCard6caspase recruitment domain-containing proteinCDSCasp9caspase recruitment domain family, member 6CDSCass4cas scaffolding protein family member 4 isoformCDSCasz1zinc finger protein castor homolog 1 isoform 1CDSCbfazt3protein CBFAzT3 isoform 23'UTRCbfazt3protein CBFAzT3 isoform 23'UTRCoblbE3 ubiquitin-protein ligase CBL-B3'UTR	Cacnb1	voltage-dependent L-type calcium channel subunit	5'UTR
Cadpscalcium-dependent secretion activator 1 isoform5'UTRCalyneuron-specific vesicular protein calcyon3'UTRCamta2calmodulin-binding transcription activator 2CDSCamta2calmodulin-binding transcription activator 23'UTRCand2cullin-associated NEDD8-dissociated protein 2CDSCapp1caprin-53'UTRCapzbF-actin-capping protein subunit beta isoform a3'UTRCard6capsase recruitment domain-containing proteinCDSCasp9capsase recruitment domain-containing proteinCDSCasp9capsase-9CDSCasz1zinc finger protein castor homolog 1 isoform 1CDSCbfazt3protein CBFAzT3 isoform 2CDSCbfazt3protein CBFAzT3 isoform 23'UTRCholbja ubiquitin-protein ligase CBL-B3'UTR	Cacng4	voltage-dependent calcium channel gamma-4	CDS
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Camta2calmodulin-binding transcription activator 2CDSCamta2calmodulin-binding transcription activator 23'UTRCand2cullin-associated NEDD8-dissociated protein 2CDSCapn5calpain-53'UTRCaprin2caprin-25'UTRCard10caspase recruitment domain-containing proteinCDSCard6caspase recruitment domain family, member 6CDSCass4cas scaffolding protein family member 4 isoform 1CDSCasz1zinc finger protein castor homolog 1 isoform 1CDSCbfa2t3protein CBFA2T3 isoform 23'UTRCbfa2t3protein CBFA2T3 isoform 23'UTRCbfa2t3protein CBFA2T3 isoform 2CDSContinued on next nare3'UTR	Caly	neuron-specific vesicular protein calcyon	3'UTR
Camta2calmodulin-binding transcription activator 23'UTRCand2cullin-associated NEDD8-dissociated protein 2CDSCaprincalpain-53'UTRCaprin2caprin-25'UTRCard10caspase recruitment domain-containing proteinCDSCard6caspase recruitment domain-containing proteinCDSCard6caspase recruitment domain-containing proteinCDSCard6caspase recruitment domain-containing proteinCDSCasp3caspase recruitment domain-containing proteinCDSCard6caspase recruitment domain family, member 6CDSCasp4cas scaffolding protein family member 4 isoformCDSCasz1zinc finger protein castor homolog 1 isoform 1CDSCbfa2t3protein CBFA2T3 isoform 2CDSCbfa2t3protein CBFA2T3 isoform 23'UTRCblbis ubiquitin-protein ligase CBL-B3'UTR	Camta2	calmodulin-binding transcription activator 2	CDS
Canday Unit associated NEDD8-dissociated protein 2y UnitCandacullin-associated NEDD8-dissociated protein 2CDSCappicalpain-53'UTRCaprin2caprin-25'UTRCapzbF-actin-capping protein subunit beta isoform a3'UTRCard10caspase recruitment domain-containing proteinCDSCard6caspase recruitment domain-containing proteinCDSCard6caspase recruitment domain family, member 6CDSCasp9caspase-9CDSCasz1zinc finger protein castor homolog 1 isoform 1CDSCbfa2t3protein CBFA2T3 isoform 2CDSCbfa2t3protein CBFA2T3 isoform 23'UTRCblbE3 ubiquitin-protein ligase CBL-B3'UTR	Camta2	calmodulin-binding transcription activator 2	3'UTR
CapitalCabinal associated responsibilityContinue protein 2Capitalcalpain-53'UTRCaprinacaprin-25'UTRCapitalF-actin-capping protein subunit beta isoform a3'UTRCardiocaspase recruitment domain-containing proteinCDSCard6caspase recruitment domain family, member 6CDSCass4cas scaffolding protein family member 4 isoformCDSCasz1zinc finger protein castor homolog 1 isoform 1CDSCbfazt3protein CBFAzT3 isoform 2CDSCbfazt3protein CBFAzT3 isoform 23'UTRCblbE3 ubiquitin-protein ligase CBL-B3'UTR	Canda	cullin-associated NEDD8-dissociated protein 2	CDS
Capity3 URCapitycapity5 UTRCapityGaptin-25 UTRCapzbF-actin-capping protein subunit beta isoform a3 UTRCardtocaspase recruitment domain-containing proteinCDSCard6caspase recruitment domain family, member 6CDSCasp9caspase-9CDSCasz1zinc finger protein castor homolog 1 isoform 1CDSCbfa2t3protein CBFA2T3 isoform 2CDSCbfa2t3protein CBFA2T3 isoform 23'UTRCblbE3 ubiquitin-protein ligase CBL-B3'UTR	Cappe	calmain-r	o'UTR
Capini2Capini25 UIKCapini2F-actin-caping protein subuni beta isoform a3'UTRCardiocaspase recruitment domain-containing proteinCDSCardócaspase recruitment domain family, member 6CDSCasp9caspase-9CDSCasz4cas scaffolding protein family member 4 isoform 1CDSCbfa2t3protein CBFA2T3 isoform 2CDSCbfa2t3protein CBFA2T3 isoform 23'UTRCbbE3 ubiquitin-protein ligase CBL-B3'UTR	Capring	carpan-2	-/ UTD
LapzoF-actin-capping protein subunit beta isoform a3'UTRCard10caspase recruitment domain-containing proteinCDSCard6caspase recruitment domain family, member 6CDSCasp9caspase-9CDSCas21zinc finger protein castor homolog 1 isoform 1CDSCbfa2t3protein CBFA2T3 isoform 2CDSCbfa2t3protein CBFA2T3 isoform 23'UTRCblbE3 ubiquitin-protein ligase CBL-B3'UTR	Caprin2	caprin-2	5 UIK
Cardiocaspase recruitment domain-containing proteinCDSCardócaspase recruitment domain family, member 6CDSCasp9caspase-9CDSCass4cas scaffolding protein family member 4 isoformCDSCasz1zinc finger protein castor homolog 1 isoform 1CDSCbfazt3protein CBFA2T3 isoform 2CDSCbfazt3protein CBFA2T3 isoform 23'UTRCbfazt3go upiquitin-protein ligase CBL-B3'UTR	Capzb	r-actin-capping protein subunit beta isoform a	3 UIK
Card6caspase recruitment domain family, member 6CDSCasp9caspase-9CDSCass4cas scaffolding protein family member 4 isoformCDSCasz1zinc finger protein castor homolog 1 isoform 1CDSCbfazt3protein CBFA2T3 isoform 2CDSCbfazt3protein CBFA2T3 isoform 23'UTRCblbE3 ubiquitin-protein ligase CBL-B3'UTR	Card10	caspase recruitment domain-containing protein	CDS
Casp9caspase-9CDSCass4cas scaffolding protein family member 4 isoformCDSCasz1zinc finger protein castor homolog 1 isoform 1CDSCbfa2t3protein CBFA2T3 isoform 2CDSCbfa2t3protein CBFA2T3 isoform 23'UTRCbb3 ubiquitin-protein ligase CBL-B3'UTR	Card6	caspase recruitment domain family, member 6	CDS
Cass4cas scaffolding protein family member 4 isoformCDSCasz1zinc finger protein castor homolog 1 isoform 1CDSCbfazt3protein CBFAzT3 isoform 2CDSCbfazt3protein CBFAzT3 isoform 23'UTRCblbE3 ubiquitin-protein ligase CBL-B3'UTR	Casp9	caspase-9	CDS
Casz1     zinc finger protein castor homolog 1 isoform 1     CDS       Cbfa2t3     protein CBFA2T3 isoform 2     CDS       Cbfa2t3     protein CBFA2T3 isoform 2     3'UTR       Cblb     E3 ubiquitin-protein ligase CBL-B     3'UTR	Cass4	cas scaffolding protein family member 4 isoform	CDS
Cbfa2t3     protein CBFA2T3 isoform 2     CDS       Cbfa2t3     protein CBFA2T3 isoform 2     3'UTR       Cblb     E3 ubiquitin-protein ligase CBL-B     3'UTR	Caszı	zinc finger protein castor homolog 1 isoform 1	CDS
Cbfa2t3     protein CBFA2T3 isoform 2     3'UTR       Cblb     E3 ubiquitin-protein ligase CBL-B     3'UTR	Cbfa2t3	protein CBFA2T3 isoform 2	CDS
Cblb E3 ubiquitin-protein ligase CBL-B 3'UTR Continued on next nage	Cbfa2t3	protein CBFA2T3 isoform 2	3'UTR
Continued on next nage	Cblb	E3 ubiquitin-protein ligase CBL-B	3'UTR
Cantonication			Continued on next page

Table 6.3 – continued from previou	is page	
Transcript Symbol	Transcript Name	Methylation site
Ccbe1	collagen and calcium-binding EGF	CDS
Ccbp2	chemokine-binding protein 2	3'UTR
Ccdc102a	coiled-coil domain-containing protein 102A	CDS
Ccdc120	coiled-coil domain containing 120	CDS
Ccdc142	coiled-coil domain-containing protein 142	CDS
Code48	coiled-coil domain-containing protein 48	CDS
Cadagga	coned-con domani-containing protein 40	-/11TP
Ccdc88a		5 UIR
Ccdc88b	colled-coll domain-containing protein 88B	CDS
Ccdc96	coiled-coil domain-containing protein 96	3'UTR
Ceng1	cyclin-G1	5'UTR
Ccnl1	cyclin-L1	5'UTR
Cd248	endosialin precursor	CDS
Cd248	endosialin precursor	3'UTR
Cd33	myeloid cell surface antigen CD33 isoform 1	CDS
Cd40		3'UTR
Cd93	complement component C1q receptor	CDS
Cd93	complement component C1g receptor	3'UTR
Cdan1	codanin-1	CDS
Cdc25b	M-phase inducer phosphatase 2 isoform b	CDS
Cdc42bph	serine /threenine-protein kinase MRCK heta	-/IITR
Cdc42000	CDC (2 small affector protein 1 isoform 2	CDS
Callere	CDC42 small effector protein 1 isoform 2	CDS CDS
Caniz	cadnerin-13 precursor	CDS
Cdh2	cadherin-2 precursor	5'UIR
Cdh22	caunerin-22 precursor	5 UIK
Cdh24	cadherin-24 precursor	CDS
Cdh5	cadherin-5 precursor	CDS
Cdh5	cadherin-5 precursor	3'UTR
Cdhr1	cadherin-related family member 1 precursor	CDS
Cdk12	cell division protein kinase 12 isoform 2	5'UTR
Cdk18	cell division protein kinase 18	3'UTR
Cdkl3	cyclin-dependent kinase-like 3 isoform 6	5'UTR
Cdkn1a	cyclin-dependent kinase inhibitor 1	CDS
Cdea	phosphatidate cytidylyltransferase 2	CDS
Celfa	CUCRP Flav-like family member 2	2/UTR
Colorr	codharin ECE LAC coven page C type recentor 1	CDS
Colorr	cadherin EGE LAG seven pass G type receptor 1	CD3
Celsri	cadnerin EGF LAG seven-pass G-type receptor 1	3 UIR
Celsr3	cadherin EGF LAG seven-pass G-type receptor 3	3'UTR
Cenpm	centromere protein M isoform 2	3'UTR
Cep350	centrosome-associated protein 350	5'UTR
Cftr	cystic fibrosis transmembrane conductance	3'UTR
Chadl	chondroadherin-like	CDS
Chd4	chromodomain-helicase-DNA-binding protein 4	5'UTR
Chga	chromogranin-A precursor	3'UTR
Chmp2b	charged multivesicular body protein 2b	5'UTR
Chrm3	muscarinic acetylcholine receptor M3	5'UTR
Chrna3	neuronal acetylcholine receptor subunit alpha-3	CDS
Chrnb2	neuronal acetylcholine receptor subunit beta-2	5'UTR
Chst1	carbohydrate sulfotransferase 1	5'UTR
Chetta	carbohydrate culfotransferace 14	CDS
Chista	carbohydrate sulfotransferase a	CDS CDS
Chata	carbonydrate sufficiences a	CDS CDS
Clist5	carbonyurate suirotransferase 5	
	citron kno-interacting kinase	CDS CDS
Cited4	cbp/p300-interacting transactivator 4	CDS
Clcn1	chloride channel protein 1	CDS
Clcn4-2	H(+)/Cl(-) exchange transporter 4	5'UTR
Clcn7	H(+)/Cl(-) exchange transporter 7	3'UTR
Cldn11	claudin-11	CDS
Cldn26		5'UTR
Cldn3	claudin-3	CDS
Clec16a	protein CLEC16A	5'UTR
Clip3	CAP-Gly domain-containing linker protein 3	5'UTR
Clk3	dual specificity protein kinase CLK3	CDS
Clmn	calmin isoform b	CDS
Clnk	cytokine-dependent hematopoietic cell linker	2'UTR
Clth	clathrin light chain B	=/LITR
Cmpka	IMP-CMP kinase a mitochondrial program	CDS
Cmpk2	CVLE like MADVEL transmontheres density control	CDS
Cmtm3	CKLF-IIKE MAKVEL transmembrane domain-containing	
Cmya5	cardiomyopathy-associated protein 5	CDS
Cnga3	cyclic nucleotide-gated cation channel alpha-3	CDS
Cnksr3	connector enhancer of kinase suppressor of ras	CDS
Cnnm1	metal transporter CNNM1	3'UTR
Cnr1	cannabinoid receptor 1	5'UTR
Cntn2	contactin-2 precursor	5'UTR
Cntnap1	contactin-associated protein 1 precursor	CDS
Cntnap5c	contactin-associated protein like 5-3 precursor	CDS
Cobrai	negative elongation factor B	3'UTR
Cobra1	negative elongation factor B	5′UTR
Cog7	conserved oligometric Golgi complex subunit 7	3'UTR
- 0/		J

Table 6.3 – continued from previous page

Transcript Symbol	Transcript Name	Methylation site
Col27a1	collagen alpha-1(XXVII) chain precursor	CDS
Col5a1	collagen alpha-1(V) chain precursor	3'UTR
Col6a2	collagen alpha-2(VI) chain precursor	CDS
Commd8	COMM domain-containing protein 8	CDS
Cops6	COP9 signalosome complex subunit 6	3'UTR
Cops7a	COP9 signalosome complex subunit 7a isoform 1	CDS
Cops7a	COP9 signalosome complex subunit 7a isoform 1	3'UTR
Cops7a	COP9 signalosome complex subunit 7a isoform 1	5'UTR
Coro1b	coronin-1B	5'UTR
Coro2b	coronin-2B	CDS
Cox8a	cytochrome c oxidase subunit 8A, mitochondrial	CDS
Cpne5	copine-5	3'UTR
Cpne6	copine-6 isoform a	5'UTR
Cpne7	copine-7	CDS
Cpne8	copine-8 isoform 1	3'UTR
Срох	coproporphyrinogen-III oxidase, mitochondrial	CDS
Cpsf4	cleavage and polyadenylation specificity factor	5'UTR
Cpxm1	probable carboxypeptidase X1 precursor	3'UTR
Crebl2	cAMP-responsive element-binding protein-like 2	5′UTR
Creg1	protein CREG1	CDS
Crim1	cysteine-rich motor neuron 1 protein precursor	5′UTR
Crtc1	CREB-regulated transcription coactivator 1	3'UTR
Crtc2	CREB-regulated transcription coactivator 2	CDS
Cry2	cryptochrome-2	CDS
Crvab	alpha-crystallin B chain	CDS
Crybga	beta/gamma crystallin domain-containing protein	3'UTR
Csdc2	cold shock domain-containing protein C2	a'UTR
Csfir	macrophage colony-stimulating factor 1 receptor	2/UTR
Csf2ra	granulocyte-macrophage colony-stimulating factor	2/UTR
Cenkid	casein kinase Lisoform delta isoform 1	-/UTR
Cepga	chondroitin sulfate protocolucan 4 procursor	2/UTR
Cspg4 Ctdcpl	CTD cmall phoephatace like protoin	CDS
Ctuspi	catonin hota 1	-/LITE
Chanda	caterini delta a	CDC
Child2	CTP combace a icoform a	-/LITR
Ctps2 Cttphpapl	CTT Synthase 2 Isolorin a	CDS
Ctubp2h	CHE 1 CHE 1 CHE	CD3
Cuedci	CUE domain-containing protein 1 isoform 2	5'UIR
Cynpi	cytoplasmic FMR1-interacting protein 1 isoform	5'UIK
Cynp2	cytoplasmic FMR1-interacting protein 2	CDS (DS
Cyp2d22	cytochrome P450, family 2, subfamily d,	CDS
Cyp2d22	cytochrome P450, family 2, subfamily d,	5'UIK
Cyp2s1	cytochrome P450 2S1	CDS
Cyp2s1	cytochrome P450 251	3'UTR
Cyp4f16	cytochrome P450, family 4, subfamily f,	3'UTR
D16Ertd472e	protein EURL homolog	5'UTR
D430042O09R1k	hypothetical protein LOC233865	CDS
D630003M21Rik	hypothetical protein LOC228846 isoform 2	CDS
D630045J12R1k	hypothetical protein LOC330286	CDS
D630045J12Rik	hypothetical protein LOC330286	3'UTR
Daam2	disheveled-associated activator of morphogenesis	5'UTR
Dab2	disabled homolog 2 isoform b	CDS
Dag1	dystroglycan precursor	5'UTR
Dap	death-associated protein 1	3'UTR
Darc	Duffy antigen/chemokine receptor	CDS
Dbn1	drebrin isoform 2	CDS
Dcat1211	DDB1- and CUL4-associated factor 12-like protein	5 UTR
Dcat1212	DDB1- and CUL4-associated factor 12-like protein	CDS
Dcbld2	discoidin, CUB and LCCL domain-containing	3'UTR
Dclk1	serine/threonine-protein kinase DCLK1 isoform 3	CDS
Dctn1	dynactin subunit 1	CDS
Ddx17	probable ATP-dependent RNA helicase DDX17	5'UTR
Ddx39b		5'UTR
Ddx54	ATP-dependent RNA helicase DDX54	CDS
Dennd1a	DENN domain-containing protein 1A	CDS
Dennd1a	DENN domain-containing protein 1A	3'UTR
Dennd3	DENN domain-containing protein 3	CDS
Dennd3	DENN domain-containing protein 3	3'UTR
Dgke	diacylglycerol kinase epsilon	5'UTR
Dhcr24	24-dehydrocholesterol reductase precursor	CDS
Dhx38	pre-mRNA-splicing factor ATP-dependent RNA	3'UTR
Diap1	protein diaphanous homolog 1	3'UTR
Dimt1	probable dimethyladenosine transferase	CDS
Dio2	type II iodothyronine deiodinase	5'UTR
Dio3	type III iodothyronine deiodinase	3'UTR
Dip2c	disco-interacting protein 2 homolog C	5'UTR
Dis3l	DIS3-like exonuclease 1 isoform 2	5'UTR
Disp2	protein dispatched homolog 2	CDS
Disp2	protein dispatched homolog 2	5'UTR
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Table 6.3 – continued from previo	bus page	
Iranscript Symbol	Iranscript Name	Methylation site
Dlgap1	disks large-associated protein 1 isoform 4	3'UTR
Dlx2	homeobox protein DLX-2	3'UTR
Dmp1	dentin matrix acidic phosphoprotein 1 precursor	3'UTR
Dnahc9	dynein heavy chain 9, axonemal	CDS
Dnajb5	dnaJ homolog subfamily B member 5	CDS
Dnm1	dynamin-1	CDS
Dnm1	dynamin-1	3'UTR
Dock9	dedicator of cytokinesis protein 9 isoform 4	CDS
Dopev2	protein dopey-2 isoform 2	3'UTR
Dopev2	protein dopey-2 isoform 2	5'UTR
Dot1	histone-lysine N-methyltransferase H2 lysine-70	2'UTR
Dpp6	dipentidyl aminopentidase-like protein 6 isoform	='ITR
Dppo	dipentidyl pentidase o	2/UTR
Dovela	dihydronyrimidinaso rolatod protoin a	-/11TP
Dpysiz	dihydropyfinidinase-related protein 2	-/UTB
Dysis	D(x) demonstration means for	SOL
Dra3	D(3) dopamine receptor	CDS
Dscamii	Down syndrome cell adhesion molecule-like	CD5
Dscamli	Down syndrome cell adhesion molecule-like	3'UTR
Dse	dermatan-sulfate epimerase precursor	5'UTR
Dtx3	protein deltex-3	CDS
Dtx3l	E3 ubiquitin-protein ligase DTX3L	CDS
Dtx4	protein deltex-4	5'UTR
Dus1l	tRNA-dihydrouridine synthase 1-like	CDS
Dusp4	dual specificity protein phosphatase 4	CDS
Dvl3	segment polarity protein dishevelled homolog	CDS
Dzip1	zinc finger protein DZIP1	3'UTR
E130308A19Rik	hypothetical protein LOC230259 isoform 2	3'UTR
E130309D14Rik	hypothetical protein LOC432582	CDS
Ebf2	transcription factor COE2	3'UTR
Ece1	endothelin-converting enzyme 1	CDS
Ece1	endothelin-converting enzyme 1	3'UTR
Ece2	endothelin-converting enzyme 2 isoform e	5'UTR
Edfa	endothelial differentiation-related factor 1	='UTR
Edila	ECE-like repeat and discoidin I-like	-/UTR
Edil3	EGF-like repeat and discoluli f-like	SOIR
Endi	er-nand domain-containing protein D1	CD5
Embi	ephrin-B1 precursor	3'UIR
Egr3	early growth response protein 3	3'UTR
Egr4	early growth response protein 4	CDS
Egr4	early growth response protein 4	3'UTR
Ehd4	EH domain-containing protein 4	CDS
Eif1ad	probable RNA-binding protein EIF1AD	5'UTR
Eif4g3	eukaryotic translation initiation factor 4 gamma	5'UTR
Elac2	zinc phosphodiesterase ELAC protein 2	CDS
Elfn2	leucine-rich repeat and fibronectin type-III	5'UTR
Elk3	ETS domain-containing protein Elk-3 isoform a	CDS
Elmo1	engulfment and cell motility protein 1 isoform	5'UTR
Elovl4	elongation of very long chain fatty acids	5'UTR
Emilin2	EMILIN-2 precursor	CDS
Enı	homeobox protein engrailed-1	CDS
Enho	adropin precursor	5'ITR
Eno2	gamma-enolase	5'UTR
Entrol	ectonucleoside triphosphate diphosphohydrolase	2/1 ITR
Entpd:	actonucleoside triphosphate diphosphohydrolase	JUTR
Entrd6	ectonucleoside triphosphate diphoephohydrolase 5	2/ITP
Engel	andothelial PAS domain-containing protoin t	CDS
Epha 1	hand 4 t-like protoin 1 icoform h	-/ITP
Epo4.III Epo48	onhrin tuno A recentor & producer	5 UTR
Ephao	epinini type-A receptor 8 precursor	3 UIK
Epho	epitin type-b receptor 1 isoform 2	5 UIK
Epnb3	epnrin type-B receptor 3 precursor	CDS
Ephb3	ephrin type-B receptor 3 precursor	5'UTR
Eps15l1	epidermal growth factor receptor substrate	CDS
Eps8	epidermal growth factor receptor kinase	CDS
Erbb2	receptor tyrosine-protein kinase erbB-2	3'UTR
Ercc1	DNA excision repair protein ERCC-1 isoform b	3'UTR
Espn	espin isoform 2	CDS
Esrra	steroid hormone receptor ERR1	CDS
Esrrb	steroid hormone receptor ERR2 isoform 2	CDS
Etfdh	electron transfer flavoprotein-ubiquinone	5'UTR
Etl4	sickle tail protein isoform e	CDS
Etnk2	ethanolamine kinase 2	CDS
Ets1	protein C-ets-1 isoform 2	3′UTR
Etsi	protein C-ets-1 isoform 2	5'UTR
Ety6	transcription factor FTV6	CDS
Evol	anyonlakin	CDS
Even	envopianii	CDS CDS
EXOCI	exocyst complex component 1	
EXOC6D	SEC15-IIKE 2	5'UIK
F2r	proteinase-activated receptor 1 precursor	CDS
Faim	tas apoptotic inhibitory molecule 1 Faim-L	CDS

Table 6.3 – continued from previous p	page
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Transcript Symbol	Transcript Name	Methylation site
Faim2	fas apoptotic inhibitory molecule 2 isoform 1	CDS
Faima	fas apoptotic inhibitory molecule 2 isoform 1	2/LITP
Faime	fas apoptotic inhibitory molecule 2 isoform 1	-/1170
Faim2	ras apoptotic inhibitory molecule 2 isoform 1	501K
Fam100a	hypothetical protein LOC207740	CDS
Fam100b	hypothetical protein LOC319370	CDS
Fam102a	family with sequence similarity 102, member A	5'UTR
Fam120c	constitutive coactivator of PPAR-gamma-like	5'UTR
Fam125a	hypothetical protein I OC68187	='LITR
Familya	nypomencal protein EOC00107	-////TD
Fam159D	membrane protein FAM1596	501K
Fam160a1	hypothetical protein LOC229488	CDS
Fam16ob2	family with sequence similarity 160, member B2	CDS
Fam163b	hypothetical protein LOC109349	CDS
Fam163b	hypothetical protein LOC109349	3'UTR
Fam164c	family with sequence similarity 164, member C	3'UTR
Familera	hymothetical protein LOCate 18	CDS
Faiiit0/a	hypothetical protein LOC219148	CDS
Fam167b	hypothetical protein LOC230766	CDS
Fam174b	membrane protein FAM174B precursor	CDS
Fam178a	hypothetical protein LOC226151	5'UTR
Fam179b	hypothetical protein LOC328108	5'UTR
Fam184b	hypothetical protein LOC58227	CDS
Fam184b	hypothetical protein LOC58227	2/LTR
Fame 8 ch	hypothetical protein LOC-902-	-/1 ITD
Fain184D	hypothetical protein LOC58227	5 U I K
Fam189a2	hypothetical protein LOC381217	CDS
Fam189b	hypothetical protein LOC68521	5'UTR
Fam190a	hypothetical protein LOC232035	5'UTR
Fam196a	hypothetical protein LOC627214	3'UTR
Familoox	hypothetical protein LOC245622	5'11TR
Famaoaa	Apponential protein ECC243022	CDS
Fam203a	1 4 4 1 4 100 4	CD3
Fam65a	nypothetical protein LOC75687	CDS
Fam78a	hypothetical protein LOC241303	3'UTR
Fam78a	hypothetical protein LOC241303	5'UTR
Fam82a2	regulator of microtubule dynamics protein 3	CDS
Fam8oa	family with sequence similarity 80 member A	CDS
Fameob	anni fran sequence sinnan f 39, member 11	CDS
Fallogo		CDS
Fanci	E3 ubiquitin-protein ligase FANCL	CDS
Farp1	FERMRhoGEF (Arhgef) and pleckstrin domain	CDS
Fatı	FAT tumor suppressor homolog 1	3'UTR
Fat2	protocadherin Fat 2	CDS
Fbrs	fibrosin-1	CDS
Fbrelı	fibrosin-like 1 isoform 1	CDS
Ebula	E hou /I BB repeat motoin an icoform a	CDS
FDXI12	F-box/LKK-repeat protein 12 isoform a	CD5
FDXI17	F-box/LKK-repeat protein 17	5018
Fbxl6	F-box/LRR-repeat protein 6	CDS
Fbxl7	F-box/LRR-repeat protein 7	CDS
Fbx18	F-box/LRR-repeat protein 8	5'UTR
Fbx010	F-box only protein 10	3'UTR
Fbx042	F-box only protein 42	2'UTR
Ebyurz	E hay (WD repeat containing protain $\pi$ isoform a	-/1170
FDXW/	T-box/ wb repeat-containing protein / isotorin 2	SUIK
Fchsd2	FCH and double SH3 domains protein 2 isoform 2	5'UTR
Fcrlb	Fc receptor-like B	CDS
Fdxr	NADPH:adrenodoxin oxidoreductase, mitochondrial	CDS
Fen1	flap endonuclease 1	5'UTR
Fgd5	FYVE, RhoGEF and PH domain-containing protein 5	CDS
Føds	FYVE RhoGEF and PH domain-containing protein 5	2/1 TR
Fafi	hanarin-hinding growth factor a program	CDS
1 611 Eafra	fibushlast anouth factor of	_/IITP
FgI13	noroblast growth factor 13	5'UIK
Fgfbp3	tibroblast growth factor-binding protein 3	CDS
Flad1	FAD synthase	CDS
Flt1	vascular endothelial growth factor receptor 1	5'UTR
Fmod	fibromodulin precursor	CDS
Fnak	fructosamine-2-kinase isoform b	2/1 ITR
Enhar	formin hinding motion a isoform	-/1 ITD
FIIOPI	iorinin-binding protein 1 isoform e	5 01K
Fndc1	fibronectin type III domain-containing protein	3'UTR
Fndc3b	fibronectin type III domain-containing protein	CDS
Fos	proto-oncogene c-Fos	5'UTR
Fosl2	fos-related antigen 2	CDS
Foxa1	henatocyte nuclear factor 2-alpha	CDS
Foxci	forkhead box protein Cr	CDS
Toxel	forklead box protein C1	-(1)70
Foxd1	torkhead box protein D1	3 UTR
Foxk1	forkhead box protein K1	CDS
Foxp4	forkhead box protein P4 isoform 2	CDS
Foxp4	forkhead box protein P4 isoform 2	3'UTR
Foxa1	forkhead box protein O1	CDS
Frasi	extracellular matrix protain FRAS1 procursor	e'I ITR
F1451	EDACe related active 11.1	SOL
rrem2	rKA51-related extracellular matrix protein 2	
Frem2	FRAS1-related extracellular matrix protein 2	3'UTR
Frmd4a	FERM domain-containing protein 4A isoform 1	CDS
Frmd8	FERM domain-containing protein 8	CDS
		Continued on next page

Table 6.3 – continued from previou	15 page	
Transcript Symbol	Transcript Name	Methylation site
Fscn1	fascin	3'UTR
Fto	alpha-ketoglutarate-dependent dioxygenase FTO	3'UTR
Fut4	alpha-(1,3)-fucosyltransferase	CDS
Fyco1	FYVE and coiled-coil domain-containing protein	CDS
Fyn	tyrosine-protein kinase Fyn isoform a	CDS -/IITP
Fzdi	frizzled-1 precursor	='UTR
Fzd10	frizzled-10 precursor	3'UTR
G3bp2	ras GTPase-activating protein-binding protein 2	5'UTR
G6pdx	glucose-6-phosphate 1-dehydrogenase X	3'UTR
Gaa	lysosomal alpha-glucosidase precursor	3'UTR
Gaa	lysosomal alpha-glucosidase precursor	5'UTR
Gabı	GRB2-associated-binding protein 1	5'UTR
Gabbr2	gamma-aminobutyric acid type B receptor subunit	CDS
Gabra2	gamma-aminobutyric acid receptor subunit alpha-2	5'UTR
Gadı	glutamate decarboxylase 1	5'UTR
Gadd45g	growth arrest and DNA damage-inducible protein	CDS
Gal3st3	galactose-3-O-sulfotransferase 3	CDS
Gal3st3	galactose-3-O-sulfotransferase 3	5'UTR
Gainti4	polypeptide N-acetylgalactosaminyltransferase	5'UIK
Gainti2	CTPace activating protoin and VPSe	CDS -/IITP
Gapvar	growth arrest-specific protein 1	5 UTR
Gast	growth arrest-specific protein 7 isoform b	2/11TR
Gata2	endothelial transcription factor GATA-2	CDS
Gatsl2	GATS-like protein 2	3'UTR
Gbp7		3'UTR
Gbx2	homeobox protein GBX-2	CDS
Gcap14	granule cell antiserum positive 14 isoform 2	5'UTR
Gck	glucokinase	CDS
Gdap1l1	ganglioside-induced differentiation-associated	CDS
Gdf7	growth/differentiation factor 7	CDS
Gga3	ADP-ribosylation factor-binding protein GGA3	3'UTR
Gimap1	GTPase IMAP family member 1	CDS
Git1	ARF GTPase-activating protein GIT1	CDS
Gliz	GLI-Kruppel family member GLI2	3'UTR
Gli3	zinc finger protein GLI3	CDS
Gli3	zinc tinger protein GLI3	5'UIR -/UTP
Gitadi	glycosyltransferase 8 domain-containing protein	5 UIK
Gmt2476	hypothetical protein LOC422424 isoform 1	CDS
Gm247	hypothetical protein LOC241280	2/UTR
Gm4951	hypothetical protein LOC240327	CDS
Gm4980		CDS
Gm5151	hypothetical protein LOC381582	5'UTR
Gm52	envelope glycoprotein syncytin-A	CDS
Gm6320	hypothetical protein LOC622408	CDS
Gm6537		3'UTR
Gm7694		CDS
Gm98	myelin gene regulatory factor	CDS
Gm98	myelin gene regulatory factor	3'UTR
Gmip	GEM-interacting protein	CDS
Ghan	guarine nucleonde binding protein, alpha	5 UTK
Gnaoi	guanine nucleotide-binding protein G(0) subunit	CD3
Gnas	o nucleonat entang protein O(o) subtint	5'UTR
Gnb5	guanine nucleotide-binding protein subunit	5'UTR
Got1	aspartate aminotransferase, cytoplasmic	5'UTR
Got2	aspartate aminotransferase, mitochondrial	5'UTR
Gpatch2	G patch domain-containing protein 2	3'UTR
Gpr133	probable G-protein coupled receptor 133	3'UTR
Gpr179	probable G-protein coupled receptor 179	CDS
Gpr25	probable G-protein coupled receptor 25	CDS
Gpr4	G-protein coupled receptor 4	CDS
Gpr83	probable G-protein coupled receptor 83	5′UTR
Gprc5c	G-protein coupled receptor family C group 5	CDS
Gprc5c	G-protein coupled receptor family C group 5	3'UTR
Gramdib	GKAM domain-containing protein 1B	5 UTK
Grem1	gremiin-1 precursor	
Crikı	dutamate recentor ionotronic kainate a icoform	JUIR -/UTR
Grika	glutamate receptor, ionotropic kainate a	CDS
Grin1	glutamate [NMDA] receptor subunit zeta-1 isoform	a'UTR
Grin1	glutamate [NMDA] receptor subunit zeta-1 isoform	5'UTR
Grin2d	glutamate [NMDA] receptor subunit epsilon-4	CDS
Grin2d	glutamate [NMDA] receptor subunit epsilon-4	3'UTR
Grk6	G protein-coupled receptor kinase 6 isoform b	3'UTR
Grm2	metabotropic glutamate receptor 2 precursor	CDS

Table 6.3 - continued from previous page

Transcript Symbol	Transcript Name	Methylation site
Gse1	genetic suppressor element 1 isoform 2	CDS
Gse1	genetic suppressor element 1 isoform 2	5'UTR
Gstm1	glutathione S-transferase Mu 1	3'UTR
Gstta	glutathione S-transferase, theta 3	3'UTR
Gtf2h2	general transcription factor IIH subunit 2	5'UTR
Gtf201	general transcription factor 2C polypentide 1	CDS
Ctfact	general transcription factor 2C polypeptide 1	2/UTP
Guiger	general transcription factor of polypeptide i	-/UTD
Guijez	general transcription factor 3C polypeptide 4	5 UIK
Gucy1a2	guanyiate cyclase 1, soluble, alpha 2	5 UIK
Gucy2e	guanylyl cyclase GC-E precursor	CDS
Gys1	glycogen [starch] synthase, muscle	CDS
H13	minor histocompatibility antigen H13 isoform 4	CDS
H2afy	core histone macro-H2A.1 isoform 1	3'UTR
H47	selenoprotein S	5'UTR
Hapln3	hyaluronan and proteoglycan link protein 3	CDS
Hcn3	potassium/sodium hyperpolarization-activated	CDS
Hcn3	potassium/sodium hyperpolarization-activated	5'UTR
Hcn4	potassium/sodium hyperpolarization-activated	CDS
Hdac7	histone deacetylase 7	3'UTR
Heatrsa	HEAT repeat-containing protein 5A	2'UTR
Hepacam	hepatocyte cell adhesion molecule precursor	2'UTR
Heer	transcription factor HES-r	-/UTR
Hach	transcription ratio rHE-5	CDS
Havda	hanscription colactor HE5-0	CDS
I lexuc	heime (and an an a fearlith and a fearlith MDDM)	-/LITE
neyi	nairy/ennancer-of-split related with YKPW	3 U I K
Hgs	hepatocyte growth factor-regulated tyrosine	3'UTR
Hic1	hypermethylated in cancer 1 protein isoform 1	3'UTR
Hivep3	transcription factor HIVEP3	CDS
Hk1	hexokinase-1 isoform HK1	5'UTR
Hk2	hexokinase-2	3'UTR
Hnrnpd	heterogeneous nuclear ribonucleoprotein Do	5'UTR
Hnrnpu	heterogeneous nuclear ribonucleoprotein U	CDS
Hnrpdl	heterogeneous nuclear ribonucleoprotein D-like	5'UTR
Hnrpll	heterogeneous nuclear ribonucleoprotein L-like	5'UTR
Hooka	protein Hook homolog 3	5'UTR
Нрса	neuron-specific calcium-binding protein	5'UTR
Hpcali	hippocalcin-like protein 1	CDS
Hpci	Hormonsky Budlak syndrome & protein homolog	2/LITP
11p54	metein heidese	3 OTK
FII Haada	han and sulfate a Q sulfate suffate su	-/1/TD
HS2STI	neparan suirate 2-O-suirotransferase 1	5 UIR
Hs3st3a1	heparan sulfate glucosamine 3-O-sulfotransferase	5'UIR
Hst1	heat shock factor protein 1	3'UTR
Hspa4	heat shock 70 kDa protein 4	5'UTR
Htr6	5-hydroxytryptamine receptor 6	CDS
Htt	huntingtin	CDS
Htt	huntingtin	3'UTR
Icam2	intercellular adhesion molecule 2 precursor	3'UTR
Icam4	intercellular adhesion molecule 4 precursor	CDS
Ick	serine/threonine-protein kinase ICK	CDS
Id4	DNA-binding protein inhibitor ID-4	5'UTR
Idh2	isocitrate dehydrogenase [NADP], mitochondrial	CDS
Idhah	isocitrate dehydrogenase a beta subunit	5'UTR
Iffo2	intermediate filament family ornhan 2	CDS
Iffo2	intermediate filament family orphan 2	2/UTR
Ifrda	interferon-related developmental regulator a	CDS
Indeed	immunoalohulin aunorfamily DCC auhalasa mambar a	CDS
Iguee4	insulin like growth faster a result in	
igrir Ister	insum-like growth factor 1 receptor	5 UIK
igt2r	cation-independent mannose-6-phosphate receptor	CDS
Igtbp4	insulin-like growth factor-binding protein 4	CDS
Igsf9b	immunoglobulin superfamily, member 9B isoform 1	5'UTR
Ikbkb	inhibitor of nuclear factor kappa-B kinase	CDS
Ikbkb	inhibitor of nuclear factor kappa-B kinase	3'UTR
Il12rb1	interleukin-12 receptor subunit beta-1	CDS
ll17rc	interleukin-17 receptor C precursor	CDS
Il6ra	interleukin-6 receptor subunit alpha precursor	3'UTR
ll6st	interleukin-6 receptor subunit beta precursor	5'UTR
Ildr1	immunoglobulin-like domain-containing receptor	CDS
Ildr2	Lisch-like	CDS
Impadi	inositol monophosphatase a	5'UTR
Ina	alnha-internevin	2/11TR
Inha	inhihin alaha chain procureor	CDS
IIIIa Inkkk	nunom alpha chain procursor	-/ITP
	In the second precursor	5 UIK
Inosod	INO80 complex subunit D isoform 1	3 U I K
Inpp1	inositol polyphosphate 1-phosphatase	5'UTR
Inpp4a	type I inositol-3,4-bisphosphate 4-phosphatase	5'UTR
Inpp5e	72 kDa inositol polyphosphate 5-phosphatase	3'UTR
Inpp5j	phosphatidylinositol 4,5-bisphosphate	CDS
Iqcd	IQ domain-containing protein D	CDS
		Continued on next page

Table 6.3 – continued from previou	s page	
Transcript Symbol	Transcript Name	Methylation site
Iqsec1	IQ motif and SEC7 domain-containing protein 1	5'UTR
Irf8	interferon regulatory factor 8	3'UTR
Irs4	insulin receptor substrate 4	CDS
Irx1	iroquois-class homeodomain protein IRX-1	CDS
Irve	iroquois-class homeodomain protein IRX-5	CDS
lemi	iethmin-1 procureor	-/UTR
Isocob	isochorismataca domain containing protein aB	CDS
Isoc2D	isochorismatase domain-containing protein 2B,	CD5
ISOC2D	Isochorismatase domain-containing protein 2b,	3 UIR
lsyı	pre-mRNA-splicing factor ISY1 homolog	3'UTR
lttg1	T-cell immunomodulatory protein precursor	5'UTR
Itfg3	protein ITFG3	3'UTR
Itga3	integrin alpha-3	5'UTR
Itga4	integrin alpha-4	3'UTR
Itgav	integrin alpha-V precursor	5'UTR
Itsn1	intersectin-1 isoform 2	3'UTR
Jam2	junctional adhesion molecule B precursor	5'UTR
Imjd6	bifunctional arginine demethylase and	5'UTR
Iph4	junctophilin-4 isoform a	5'UTR
Kataa	histone acetyltransferase KAT2A isoform h	CDS
Vanak	notocsium voltage gated channel subfamily. A	-/UTP
Kenaba	voltage gated notagium shannel subunit hate a	-/UTP
Kchabi	vonage-galed polassium channel suburni bela-1	5 UIK
Kenei	potassium voltage-gated channel subfamily C	5'UIR
Kenfi	potassium voltage-gated channel subfamily F	5'UTR
Keng1	potassium voltage-gated channel subfamily G	CDS
Kcng4	potassium voltage-gated channel subfamily G	CDS
Kcnh4	potassium voltage-gated channel, subfamily H	3'UTR
Kcnj6	G protein-activated inward rectifier potassium	5'UTR
Kcnk5	potassium channel subfamily K member 5	CDS
Kcnkg	potassium channel subfamily K member 9	CDS
Kenma1	calcium-activated potassium channel subunit	CDS
Kenti	notacsium channel subfamily T member 1 isoform	CDS
Ketdra	BTB / POZ domain containing adapter for	CDS
Ketuig		CD5
Kdelci	KDEL motif-containing protein 1 precursor	CDS (UTD)
Kdelr2	EK lumen protein retaining receptor 2	3'UTR
Kdm5c	lysine-specific demethylase 5C	3'UTR
Khsrp	far upstream element-binding protein 2	5'UTR
Kif1a	kinesin-like protein KIF1A isoform a	CDS
Kif26b	kinesin-like protein KIF26B	CDS
Kif7	kinesin family member 7	CDS
Kifap3	kinesin-associated protein 3	5'UTR
Klf12	Krueppel-like factor 12	3'UTR
Klf7	Krueppel-like factor 7	5'UTR
Klhdcz	kelch domain-containing protein 2	5'UTR
Klhdc8a	kelch domain-containing protein 84	='UTR
Kible	kelch-like protein 6	CDS
Kino	nector way KIND	-/UTP
Knuci	protein very KIND	-///TD
Kpnbi	importin subunit beta-1	5 UIK
Krii	protein KRI1 homolog	CDS
Krt12	keratin, type I cytoskeletal 12	5'UTR
Krt20	keratin, type I cytoskeletal 20	CDS
Krt8o	keratin, type II cytoskeletal 80	3'UTR
Ksr1	kinase suppressor of Ras 1	3'UTR
Ksr2	kinase suppressor of Ras 2 isoform 1	5'UTR
Ky	kyphoscoliosis peptidase	CDS
L1cam	neural cell adhesion molecule L1	CDS
Lancl3	lanC-like protein 3	5'UTR
Lasp1	LIM and SH3 domain protein 1	3'UTR
Laspi	LIM and SH3 domain protein 1	5′UTR
Lassi	LAG1 longevity assurance homolog 1	CDS
Laco	LACT longavity accurance homolog 6	-/1 ITP
Lasso	EAGT IONGEVITY ASSULTANCE HOMOLOg 0	-/1170
		5 UIK
Land	probable D-lactate dehydrogenase, mitochondrial	CDS
Ldoc1l	protein LDOC1L	5'UTR
Leng8	leukocyte receptor cluster member 8 homolog	CDS
Lgals3bp	galectin-3-binding protein precursor	CDS
Lgmn	legumain precursor	CDS
Lhfpl4	lipoma HMGIC fusion partner-like 4 protein	5'UTR
Lhfpl5	tetraspan membrane protein of hair cell	5'UTR
Lhx1	LIM/homeobox protein Lhx1	5'UTR
Lhx5	LIM/homeobox protein Lhx5	3′UTR
Lipe	hormone-sensitive lipase isoform 2	CDS
Ling	endothelial linase precursor	2/1/TR
I mln	laishmanalycin-like pentidase	2/LITR
Linit	nrelamin A/C isoform Ca	-/1 ITP
	LDA demain temperature (and a LMO	-/UTD
Lmo4	Livi domain transcription factor LMO4	5 UIK
Lmtk2	serine/threonine-protein kinase LM1K2 precursor	3'UIK
Lpcat4	lysophospholipid acyltransterase LPCAT4	3 UTR
Lpin2	phosphatidate phosphatase LPIN2 isoform 1	CDS

Table 6.3 - continued from previous page

Transcript Symbol	Transcript Name	Methylation site
Lrfn1	leucine-rich repeat and fibronectin type III	3'UTR
Lrfn5	leucine-rich repeat and fibronectin type-III	5'UTR
Lrp3	low density lipoprotein receptor-related protein	3′UTR
Lrp4	low-density lipoprotein receptor-related protein	CDS
Lrp5	low-density lipoprotein receptor-related protein	CDS
Lrrc14	leucine-rich repeat-containing protein 14	5'UTR
Lrrc25	leucine-rich repeat-containing protein 25	CDS
Lrrc26	leucine-rich repeat-containing protein 26	CDS
Lrrc32	leucine rich repeat containing 32	CDS
Lrrc38	leucine-rich repeat-containing protein 38	CDS
Lrrc68	leucine-rich repeat-containing protein 68	5'UTR
Lrrc8b	leucine-rich repeat-containing protein 8B	3'UTR
Lrrfip1	leucine-rich repeat flightless-interacting	CDS
Lrsam1	E3 ubiquitin-protein ligase LRSAM1	CDS
Lxn	latexin	5′UTR
Ly6g6f	lymphocyte antigen 6 complex, locus G6F	3'UTR
Ly6h	lymphocyte antigen 6H isoform b	5'UTR
Lyst	lysosomal-trafficking regulator	3'UTR
Mab21l2	protein mab-21-like 2	CDS
Madd	MAP kinase-activating death domain protein	CDS
Madd	MAP kinase-activating death domain protein	a'UTR
Maf	transcription factor Maf	5'UTR
Maged1	melanoma-associated antigen D1	CDS
Mageh1	melanoma-associated antigen H1	5'UTR
Manibi	mannosidase, alpha, class 1B, member 1	CDS
Manici	mannosidase alpha class 10 member 1	CDS
Manici	mannosidase alpha class 1C member 1	2/UTR
Manakh	mitrogen-activated protein kinase kinase kinase	='UTR
Manako	mitogen-activated protein kinase kinase kinase	2/UTR
Map6di	MAP6 domain-containing protein 1	CDS
Mapk8ip2	C-Jun-amino-terminal kinase-interacting protein	='LITR
Mapkoip2	C-Jun-amino-terminal kinase-interacting protein	5 UIK
Маркорз	c-Jun-annio-terminal kinase-interacting protein	3 UIK
Маркорі	mitogen-activated protein kinase-binding protein	
Mapre2	E subination and a subination MARCH a manuar	5 UIK
March4	E3 ubiquitin-protein ligase MARCH4 precursor	CDS (UTD)
Marcksli	MARCKS-related protein	3 UIR
Mark2	serine/threonine-protein kinase MARK2 isoform 4	5'UTR
Mavs	mitochondrial antiviral-signaling protein	CDS
Mboat7	lysophospholipid acyltransferase 7	CDS
Mboat7	lysophospholipid acyltransferase 7	5'UTR
Mc3r	melanocortin receptor 3	3'UTR
Mcc	mutated in colorectal cancers isoform 1	3'UTR
Mchr1	melanin-concentrating hormone receptor 1	5'UTR
Mcm6	DNA replication licensing factor MCM6	CDS
Mdga1	MAM domain-containing	5'UTR
Med23	mediator of RNA polymerase II transcription	3'UTR
Med26	mediator of RNA polymerase II transcription	3'UTR
Mef2d	myocyte-specific enhancer factor 2D	CDS
Megf9	multiple epidermal growth factor-like domains	5'UTR
Mepce	7SK snRNA methylphosphate capping enzyme	5'UTR
Mettl14	methyltransferase-like protein 14	3'UTR
Mettl <sub>3</sub>	N6-adenosine-methyltransferase 70 kDa subunit	CDS
Mfap3l	microfibrillar-associated protein 3-like	5'UTR
Mfge8	lactadherin isoform 2	3'UTR
Mfsd6	major facilitator superfamily domain-containing	5'UTR
Mgat4b	alpha-1,3-mannosyl-glycoprotein	3'UTR
Mgat5b	alpha-1,6-mannosylglycoprotein	CDS
Mgrn1	E3 ubiquitin-protein ligase MGRN1	3'UTR
Mib2	E3 ubiquitin-protein ligase MIB2	3'UTR
Mib2	E3 ubiquitin-protein ligase MIB2	5'UTR
Mical2	protein MICAL-2 isoform B	CDS
Mid1	midline-1	CDS
Mid1	midline-1	3'UTR
Midn	midnolin	CDS
Midn	midnolin	5'UTR
Mif4gd	MIF4G domain-containing protein	5'UTR
Minpp1	multiple inositol polyphosphate phosphatase 1	5'UTR
Mlf2	myeloid leukemia factor 2	3'UTR
Mlf2	myeloid leukemia factor 2	5'UTR
Mlxip	MLX-interacting protein isoform 1	CDS
Mmp14	matrix metalloproteinase-14	3'UTR
Mmp15	matrix metalloproteinase-15 precursor	CDS
Mmp28	matrix metalloproteinase-28 isoform 2	3'UTR
Mmrn2	multimerin-2 precursor	3'UTR
Mnı	probable tumor suppressor protein MN1	3'UTR
Mnt	max-binding protein MNT	CDS
Mobkl2b	mps one binder kinase activator-like 2B	3'UTR
Mospd4	motile sperm domain containing 4	CDS
· · ·		Continued on next page

Table 6.3 – continued from previou	1s page	
Transcript Symbol	Transcript Name	Methylation site
Mprip	myosin phosphatase Rho-interacting protein	3'UTR
Mrgprf	mas-related G-protein coupled receptor member F	3'UTR
Mrpl4	39S ribosomal protein L4, mitochondrial	3'UTR
Mrpl46	39S ribosomal protein L46, mitochondrial	3'UTR
Mrps11	28S ribosomal protein S11, mitochondrial	3'UTR
Mrvi1	protein MRVI1 isoform a	CDS
Mslı	male-specific lethal 1 homolog	5'UTR
Mtap1a	microtubule-associated protein 1A isoform 2	5'UTR
Mtap1b	microtubule-associated protein 1B	5'UTR
Mtap2	microtubule-associated protein 2 isoform 2	CDS
Mtap7d1	MAP7 domain-containing protein 1 isoform 2	CDS
Mtdh	protein LYRIC	5'UTR
Mtfp1		5'UTR
Mtmr11	myotubularin-related protein 11	3'UTR
Mto1	protein MTO1 homolog, mitochondrial precursor	5'UTR
Mtus2	microtubule-associated tumor suppressor	3'UTR
Mycl1	protein L-Myc-1	5'UTR
Myh14	myosin-14	CDS
Myh7b	myosin-7B	CDS
Myh9	myosin-9 isoform 1	3'UTR
Myo16	myosin-XVI	CDS
My01d	myosin-Id	3'UTR
My01d	myosin-Id	5'UTR
Myo5b	myosin-Vb	CDS
Myst2	histone acetyltransferase MYST2 isoform 3	5'UTR
N28178	hypothetical protein LOC230085	CDS
Naf1	H/ACA ribonucleoprotein complex non-core subunit	5'UTR
Nagpa		CDS
Nat6	N-acetyltransferase 6	5'UTR
Nav2	neuron navigator 2 isoform 1	5'UTR
Ncam1	neural cell adhesion molecule 1 isoform 3	CDS
Ncdn	neurochondrin	3'UTR
Ncdn	neurochondrin	5'UTR
Nckap5	Nck-associated protein 5 isoform 2	CDS
Nckap5	Nck-associated protein 5 isoform 2	3'UTR
Nckap5l	nck-associated protein 5-like	CDS
Nckap5l	nck-associated protein 5-like	3'UTR
Ncor2	nuclear receptor corepressor 2	CDS
Ndel1	nuclear distribution protein nudE-like 1	3'UTR
Ndfip2	NEDD4 family-interacting protein 2	CDS
Ndrg1	protein NDRG1	5'UTR
Ndrg3	protein NDRG3 isoform 1	3'UTR
Ndufb10	NADH dehydrogenase [ubiquinone] 1 beta	5'UTR
Ndufv1	NADH dehydrogenase [ubiquinone] flavoprotein 1,	CDS
Nebl	nebulette	5'UTR
Nefl	neurofilament light polypeptide	5'UTR
Nefm	neurofilament medium polypeptide	5'UTR
Nek11	serine/threonine-protein kinase Nek11	3'UTR
Ne01	neogenin isoform 2	5'UTR
Nf1	neurofibromin	CDS
Nfam1	NFAT activation molecule 1	3'UTR
Nfat5	nuclear factor of activated T-cells 5 isoform a	CDS
Nfat5	nuclear factor of activated T-cells 5 isoform a	5'UTR
Nfatc2	nuclear factor of activated T-cells, cytoplasmic	3'UTR
Ntkbib	NF-kappa-B inhibitor beta	3'UTR
Ngef	ephexin-1 isoform 1	3'UTR
Nhlrc1	E3 ubiquitin-protein ligase NHLRC1	5'UTR
Nhsl2	NHS-like protein 2	CDS
N1d2	nidogen-2 precursor	CDS
Nipal3	NIPA-like protein 3	CDS
Nkain2	sodium/potassium-transporting ATPase subunit	5'UTR
Nkd1	protein naked cuticle homolog 1 isoform 2	CDS
Nkpd1	N1Pase KAP family P-loop domain-containing	CDS
Nktr	NK-tumor recognition protein	3'UTR
NKX2-1	nomeobox protein Nkx-2.1	
INKX2-1	nomeodox protein NKx-2.1	3 UTK
INKX2-2	nomeodox protein NKx-2.2 isoform 1	
INKX2-9	nomeodox protein NKx-2.8	
INKX2-9	nomeodox protein NKX-2.8	3 UIK
INIFX1	NLK ramily member X1 precursor	3 UTK
Nnat	neuronatin isoform beta	5 UTK
Nod1	nucleotide-binding oligomerization	3 UIK
Nog	noggin precursor	5 UIK
Notaha	numerospie logue notes homologi anticia a	3 UTK
Noteha	neurogenic tocus notch nomolog protein 1	CD5
NDae1	neuropal PAS domain-containing protein z	CDS
Np264	neuronal PAS domain-containing protein 1	-/11TR
1 Pas4	neuronal 175 domani-containing protein 4	

Table 6.3 - continued from previous page

Transcript Symbol	Transcript Name	Methylation site
Npc1	Niemann-Pick C1 protein	CDS
Npc2	epididymal secretory protein E1 precursor	CDS
Nploca	nuclear protein localization protein 4 homolog	CDS
Npri	atrial natriuretic peptide recentor 1 precursor	CDS
Nor2	atrial natriuretic peptide receptor 2 jsoform h	CDS
Netvr	nouronal pantravin 1 proguran	CDS
Netva		ells e'llTR
NptX1	neuronal pentraxin-1 precursor	3 UTR
Nptx1	neuronal pentraxin-1 precursor	5'UIR
Nptx2	neuronal pentraxin-2 precursor	3'UTR
Nptxr	neuronal pentraxin receptor	CDS
Npy2r	neuropeptide Y receptor type 2	5'UTR
Nr1d1	nuclear receptor subfamily 1 group D member 1	CDS
Nr1h2	oxysterols receptor LXR-beta	CDS
Nr4a1	nuclear receptor subfamily 4 group A member 1	5'UTR
Nrgn	neurogranin	CDS
Nrip1	nuclear receptor-interacting protein 1	5'UTR
Nsun4	putative methyltransferase NSUN4	CDS
Nsun7	putative methyltransferase NSUN7	CDS
Ntna	petrin-2 precursor	a'IITR
Ntna	netrin-2 precursor	='IITR
Ntorr	neurotanzin recenter tuno 1	CDS
Ntorr		ello
Ntsr1	neurotensin receptor type 1	3 U I K
Nuak2	NUAK family SNF1-like kinase 2 isoform B	CDS
Nudcd2	nudC domain-containing protein 2	CDS
Nudt10	diphosphoinositol polyphosphate phosphohydrolase	5'UTR
Nup210	nuclear pore membrane glycoprotein 210	3'UTR
Nup214	nuclear pore complex protein Nup214	CDS
Nup62-il4i1	Nup62-Il4i1 protein	5'UTR
Nyx	nyctalopin precursor	CDS
Oaf	out at first protein homolog precursor	5'UTR
Omp	olfactory marker protein	CDS
ORF10	WAS protein family homolog 1	CDS
ORF61	membralin	CDS
Occar	ostooclast-associated immunoglobulin-like	CDS
Oscar	osteoclast associated immunoglobulin-like	ells o'llTP
Ostar	osteoclast-associated infinunogiobulin-like	3 UIK
Ostmi	osteopetrosis-associated transmembrane protein 1	CDS
Otud5	OTU domain-containing protein 5	CDS
Otud5	OTU domain-containing protein 5	5'UTR
Ovgp1	oviduct-specific glycoprotein precursor	CDS
Oxa1l	mitochondrial inner membrane protein OXA1L	CDS
Pacsin1	protein kinase C and casein kinase substrate in	5'UTR
Pafah1b2	platelet-activating factor acetylhydrolase IB	5'UTR
Palb2	partner and localizer of BRCA2	CDS
Papd7	DNA polymerase sigma isoform 2	5'UTR
Paqr9	progestin and adipoQ receptor family member 9	CDS
Parm1	prostate androgen-regulated mucin-like protein 1	CDS
Parp10	poly (ADP-ribose) polymerase family, member 10	CDS
Parpio	poly (ADP-ribose) polymerase family, member 10	3'UTR
Phys	pro-B-cell leukemia transcription factor a	CDS
Pohnt	poly(rC) hinding protoin 1	-/11TP
Padhao	poly(iC)-binding protein i	-/UTR
Pullo		5 UIK
Pcahs	protocadnerin 8 isoform 2 precursor	5 U I K
Pcdha2	protocadherin alpha 2	3'UTR
Pcdhga8	protocadherin gamma subfamily A, 8	5'UTR
Pcdhgb5	protocadherin gamma-B5	CDS
Pcgf2	polycomb group RING finger protein 2	CDS
Pcgf6	polycomb group RING finger protein 6	CDS
Pcid2	PCI domain-containing protein 2	3'UTR
Pcif1	phosphorylated CTD-interacting factor 1	CDS
Pclo	protein piccolo isoform 2	5'UTR
Pcskin	proSAAS	CDS
Pcsk1n	proSAAS	3′UTR
Pcsk7	proprotein convertase subtilisin/kexin type 7	5'UTR
Pdcd11	protein RRPs homolog	a'UTR
Pdcd2	programmed cell death protein 2	5'UTR
Pdoth	programmed cen dealth protein 2	-/ ITP
P de te	al MD anaifia a' a' avalia nha-nha-thattarra a A	5 UIK
r de4a	CAIVIE-specific 3,5-cyclic prosphodiesterase 4A	3 UIK
Pde4c	CAIVIT-specific 3 ,5 -cyclic phosphodiesterase 4C	3 UIK
Pdgtb	platelet-derived growth factor subunit B	5'UTR
Pdpk1	3-phosphoinositide-dependent protein kinase 1	5'UTR
Pdxk	pyridoxal kinase	5′UTR
Peg3	paternally expressed 3	5'UTR
Per2	period circadian protein homolog 2	CDS
Per3	period circadian protein homolog 3	CDS
Pex14	peroxisomal membrane protein PEX14	3'UTR
Pfk1	6-phosphofructokinase, liver type	3'UTR
Pgm2	phosphoglucomutase-1	5′UTR
Pgm2l1	glucose 1,6-bisphosphate synthase	5′UTR
		Continued on pext page

Table 6.3 – continued from previo	us page	
Transcript Symbol	Transcript Name	Methylation site
Pgrmc1	membrane-associated progesterone receptor	5'UTR
Phb2	prohibitin-2	5'UTR
Phf12	PHD finger protein 12	5'UTR
Phf2	PHD finger protein 2	CDS
Phf2	PHD finger protein 2	3'UTR
Phkb	phosphorylase b kinase regulatory subunit beta	5'UTR
Phlpp1	PH domain leucine-rich repeat-containing protein	5'UTR
Pi4kb	phosphatidylinositol 4-kinase beta	5'UTR
Piasz	E3 SUMO-protein ligase PIAS3 isoform 3	CDS
Picalm	phosphatidylinositol-binding clathrin assembly	5'UTR
Pigh	GPI mannosyltransferase 2	CDS
Pigo	GPI ethanolamine phosphate transferase a	CDS
Pigy	CPI manneeultraneferase a isoform a	-/UTR
Pigz	CPI mannosyltransferase 2 isoform 3	CDS
Figz	GFT mannosyntansierase 4	CD3
Pinidi	PIH1 domain-containing protein 1	5'01K
Pik3c2b	phosphoinositide-3-kinase, class 2 beta	3'UTR
Pik3cg	phosphatidylinositol-4,5-bisphosphate 3-kinase	CDS
Pik3r5	phosphoinositide 3-kinase regulatory subunit 5	CDS
Pip4k2c	phosphatidylinositol-5-phosphate 4-kinase type-2	CDS
Pkmytı	membrane-associated tyrosine- and	CDS
Plagl2	zinc finger protein PLAGL2	CDS
Plagl2	zinc finger protein PLAGL2	3'UTR
Plbd2	putative phospholipase B-like 2	3'UTR
Plcb1	1-phosphatidylinositol-4.5-bisphosphate	5'UTR
Plcb3	1-phosphatidylinositol-4.5-bisphosphate	CDS
Plda	phospholipase Da	2/11TR
Pld	phospholipase D4	CDS
Plokha	plosketrin homology domain containing family A	
Dalahia	plecksum nomology domain-containing family A	3 U I K
Plekhji	pleckstrin homology domain-containing family J	5'UIK
Plekhm1	pleckstrin homology domain-containing family M	3'UTR
Plekhm2	pleckstrin homology domain-containing family M	3'UTR
Plod3	procollagen-lysine,2-oxoglutarate 5-dioxygenase	5'UTR
Plxdc1	plexin domain-containing protein 1 isoform 1	CDS
Plxna4	plexin-A4 precursor	5'UTR
Plxnb2	plexin B2	CDS
Plxnb3	plexin-B3	CDS
Plxnci	plexin-C1 precursor	CDS
Plxnd1	plexin D1	CDS
Plyndi	plexin D1	2'UTR
Pm2od2	picial D1	='ITR
Pnkd	probable hydrolase PNKD jeoform 1	2/UTR
Primar	probable hydrolase i NKD isolomi i	-/1172
Podula	paraneopiastic antigen mar nomolog	5 UIK
Podxi2	podocaryxin-like protein 2	3 UIK
Pogk	pogo transposable element with KKAB domain	5 UIR
Polría	DNA-directed RNA polymerase I subunit RPA1	3'UIK
Polr2f	DNA-directed RNA polymerases I, II, and III	CDS
Polr3d	DNA-directed RNA polymerase III subunit RPC4	CDS
Pom121	nuclear envelope pore membrane protein POM 121	CDS
Pom121	nuclear envelope pore membrane protein POM 121	3'UTR
Pou2f1	POU domain, class 2, transcription factor 1	CDS
Pou2f2	POU domain, class 2, transcription factor 2	3'UTR
Pou6f1	POU domain, class 6, transcription factor 1	5'UTR
Ppap2b	lipid phosphate phosphohydrolase 3	3'UTR
Ppapdc3	probable lipid phosphate phosphatase PPAPDC3	CDS
Ppard	peroxisome proliferator-activated receptor	CDS
Ppard	peroxisome proliferator-activated receptor	3'UTR
Ppfia4	liprin-alpha-4	5'UTR
Ppil2	peptidyl-prolyl cis-trans isomerase-like 2	CDS
Ppm1l	protein phosphatase 1L	CDS
Ppm1	protein phosphatase 1	5'UTR
Ppp1rio	serine/threenine-protein phoenhatase 1	CDS
Provent all	serine/ uneonine-protein phosphatase 1	-/ITP
Ppp1150	protein phosphatase i regulatory suburili 150	-/1 ITD
Pppiria	protein phosphatase 1 regulatory subunit 1A	5 UIK
Ppp5c	serine/threonine-protein phosphatase 5	CDS
Prams	rk domain zinc tinger protein 8	
Prelp	prolargin precursor	CDS
Prelp	prolargin precursor	3'UTR
Prickle2	prickle-like protein 2 isoform b	5'UTR
Prkar2b	cAMP-dependent protein kinase type II-beta	3'UTR
Prkca	protein kinase C alpha type	5'UTR
Prmt5	protein arginine N-methyltransferase 5	CDS
Prox1	prospero homeobox protein 1	3'UTR
Prpf8	pre-mRNA-processing-splicing factor 8	5'UTR
Prps2	ribose-phosphate pyrophosphokinase 2	5′UTR
Prr12	proline rich 12	3′UTR
Prr22		CDS
Prr3	proline-rich protein 3 isoform b	a'UTR
Prrto	proline-rich transmembrane protein 2	5'UTR
	r nen unionenterne protein 2	Continued on part page
		Continued on next page

Rcc1

Rcn2

Reep6

Rela

Rere Rfx7

Rgag4 Rgl2

Rgma

Transcript Symbol	Transcript Name	Methylation site
Prrt4	proline-rich transmembrane protein 4	CDS
rrx1	paired mesoderm homeobox protein 1 isoform b	CDS
sap	sulfated glycoprotein 1 isoform D preproprotein	5'UTR
'sd	PH and SEC7 domain-containing protein 1	CDS
sd2	PH and SEC7 domain-containing protein 2	5/UTR
Son1	precentiin-1	CDS
Selebr	corine /threening protein kinges H	o'UTP
SKIII	serine/ uneonine-protein kinase H1	3 UIK
Smri	proteasome innibitor P131 subunit	301K
'th2r	parathyroid hormone 2 receptor precursor	CDS
'tk7	tyrosine-protein kinase-like 7 precursor	3'UTR
'tms	parathymosin	5'UTR
°tp4a3	protein tyrosine phosphatase type IVA 3 isoform	CDS
²tplb	3-hydroxyacyl-CoA dehydratase 2	CDS
'tpmt1	protein-tyrosine phosphatase mitochondrial 1	5'UTR
rtpn21	tyrosine-protein phosphatase non-receptor type	3'UTR
2 2 2 1 2 1 2 2 2 2 2 2 2 2 2 2 2 2 2 2	tyrosine-protein phosphatase non-receptor type	CDS
2tons	tyrosine-protein phosphatase non-receptor type	CDS
tpiis	tyrosine-protein prospiratase non-receptor type	-// ITP
uprint	receptor-type tyrosine-protein phosphatase inu	SOIR
tpro	protein tyrosine phosphatase, receptor type, O	CDS
tpro	protein tyrosine phosphatase, receptor type, O	5'UTR
tprs	receptor-type tyrosine-protein phosphatase S	3'UTR
tprz1	receptor-type tyrosine-protein phosphatase zeta	5'UTR
°trf	polymerase I and transcript release factor	3'UTR
'um1	pumilio homolog 1 isoform 2	3'UTR
vrl2	poliovirus receptor-related protein 2 isoform 2	CDS
vrl2	poliovirus receptor-related protein 2 isoform 2	5'UTR
2xdn	peroxidasin homolog precursor	CDS
2vn	pavillin jeoform alpha	2/LITR
XII Droomd	paximit isotorin appla	3 UIK
ycard	apoptosis-associated speck-like protein	CD5
ygb	glycogen phosphorylase, brain form	5'UTR
'ygo1	pygopus homolog 1	5'UTR
'ygo2	pygopus homolog 2	CDS
2prt	nicotinate-nucleotide pyrophosphorylase	CDS
R3hdm2	R3H domain-containing protein 2 isoform 2	3'UTR
Rab10	ras-related protein Rab-10	CDS
Rab11b	ras-related protein Rab-11B	5'UTR
Rab11fip1	rab11 family-interacting protein 1 isoform 1	CDS
abiifini	rabii family-interacting protein 1 isoform 1	a'IITR
abiiipi ?abi4	rac-related protein Rah-14	-/UTR
abia Jahaa	ras-related protein Rab-14	-/1170
kab3a	ras-related protein Kab-3A	5 UIR
ab3111	guanine nucleotide exchange factor for Kab-3A	5'UTR
lad23b	UV excision repair protein RAD23 homolog B	5'UTR
lad50	DNA repair protein RAD50	3'UTR
lad51l3	DNA repair protein RAD51 homolog 4	CDS
Radil	ras-associating and dilute domain-containing	CDS
Raiı	retinoic acid-induced protein 1	3'UTR
Ramp3	receptor activity-modifying protein 3 precursor	3'UTR
ap1gap2	rap1 GTPase-activating protein 2	3'UTR
angefli	ran guanine nucleotide exchange factor-like 1	2/1171
angofi	rap guanine nucleotide exchange factor like i	-/1 ITD
apgeni	rap guanne nucleonde exchange factor-like 1	SUIK
ara	retinoic acid receptor alpha isoform 1	CDS
Cara	retinoic acid receptor alpha isoform 1	5'UTR
larg	retinoic acid receptor gamma isoform 2	3'UTR
asa3	ras GTPase-activating protein 3	3'UTR
lasalı	rasGAP-activating-like protein 1	CDS
lasgrf1	ras-specific guanine nucleotide-releasing factor	5'UTR
asl10b	ras-like protein family member 10B precursor	CDS
asl11b	ras-like protein family member 11B	5'UTR
as112	ras-like protein family member 12 jeaform 1	2/1178
10112	ras inceptoent family member 12 Bolofin 1	5 UIK
ass15	ras association domain-containing protein 5	3 UTK
aver1	ribonucleoprotein PIB-binding 1	3'UTR
bfox1	fox-1 homolog A isoform alpha	5'UTR
lbfox3		CDS
bm20	probable RNA-binding protein 20	CDS
bm20	probable RNA-binding protein 20	3'UTR
bm24	RNA-binding protein 24	5'UTR
hm42	RNA-binding protein 42	CDS
hm 45	RNA-binding protein 42	-/1 ITD
1	notice 1 his disc sectors a	SUIK
whi	remoi-binding protein 1	CD5

regulator of chromosome condensation isoform 2

receptor expression-enhancing protein 6

transcription factor p65 arginine-glutamic acid dipeptide repeats

regulatory factor X domain containing 2

ral guanine nucleotide dissociation repulsive guidance molecule A precursor

reticulocalbin-2 precursor

Continued on next page

3'UTR

5'UTR

3'UTR

3'UTR

3'UTR 5'UTR

5'UTR 5'UTR

3'UTR

Table 6.3 – continued from previou	is page	
Transcript Symbol	Transcript Name	Methylation site
Rimklb	ribosomal protein S6 modification-like protein	5'UTR
Rims4	regulating synaptic membrane exocytosis protein	CDS
Rin1	ras and Rab interactor 1	CDS
Ring1	E3 ubiquitin-protein ligase RING1	5'UTR
Rnaseh1	ribonuclease H1	3'UTR
Rnaseh2a	ribonuclease H2 subunit A	CDS
Rnasel	2-5A-dependent ribonuclease	3'UTR
Knf103	E3 ubiquitin-protein ligase KNF103	5 UTR
Knt152	KING tinger protein 152	5 UTR
Knf165	ring tinger protein 165	3 UTK
Knt214	KING Inger protein 214	5 UIK
Knr220	E3 ubiquitin-protein ligase Knt220	3 UIK
Rufta	PINC finger protein 39	
Rutt43	NING Inger protein 43 precursor	-/ITP
Ripc3	NNA-ununing protein 40	5 U I K
Romat	reactive evident species modulator 1	CDS
Rogring	Y-linked retinitis nigmentosa CTPase	2/UTR
Rppa	dolichyl-dinhosphooligosaccharide_protein	-/UTR
Rprd1a	regulation of nuclear pro-mRNA domain-containing	-/UTR
Rps6ka1	ribosomal protein S6 kinase alpha-1	CDS
Rrebi	noosonaa protent oo kuuse uiptu 1	a'UTR
Rsad2	radical S-adenosyl methionine domain-containing	3'UTR
Rtn4rl2	reticulon-4 receptor-like 2 precursor	CDS
Runx2	runt-related transcription factor 2 isoform type	5′UTR
Rxrb	retinoic acid receptor RXR-beta	5′UTR
Rvr1	ryanodine receptor 1, skeletal muscle	CDS
S1pr2	sphingosine 1-phosphate receptor 2	CDS
S1pr4	sphingosine 1-phosphate receptor 4	CDS
Safb	scaffold attachment factor B	CDS
Sall3	sal-like protein 3	CDS
Samd14	sterile alpha motif domain-containing protein 14	5'UTR
Samd4b	protein Smaug homolog 2	CDS
Samd4b	protein Smaug homolog 2	3'UTR
Samhdı	SAM domain and HD domain-containing protein 1	CDS
Samhdı	SAM domain and HD domain-containing protein 1	3'UTR
Sarm1	sterile alpha and TIR motif-containing protein 1	CDS
Sart1	U4/U6.U5 tri-snRNP-associated protein 1	CDS
Sash3	SAM and SH3 domain-containing protein 3	3'UTR
Satb2	DNA-binding protein SATB2	3'UTR
Sbno2	protein strawberry notch homolog 2	CDS
Scarb1	scavenger receptor class B member 1	CDS
Scarf1	scavenger receptor class F, member 1	CDS
Scarf2	scavenger receptor class F member 2 precursor	CDS
Scd2	acyl-CoA desaturase 2	CDS
Scg3	secretogranin-3 isoform 2 precursor	5'UTR
Scn3b	sodium channel subunit beta-3 precursor	5'UTR
Scn5a	sodium channel protein type 5 subunit alpha	3'UTR
Scrt2	transcriptional repressor scratch 2	CDS
Sdc4	syndecan-4 precursor	CDS
Sdf2	stromal cell-derived factor 2	5'UTR
Saha	succinate dehydrogenase [ubiquinone]	CDS
Sak2	protein sidekick-2 precursor	
Sar39u1	epimerase tamily protein SDK39U1	3 UIK
Seci	galactoside 2-alpha-L-fucosyltransferase 3	
Sec24D	protein transport protein Sec248	
Sector	protein transport protein Sec31A	3 U I K - 'I ITP
Solal	protein transport protein secol subunit alpha	-/UTR
Somala	protein sei-i nonolog i isolorin o	5 U I K
Semata	semaphorin-6A precursor	3 U I K
Semale	semaphorin-6C precursor	CDS
Sematic	semaphorin-6C precursor	2/1TR
Sema6d	semanhorin-6D isoform 4	='ITR
Sents	septin-5	CDS
Sept6	septin-6 isoform 3	5'UTR
Septo	septin-q isoform a	CDS
Serbl	serine hydrolase-like protein	CDS
Serpinh	serpin H1 precursor	CDS
Serpinii	neuroserpin precursor	5′UTR
Sesna	sestrin-3	CDS
Sestd1	SEC14 domain and spectrin repeat-containing	CDS
Setd1a	SET domain containing 1A	CDS
Setd4	SET domain-containing protein 4	CDS
Sez6l	seizure 6-like protein	CDS
Sez6l	seizure 6-like protein	5′UTR
Sf1	splicing factor 1 isoform 2	CDS
Sfi1	protein SFI1 homolog	CDS
#### 6 Appendix

Table 6.3 - continued from previous page

Transcript Symbol	Transcript Name	Methylation site
Sfmbt1	scm-like with four MBT domains protein 1	5'UTR
Sfn	14-3-3 protein sigma	5'UTR
Sfpi1	transcription factor PU.1	3'UTR
Sfrp2	secreted frizzled-related protein 2 precursor	CDS
Sfswap	splicing factor, argining/serine-rich 8	CDS
Sepli	sphingosine-1-phosphate lyase 1	5'UTR
Sosh	N-sulfoglucosamine sulfohydrolase	2'UTR
Sgemt	small C protein signaling modulator 1 isoform a	CDS
Shahpi	Shan G protein signaling modulator 1 isotorin a	-/1178
Sh3bp1	SH3 domain-binding protein 1	5 UIK
Sh3bp5	SH3 domain-binding protein 5	5 UIR
Sh3rf2	putative E3 ubiquitin-protein ligase SH3KF2	CDS (UTT)
Sh3rt3	SH3 domain-containing RING tinger protein 3	3'UTR
Shank2	SH3 and multiple ankyrin repeat domains protein	3'UTR
Shank3	SH3 and multiple ankyrin repeat domains protein	3'UTR
Shb	SH2 domain-containing adapter protein B	CDS
Shb	SH2 domain-containing adapter protein B	5'UTR
Shh	sonic hedgehog protein precursor	CDS
Shisa6	protein shisa-6 homolog precursor	3'UTR
Shisa7	protein shisa-7 precursor	CDS
Shmt1	serine hydroxymethyltransferase, cytosolic	3'UTR
Shpk	sedoheptulokinase	CDS
Shroom2	protein Shrooma isoform a	CDS
Shroom	protein Shroom	CDS
Siaha	seven in absentia homolog 2	CDS
Sidta	SEVEN IN absentia nontolog 3	cD3
Sincele	signal induced multifunction according to the	JUIN
Sipalli	signal-induced proliferation-associated 1-like	3 U1K
Sipa112	signal-induced proliferation-associated 1-like	3 UTK
Sipa113	signal-induced proliferation-associated 1-like	3'UTR
Slain1	SLAIN motif-containing protein 1	CDS
Slamf9	SLAM family member 9 precursor	CDS
Slamf9	SLAM family member 9 precursor	3'UTR
Slc10a4	sodium/bile acid cotransporter 4	5'UTR
Slc12a7	solute carrier family 12 member 7	3'UTR
Slc12a8	solute carrier family 12 member 8 isoform 2	CDS
Slc13a5	solute carrier family 13 member 5	3'UTR
Slc15a3	solute carrier family 15 member 3	CDS
Slc16a1	monocarboxylate transporter 1	5'UTR
Slc16a12	monocarboxylate transporter 12	CDS
Slc1626	monocarboxylate transporter 7 jeoform h	2/UTR
Slotzaz	vocicular glutamata transporter /	2/1 ITP
Sicryay		CDS
5101883	vesicular acetylcholine transporter	CD5
SICIAI	excitatory amino acid transporter 3	5'UIR
SIc1a2	excitatory amino acid transporter 2 isoform 3	CDS
Slc1a2	excitatory amino acid transporter 2 isoform 3	5'UTR
Slc1a4	neutral amino acid transporter A	CDS
Slc22a15	solute carrier family 22 member 15	5'UTR
Slc22a17	solute carrier family 22 member 17	5'UTR
Slc22a23	solute carrier family 22 member 23	5'UTR
Slc22a4	solute carrier family 22 member 4	CDS
Slc24a4	sodium/potassium/calcium exchanger 4 precursor	5'UTR
Slc25a30	kidney mitochondrial carrier protein 1	3'UTR
Slc25a42	solute carrier family 25 member 42	3'UTR
Slc26a4	pendrin	5'UTR
Slc27a1	long-chain fatty acid transport protein 1	5'UTR
Slc27a4	long-chain fatty acid transport protein 4	CDS
Slc2022	equilibrative nucleoside transporter 2	2/UTR
Sleadaa	equilibrative nucleoside transporter 2	CDS
Sleepe	equinorative nucleositie transporter 3	-/11TP
SIC245	source carrier family 2, facilitated glucose	5 UIK
5163083	zinc transporter 3	3 U1K
Slc35c1	GDP-tucose transporter 1 isoform 1	CDS
Slc35c1	GDP-tucose transporter 1 isoform 1	5'UTR
Slc36a1	proton-coupled amino acid transporter 1	5'UTR
Slc39a6	zinc transporter ZIP6 precursor	5'UTR
Slc43a2	large neutral amino acids transporter small	CDS
Slc43a2	large neutral amino acids transporter small	5'UTR
Slc6a1	sodium- and chloride-dependent GABA transporter	CDS
Slc6a1	sodium- and chloride-dependent GABA transporter	3'UTR
Slc6a11	sodium- and chloride-dependent GABA transporter	CDS
Slc6a11	sodium- and chloride-dependent GABA transporter	3'UTR
SIc6a12	sodium- and chloride-dependent betaine	3'UTR
Slebar	ornhan sodium- and chlorida donondont	-/ITR
Slater	orphan soutume and chloride dependent transmerter	2 UIN
Sicoazua Siacaz	sourum- and chloride dependent transporter	j UIK CDC
510085	sourum- and chioride-dependent glycine	
Slc7a1	high attinity cationic amino acid transporter 1	CDS
SIC7a10	asc-type amino acid transporter 1	5'UTR
Slc8a3	solute carrier family 8 (sodium/calcium	5'UTR
Slc9a1	sodium/hydrogen exchanger 1	CDS
Slc9a1	sodium/hydrogen exchanger 1	3'UTR
		Continued on next page

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Table 6.3 – continued from previou	is page	
Transcript Symbol	Transcript Name	Methylation site
Slc9a1	sodium/hydrogen exchanger 1	5'UTR
Slc9a5	sodium/hydrogen exchanger 5	CDS
Slc9a5	sodium/hydrogen exchanger 5	3'UTR
Slc9a7	sodium/hydrogen exchanger 7	5'UTR
Slc9a8	sodium/hydrogen exchanger 8 isoform b	3'UTR
Slco5a1	solute carrier organic anion transporter family,	5'UTR
Slit3	slit homolog 3 protein precursor	3'UTR
Slitrk3	SLIT and NTRK-like protein 3 precursor	5'UTR
Smad6	mothers against decapentaplegic homolog 6	CDS
Smarch1	SWI/SNF-related matrix-associated	2/LITR
Smarcol	SWI/SNE complex subunit SMARCC1	2/11TR
Smarcer	structural maintenance of chromosomes protein =	CDS
Smelt	sering /threaning protein phoephatasa (	-/1178
Smexi	serine/ inconne-protein phosphatase 4	CDC
Smo	smoothened nomolog precursor	CDS
Smurt2	E3 ubiquitin-protein ligase SMURF2	5'UIR
Smyd3	SET and MYND domain-containing protein 3	5'UTR
Sncb	beta-synuclein	5'UTR
Snrnp70	U1 small nuclear ribonucleoprotein 70 kDa	5'UTR
Sntb1	beta-1-syntrophin	CDS
Snx19	sorting nexin-19	5'UTR
Snx29	sorting nexin-29	CDS
Snx3	sorting nexin-3	CDS
Sod3	extracellular superoxide dismutase [Cu-Zn]	CDS
Sorbs1	sorbin and SH3 domain-containing protein 1	5'UTR
Sos1	son of sevenless homolog 1	5'UTR
Sostdc1	sclerostin domain-containing protein 1	3'UTR
Sox10	transcription factor SOX-10	5'UTR
Sox13	transcription factor SOX-13	CDS
Sox18	transcription factor SOX-18	CDS
Sox21	transcription factor SOX-21	CDS
Sox2	transcription factor SOX-2	CDS
Sova	transcription factor SOX-7	CDS
Soxy	transcription factor Sox-7	CDS
5p2	transcription factor Sp2 Isoform 2	CD5
Sp8	transcription factor Sp8	CDS
Spcs3	signal peptidase complex subunit 3	5'UTR
Specc1		3'UTR
Spice1		CDS
Spint1	kunitz-type protease inhibitor 1 precursor	CDS
Spock2	testican-2 precursor	5'UTR
Spon1	spondin-1 precursor	3'UTR
Spon1	spondin-1 precursor	5'UTR
Spred2	sprouty-related, EVH1 domain-containing protein	3'UTR
Spred3	sprouty-related, EVH1 domain-containing protein	CDS
Spty2d1	protein SPT2 homolog	3'UTR
Srcin1	SRC kinase signaling inhibitor 1	CDS
Srebf2	sterol regulatory element-binding protein 2	CDS
Srgap1	SLIT-ROBO Rho GTPase-activating protein 1	CDS
Srgap2	SLIT-ROBO Rho GTPase-activating protein 2	CDS
Srrm2	serine /arginine repetitive matrix protein 2	2/1 TR
Set	somatostatin precursor	='IITR
Stra	here-interacting protain	-/UTR
Stra	alpha a 8 cialultraneforaça 8B	CDS
St8siaa	alpha-2 8-sialvitraneforaço 8B	2/1/TR
Stosia2	aipha-2,0-Siaiyittalistetase ob	-/1170
CtRoine	alaba a 8 cialultranoforaco 8E icoform middle	CDS
Stosia=	aipha-2,0-siaiyittansierase on isolorin midale	-/1170
Stoslab	aipna-2,0-statyttransterase on isotorm middle	5 UIK
Stat5b	signal transducer and activator of transcription	3'UIR
Stato	signal transducer and transcription activator 6	3 UIK
5tK40	serine/threonine-protein kinase 40 isoform a	3'UTK
Strn	striatin	CDS
Stt3b	dolichyl-diphosphooligosaccharide-protein	5'UTR
Stub1	STIP1 homology and U box-containing protein 1	5'UTR
Stx1a	syntaxin-1A	3'UTR
Stx1b	syntaxin-1B	3'UTR
Stx3	syntaxin-3 isoform A	5'UTR
Stxbp1	syntaxin-binding protein 1 isoform b	3'UTR
Stxbp1	syntaxin-binding protein 1 isoform b	5'UTR
Sufu	suppressor of fused homolog isoform 2	3'UTR
Supt6h	transcription elongation factor SPT6	CDS
Surf4	surfeit locus protein 4	5'UTR
Susd2	sushi domain-containing protein 2 isoform 2	2'UTR
Susda	sushi domain-containing protein 2	CDS
Sueda	suchi domain-containing protein 2	2/LITR
Susa	subantic vociale alveopratein a A	-/ ITP
Sv2d Sv2d	synaptic vesicle glycoprotein 2A	5 UIK
3v2C	synapue vesicle giycoprotein 2C	JUIN -/UTD
Sv2C	synaptic vesicle glycoprotein 2C	5 UIK
Swap70	switch-associated protein 70	
Sympk	symplekin	(1)5

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Transcript Symbol	Transcript Name	Methylation site
Syn1	synapsin-1 isoform b	CDS
Syn1	synapsin-1 isoform b	3'UTR
Syn1	synapsin-1 isoform b	5'UTR
Svn2	synapsin-2 isoform IIa	CDS
Syn2	synapsin-2 isoform IIa	5'UTR
Syngra	synapting 2 isotorin in	='UTR
Syngra	synaptogynn-3	2/UTP
Synn	synemin isolorin in	CDC
Зур	synaptopriysin	CD3
Syt12	synaptotagmin-12	5 UIK
Syt3	synaptotagmin-3	CDS
Syvni	E3 ubiquitin-protein ligase synoviolin	3'UTR
Tacr1	substance-P receptor	5'UTR
Taokı	serine/threonine-protein kinase TAO1	5'UTR
Tap1	antigen peptide transporter 1 isoform 2	CDS
Tapbp	tapasin isoform 1	CDS
Tapbp	tapasin isoform 1	5'UTR
Tarbp1	TAR (HIV-1) RNA binding protein 1	CDS
Tasıra	taste receptor type 1 member 3 precursor	CDS
Tatdn2	TatD DNase domain containing 2	5'UTR
Theidioc	carabin	CDS
Therda	TRCs domain family member a	o'UTP
Theodoria	TBC: domain family, member 2	3 UIK
IDC1d22D	The last family member 22b	CDS
1DC1d22D	IDC1 domain family member 22B	3 UIK
Tbc1d30	TBC1 domain family member 30	5'UTR
Tbc1d5	TBC1 domain family member 5	3'UTR
Tbc1d8	TBC1 domain family member 8	3'UTR
Tbc1d9	TBC1 domain family member 9 isoform 1	5'UTR
Tbrg4	protein TBRG <sub>4</sub>	CDS
Tbx2	T-box transcription factor TBX2	CDS
Tbx3	T-box transcription factor TBX3 isoform 1	CDS
Thya	T-box transcription factor TBX2 isoform 1	2'UTR
Thyaar	thrombovane A a recentor	o'UTR
Tean	taleth onin	2/UTP
Т		3 UIK
Icea1	transcription elongation factor A protein 1	5'UTR
Tcf12	transcription factor 12	5'UTR
Tcf25	transcription factor 25 isoform c	5'UTR
Tcf3	transcription factor E2-alpha isoform 7	CDS
Tcf7l2	transcription factor 7-like 2 isoform 7	CDS
Tcfe3	transcription factor E3 isoform a	CDS
Tcfe3	transcription factor E3 isoform a	5'UTR
Tchh	trichohyalin	CDS
Tcter	T-compley-associated testis-expressed protein 1	CDS
Tead	transcriptional enhancer factor TEE-1 isoform a	o'UTR
Towner	transcriptional emiliar remeat containing	CDC
Theoperation	tectorini beta-propener repeat-containing	CDS
Tekt4	tektin-4	CDS
Tekt5	tektin-5	CDS
Tesk1	dual specificity testis-specific protein kinase	5'UTR
Tgfb1	transforming growth factor beta-1 precursor	5'UTR
Tgfbr3	transforming growth factor beta receptor type 3	CDS
Tgfbr3	transforming growth factor beta receptor type 3	3'UTR
Thpo	thrombopoietin precursor	CDS
Thra	thyroid hormone receptor alpha	3'UTR
Thrsp	thyroid hormone-inducible hepatic protein	CDS
Thrsp	thyroid hormone-inducible hepatic protein	3'UTR
Thsd4	thrombospondin type-1 domain-containing protein	CDS
Thsd4	thrombospondin type-1 domain-containing protein	3'UTR
Timm17a	mitochondrial import inner membrane translocase	CDS
Timmeo	mitochondrial import inner membrane translocase	CDS
Timpo	matellongate inhibitor a program	-/ITP
Timp2	metanoprotentase minoror 2 precursor	- / ITD
Timp3	metanoproteinase innibitor 3 precursor	3 UTK
linaglı	tubulointerstitial nephritis antigen-like	CDS
Tle3	transducin-like enhancer protein 3 isoform 2	5'UTR
Tln1	talin-1	5'UTR
Tmem102	transmembrane protein 102	CDS
Tmem104	transmembrane protein 104	CDS
Tmem104	transmembrane protein 104	3'UTR
Tmem108	transmembrane protein 108 precursor	CDS
Tmem126b	transmembrane protein 126B	3'UTR
Tmem127	transmembrane protein 127	5'UTR
Tmem128	transmembrane protein 128	CDS
Tmem120	transmembrane protein 120	CDS
Tmoment 30	transmembrane protein 130 precursor	CDC
Tinem131	transmembrane protein 131	
1mem132d	transmembrane protein 132D precursor	5 UIK
Imem132e	transmembrane protein 132E precursor	5 UTR
Tmem145	transmembrane protein 145	3'UTR
Tmem194	transmembrane protein 194A isoform 1	3'UTR
Tmem200c		5'UTR
Tmem201	transmembrane protein 201 isoform b	CDS
		Continued on next page

Table 6.3 – continued from previo	bus page	
Transcript Symbol	Transcript Name	Methylation site
Tmem25	transmembrane protein 25 precursor	3'UTR
Tmem38b	trimeric intracellular cation channel type B	CDS
Tmem59l	transmembrane protein 59-like precursor	CDS
Tmem63b	transmembrane protein 63B	CDS
Tmem63b	transmembrane protein 63B	3'UTR
Tmem8o		5'UTR
Tmtc2	transmembrane and TPR repeat-containing protein	5'UTR
Tnc	tenascin	CDS
Tnfrsf1a	tumor necrosis factor receptor superfamily	3'UTR
Tnik	traf2 and NCK-interacting protein kinase isoform	5'UTR
Tnip1	TNFAIP3-interacting protein 1	3'UTR
Tnpo2	transportin-2	3'UTR
Tnrc6c	trinucleotide repeat-containing gene 6C protein	5'UTR
Inxb	tenascin-X	CDS
Tom112	TOM1-like protein 2 isoform b	CDS
Tomm6	mitochondrial import receptor subunit TOM6	CDS
Tor1aip1	torsin-1A-interacting protein 1 isoform 2	5'UTR
Iox2	TOX high mobility group box family member 2	3'UTR
Tpcn2	two pore calcium channel protein 2	3'UIK -// ITD
Iprai Tra faina	transmembrane protein adipocyte-associated 1	5 UIR
Trans1122	to find and the sector of the second sector of the sector	-/ITP
таррс5	trafficking protein particle complex subunit 5	5 UTK
парред	transcriptional regulating faster a information	3 UTK
Triba	tribles homolog z	5 UTK -/UTP
TL:1	tribbles noniolog 1	5 UTK -/UTD
IIII Trim 17	Ea ubiquitin protein ligger TDD (-	5 UTK
Trimas	E3 ubiquitin-protein igase TRIM17	CDS
Trim26	E3 ubiquitin/15G15 ligase 1Kivi25	-/1178
Trim 44	Ea ubiquitia protoin ligaço TPIM44	-/1 ITP
Trimes	E3 ubiquitit-protein ligase 1 Kiwi41	5 UIK
Trim66	tripartite motif containing protein 62	2/LITP
Trim67	tripartite motif-containing protein 67	CDS
Trim68	E2 ubiguitin-protein ligase TRIM68	CDS
Trimz	tripartite motif-containing protein 7	2/LITR
Trimo	E2 ubiguitin-protein ligase TRIMo isoform c	CDS
Trimo	E3 ubiquitin protein ligase TRIMg isoform c	cD3
Trant	TME regulated puckers protein 1	CDS
Trasabaa	apoptosis-stimulating of pra protein a	-/UTR
Trpsziji	tumor protein p52-inducible protein 11	2/11TR
Trp73	tumor protein p33 inducible protein 11	CDS
Trp72	tumor protein p72 isoform c	2/IITR
Trrap	transformation / transcription domain-associated	2/UTR
Tsc22d4	TSC 22 domain family protein 4	CDS
Tsku	tsukushin precursor	CDS
Tsn	translin	CDS
Tspan17	tetraspanin-17	3′UTR
Ttc28	tetratricopeptide repeat protein 28	3'UTR
Ttc7b	tetratricopeptide repeat domain 7B	CDS
Ttll1	probable tubulin polyglutamylase TTLL1	CDS
Ttll4	tubulin polyglutamylase TTLL4	3′UTR
Ttyh1	protein tweety homolog 1 isoform 2	CDS
Ttyh2	protein tweety homolog 2	CDS
Tubb4	tubulin beta-4 chain	3'UTR
Tubb4	tubulin beta-4 chain	5′UTR
Tubg2	tubulin gamma-2 chain	CDS
Tubgcp4	gamma-tubulin complex component 4	5'UTR
Tulp4	tubby-related protein 4 isoform b	3'UTR
Txndc5	thioredoxin domain-containing protein 5	CDS
Txnrd1	thioredoxin reductase 1, cytoplasmic isoform 2	5'UTR
Tysnd1	peroxisomal leader peptide-processing protease	CDS
U2af2	splicing factor U2AF 65 kDa subunit	3'UTR
Uapılı	UDP-N-acetylhexosamine pyrophosphorylase-like	CDS
Ubc	polyubiquitin-C	CDS
Ube2m	NEDD8-conjugating enzyme Ubc12 isoform 2	5'UTR
Ube2q2	ubiquitin-conjugating enzyme E2 Q2	CDS
Ube2ql1	ubiquitin-conjugating enzyme E2Q-like protein 1	5'UTR
Ubqln4	ubiquilin-4	CDS
Ubr2	E3 ubiquitin-protein ligase UBR2 isoform 1	5'UTR
Ubxn4	UBX domain-containing protein 4	5'UTR
Unc5a	netrin receptor UNC5A precursor	CDS
Unc5a	netrin receptor UNC5A precursor	3'UTR
Unc5b	netrin receptor UNC5B precursor	3'UTR
Unc5b	netrin receptor UNC5B precursor	5'UTR
Unc5c	netrin receptor UNC5C precursor	5'UTR
Unc5d	netrin receptor UNC5D precursor	5'UTR
Uncx	homeobox protein unc-4 homolog	CDS
Unex	homeobox protein unc-4 homolog	3'UTR

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Table 6.3 – continued from previous p	oage
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Transcript Symbol	Transcript Name	Methylation site
Ung	uracil-DNA glycosylase isoform a	3'UTR
Upf1	regulator of nonsense transcripts 1 isoform a	CDS
Upf1	regulator of nonsense transcripts 1 isoform a	5'UTR
Urod	uroporphyrinogen decarboxylase	CDS
Usf2	upstream stimulatory factor 2	3'UTR
Usp19	ubiquitin carboxyl-terminal hydrolase 19 isoform	5'UTR
Usp2	ubiquitin carboxyl-terminal hydrolase 2 isoform	5'UTR
Usp22	ubiquitin carboxyl-terminal hydrolase 22	3'UTR
Usp30	ubiquitin carboxyl-terminal hydrolase 30	CDS
Usp33	ubiquitin carboxyl-terminal hydrolase 33 isoform	5'UTR
Usp43	ubiquitin carboxyl-terminal hydrolase 43	CDS
Ust	uronyl 2-sulfotransferase	CDS
Vac14	protein VAC14 homolog	CDS
Vatı	synaptic vesicle membrane protein VAT-1 homolog	CDS
Vgf	VGF nerve growth factor inducible	5'UTR
Vim	vimentin	CDS
Vps26b	vacuolar protein sorting-associated protein 26B	3'UTR
Vps37a	vacuolar protein sorting-associated protein 37A	5'UTR
Vps37d	vacuolar protein sorting-associated protein 37D	CDS
Vps37d	vacuolar protein sorting-associated protein 37D	3'UTR
Vps53	vacuolar protein sorting-associated protein 53	3'UTR
Vps8	vacuolar protein sorting-associated protein 8	3'UTR
V SX2	visual system homeobox 2	
Vm	vitronectin precursor	CDS CDS
Vwt	von Willebrand factor precursor	
wast2	wiskott-Aldrich syndrome protein family member	3 UTK
Wast3	wiskott-Aldrich syndrome protein family member	3'UTR
Wbscr27	Williams-Beuren syndrome chromosomal region 27	5'UTR
Wdfy4	WD repeat and FYVE domain containing 4	CDS
Wdr33	WD repeat domain 33 isoform 2	5'UIR
Wdr45l	WD repeat domain phosphoinositide-interacting	CDS
Wdr6	WD repeat-containing protein 6	3'UTR
Wdr82	WD repeat-containing protein 82	5'UTR
Wdtc1	WD and tetratricopeptide repeats protein 1	3'UTR
Wfikkn2	WAP, kazal, immunoglobulin, kunitz and NTR	CDS
Wfs1	wolframin	CDS
Whrn	whirlin isoform 5	3'UTR
Whrn	whirlin isoform 5	5'UTR
Wipf2	WAS/WASL-interacting protein family member 2	3'UTR
Wnkı	serine/threonine-protein kinase WNK1	5'UTR
Wntı	proto-oncogene Wnt-1 precursor	5'UTR
Wnt7b	protein Wnt-7b isoform 1	CDS
X99384	paladin	CDS
Xpnpep1	xaa-Pro aminopeptidase 1	CDS
Хроб	exportin-6	5'UTR
Xpot	exportin-T	CDS
Xylb	xylulose kinase	3'UTR
Ybey		CDS
Yipf2	protein YIPF2	3'UTR
Yipf2	protein YIPF2	5'UTR
Yipf3	protein YIPF3	5'UTR
Ywhag	14-3-3 protein gamma	5'UTR
Yy1	transcriptional repressor protein YY1	CDS
Zbtb26	zinc tinger and BTB domain-containing protein	5'UTR
Zbtb33	transcriptional regulator Kaiso	5 UTK
Zbtb39	zinc tinger and BTB domain-containing protein	
ZDtD39	zinc inger and B1B domain-containing protein	3 UIK
Zbtb40	zinc ringer and BTB domain-containing protein	
Zbtb40	zinc tinger and BTB domain-containing protein	3 U I K
Zbtb7a	zinc iinger and BTB domain-containing protein	5 UTK
Zbtb7c	zinc iinger and BTB domain-containing protein	3 UTK
Zc3h15	zinc tinger CCCH domain-containing protein 15	CDS
Zc3h7b	zinc tinger CCCH domain-containing protein 7B	
Zdhhci4	probable palmitoyltransterase ZDHHC14	
Zdhhci4	probable palmitoyitransterase ZDHHC14	5 UIK
Zdhhc5	probable palmitoyltransterase ZDHHC5	
Zdhhca	probable palmitoyitransterase ZDHHC8	3 UIK
Zanneg	paimitoyitransterase ZDHHC9	
Zahne9	paimitoyitransterase ZDHHC9	3 U1K
Zeb2	zinc inger E-box-binding homeobox 2 isoform 2	5 U I K
Zeri	protein zer-1 homolog	3 UTR
Ztand3	AN1-type zinc tinger protein 3	CDS
Zthx2	zinc iinger homeobox protein 2	
Zthx2	zinc tinger homeobox protein 2	3'UTR
Ztp142	zinc tinger protein 142	CDS
Zip148	zinc tinger protein 148	5 UTK
Z1p213	zin tinger protein 213	5 UIK
Ztp335	zinc tinger protein 335	3 UTK
		Continued on next page

Table 6.3 – continued from previous page			
Transcript Symbol	Transcript Name	Methylation site	
Zfp358	zinc finger protein 358	CDS	
Zfp366	zinc finger protein 366	CDS	
Zfp36l1	zinc finger protein 36, C3H1 type-like 1	CDS	
Zfp36l2	zinc finger protein 36, C3H1 type-like 2	CDS	
Zfp385a	zinc finger protein 385A	CDS	
Zfp385a	zinc finger protein 385A	5'UTR	
Zfp395	zinc finger protein 395	CDS	
Zfp395	zinc finger protein 395	3'UTR	
Zfp414	zinc finger protein 414	CDS	
Zfp414	zinc finger protein 414	5'UTR	
Zfp423	zinc finger protein 423	CDS	
Zfp428	zinc finger protein 428	5'UTR	
Zfp592	zinc finger protein 592	3'UTR	
Zfp598	zinc finger protein 598	3'UTR	
Zfp628	zinc finger protein 628	CDS	
Zfp652	zinc finger protein 652	5'UTR	
Zfp655	zinc finger protein 655 isoform a	5'UTR	
Zfp689	zinc finger protein 689	5'UTR	
Zfp747	zinc finger protein 747	5'UTR	
Zfp831	zinc finger protein 831	3'UTR	
Zic2	zinc finger protein ZIC 2	CDS	
Zic4	zinc finger protein ZIC 4	CDS	
Zmiz1	zinc finger MIZ domain-containing protein 1	3'UTR	
Znhitı	zinc finger HIT domain-containing protein 1	5'UTR	
Znrf1	E3 ubiquitin-protein ligase ZNRF1 isoform c	CDS	
Zscan2	zinc finger and SCAN domain-containing protein	3'UTR	
Zswim1	zinc finger SWIM domain-containing protein 1	CDS	
Zswim1	zinc finger SWIM domain-containing protein 1	3'UTR	
Zswim5	zinc finger SWIM domain-containing protein 5	5'UTR	
Zzef1	zinc finger ZZ-type and EF-hand	CDS	

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#### Erklärung

Die vorliegende Arbeit wurde in der Zeit von November 2009 bis November 2013 am Institut für Genetik, Arbeitsgruppe Modern Mouse Genetics and Metabolism, Universität zu Köln und im Max Planck Institut für Neurologische Forschung Köln, Forschungsgruppe Neuronal Control of Metabolism unter Anleitung von Herrn Prof. Dr. Jens C. Brüning angefertigt.

Ich versichere, dass ich die von mir vorgelegte Dissertation selbständig angefertigt, die benutzten Quellen und Hilfsmittel vollständig angegeben und die Stellen der Arbeit - einschließlich Tabellen, Karten und Abbildungen -, die anderen Werken im Wortlaut oder dem Sinn nach entnommen sind, in jedem Einzelfall als Entlehnung kenntlich gemacht habe; dass diese Dissertation noch keiner anderen Fakultät oder Universität zur Prüfung vorgelegen hat; dass sie - abgesehen von unten angegebenen Teilpublikationen - noch nicht veröffentlicht worden ist sowie, dass ich eine solche Veröffentlichung vor Abschluss des Promotionsverfahrens nicht vornehmen werde. Die Bestimmungen dieser Promotionsordnung sind mir bekannt.

Köln, März 2014

(Martin Heß)

## Teilpublikation

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# Curriculum vitae

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Titel	The role of octopamine and DUM neurons in the modulation of motor activity in the stick insect <i>Carausius morosus</i>
Betreuer	PD Dr. Joachim Schmidt

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	activity of the dopaminergic midbrain circuitry.
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#### Konferenz Teilnahmen

03/2013	Keystone Symposium:
	Neuronal Control of Appetite, Metabolism and Weight,
	Banff, Kanada
	Poster: The Obesity-Associated Fto Gene Regulates the Activity of the Dopa-
	minergic Midbrain Circuitry
09/2012	EMBO-Symposium: Diabetes and Obesity,
	Heidelberg, Deutschland
	Poster: The Obesity-Associated Fto Gene Regulates the Activity of the Dopa-
	minergic Midbrain Circuitry
01/2012	Keystone Symposium:
	Genetic and Molecular Basis of Obesity and Body Weight Regulation,
	Santa Fe, NM, USA

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