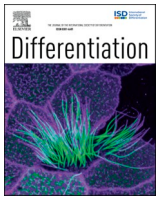
Differentiation 142 (2025) 100838

Contents lists available at ScienceDirect

Differentiation

journal homepage: www.elsevier.com/locate/diff



# The fundamentals of WNT10A

Erica L. Benard [a,*], Matthias Hammerschmidt [a,b]

[a] Institute of Zoology, Developmental Biology Unit, University of Cologne, Cologne, Germany
[b] Center for Molecular Medicine Cologne, University of Cologne, Cologne, Germany

ARTICLE INFO

*Keywords:*
*wnt10a*
Mouse
Zebrafish
Tooth agenesis
Odonto-oncho-dermal dysplasia
Schöpf–schulz–passarge syndrome

ABSTRACT

Human wingless-type MMTV integration site family member 10A (*WNT10A*) is a secreted glycoprotein that is involved in signaling pathways essential to ectodermal organogenesis and tissue regeneration. *WNT10A* was first linked to human disorders in 2006, demonstrating a *WNT10a* variant to be associated with cleft lip with/without cleft palate. Numerous publications have since then identified the importance of *WNT10A* in the development of ectodermal appendages and beyond. In this review, we provide information on the structure of the *WNT10A* gene and protein, summarize its expression patterns in different animal models and in human, and describe the identified roles in tissue and organ development and repair in the different animal model organisms. We then correlate such identified functions and working mechanisms to the pathophysiology of a spectrum of human diseases and disorders that result from germline loss-of-function mutations in *WNT10A*, including ectodermal dysplasia (ED) syndromes Odonto-oncho-dermal dysplasia (OODD), Schöpf–Schulz–Passarge syndrome (SSPS), and selective tooth agenesis, as well as pathological conditions like fibrosis and carcinogenesis that can be correlated with increased WNT10A activity (Section 5).

## 1. Introduction

Human *WNT10A* has been subject to former reviews (Bonczek et al., 2021; Clauss et al., 2014; Doolan et al., 2021; Katoh, 2002; Lan et al., 2023; Letra, 2022; Nie et al., 2020; Wright et al., 1993; Yu et al., 2019) on which this primer is based, while adding most recent human work published since and extending to *Wnt10a* function in other model species. Like other "canonical" WNTs, WNT10A is a secreted growth factor that upon binding to its cell surface receptor activates the intracellular β-catenin signal transduction pathway by attenuating β-catenin's targeting for proteasomal degradation. Stabilized β-catenin then interacts directly with region-specific T cell factor/lymphoid enhancer factor (TCF/LEF), which in cooperation with other transcription factors, as for instance Krüppel-like factor 4 (KLF4) in differentiating, but not proliferating cells, promotes the expression of specialized genes, as for instance keratins, required for normal tissue structure and integrity (Xu et al., 2017). In this and multiple other cases, this pathway allows *WNT10A* to play a crucial role in the development of tissues that arise from the ectoderm, one of the three embryonic germ layers. However, WNT10A also acts in other germ layers and their derivatives, as described in more detail below (Sections 3 and 4). In addition, in some mammalian conditions of tissue regeneration and carcinogenesis, WNT10A signaling has also been described to occur in a "non-canonical", β-catenin-independent manner (Fan et al., 2017; Teiken et al., 2018).

Most of the *WNT* genes are organized in gene clusters that are evolutionary conserved. For example, human *WNT10A* and *WNT6* are located in a head-to-tail orientation within an interval of less than 7.0 kb in chromosomal region 2q35 (Kirikoshi et al., 2001b) and *WNT10B* and *WNT1* are located in chromosomal region 12q13. Among the human WNT family, *WNT10A* is most homologous to *WNT10B* (59.2% amino-acid identity), and *WNT6* most homologous to *WNT1* (47.4% amino-acid identity) (Kirikoshi et al., 2001b), suggesting that already the ancestors of these apparent paralogues were clustered and duplicated together during evolution of the jawed vertebrate lineage (Nusse, 2001; Sidow, 1992). In addition, the synteny of such *WNT10A/WNT6* gene clusters and their immediate gene neighbors has been shown to be conserved among human (*Homo sapiens*) and other vertebrate species, such as the primate macaque (*Macaca mulatta*), the rodent mouse (*Mus musculus*) and the teleost zebrafish (*Danio rerio*) (Qurrat Ul et al., 2011).

Of all vertebrate species, *wnt10a* was first published in zebrafish in 1993 and shown to be expressed in the central nervous system of

This article is part of a special issue entitled: Wnt primers issue published in Differentiation.

* Corresponding author.
*E-mail address:* ericaleannewolff@gmail.com (E.L. Benard).

https://doi.org/10.1016/j.diff.2025.100838
Received 25 August 2024; Received in revised form 22 January 2025; Accepted 25 January 2025
Available online 30 January 2025

embryos, suggesting a role during the regionalization of the developing brain (Kelly et al., 1993). A few years later (1996), murine *Wnt10a* was cloned and shown to be expressed in limbs, the face and the skin of developing embryos and adults (Wang and Shackleford, 1996). In 1997, involvement of *Wnt10a* was described in axial patterning during newt tail regeneration, a process that is enabled through reactivation of genes involved in embryonic development (Caubit et al., 1997). It was only in 2001 that human *WNT10A* was cloned and characterized for the first time. This research showed that W*NT10A* mRNAs were not only expressed in different tissues of human fetuses as well as in different organs of adult humans, but also - in much up-regulated levels - in cells isolated from the large intestine of a colorectal cancer patient, in promyeloblast cells of an acute promyelocytic leukemia patient and in lymphoblast-like cells from a Burkitt's lymphoma patient. This suggests that overexpression of *WNT10A* might play a key role in human carcinogenesis (Kirikoshi et al., 2001a). Later, *Wnt10a* was found to be expressed in the apical ectodermal ridge (AER) of developing chicken and mouse limbs and, based on misexpression (gain-of-function) studies, shown to be involved AER formation in the chick limb bud through the Wnt/β-catenin signaling pathway (Narita et al., 2005). A connection between *WNT10A* function and a human disorder was first published in 2006, with genetic linkage analyses implicating *WNT10A* in cleft lip with/without cleft palate (CL/P), but without providing direct evidence that such defects are indeed caused by a gain- or loss of WNT10a function (Beaty et al., 2006). However, numerous publications, including genetic loss-of-functions studies in the mouse, have in the meantime confirmed that *WNT10A* is essential for the formation of multiple tissues that arise from the embryonic ectoderm, such as teeth, hair, skin, sweat glands and salivary glands (reviewed by (Doolan et al., 2021)). All of these organs have in common that they develop via tight and mutual interactions between epithelial cells and the underlying mesenchyme, a concept of WNT10A dependence that can be extended to organs and structures also deriving from the two other embryonic germ layers (see below).

## 2. Genomic and protein structure of *WNT10A*

### 2.1. Genomic architecture

The human *WNT10A* gene resides on chromosome 2 (2q35) and spans approximately 13.4 kilobases (kb) (Fig. 1A). The mouse *Wnt10a* gene resides on chromosome 1 and zebrafish *wnt10a* gene resides on chromosome 9. All of the aforementioned genes contain four exons and three introns. Transcription proceeds on the forward strand and a 417-amino acid protein (Fig. 1B) (human and mouse) or 442-amino acid protein (zebrafish) is encoded. There may be additional transcripts of *WNT10a*, *Wnt10a* and *wnt10a* present, however, direct experimental evidence for splice variants is lacking.

### 2.2. Regulatory sequences

To date, direct experimental evidence for regulatory sequences of WNT10A is lacking, however, putative transcription factor binding sites (TFBSs) of *WNT10A* have been predicted by examining about 7 kb of upstream and downstream regulatory sequences of all four homologs *WNT1*, *WNT6*, *WNT10A* and *WNT10B* (Qurrat Ul et al., 2011). This *in-silico* study revealed that the 5' upstream region of *WNT10A* contains binding sites for MYC family (N-MYC and C-MYC), TCF4 and SOX family (SOX2) transcription factors (Qurrat Ul et al., 2011). SOX9 binding sites were localized at the downstream region of *WNT10A* (Qurrat Ul et al., 2011). Analysis revealed that all these conserved non-coding elements (CNEs) are present in *Homo sapiens*, *Macaca mulata, Mus musculus* and *Danio rerio*, irrespective of the exact orientation on the genome. This led to the speculation that TCF4 and SOX9 are the responsible regulatory

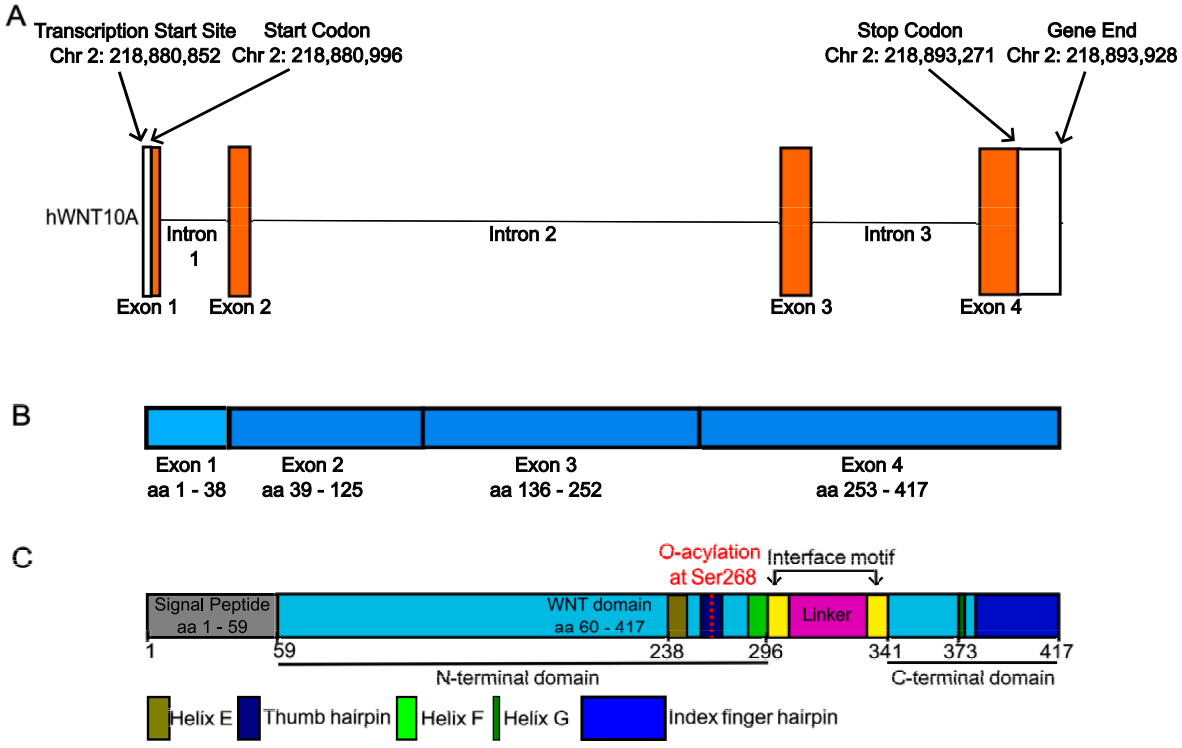



**Fig. 1.** Genomic and domain structure of human *WNT10A*.
**A.** Genomic organization of human *WNT10A*. Base location are derived from Genome Reference Consortium Human Build 38 (GRCh38.p14). **B.** Exon structure of WNT10A. **C.** Schematic diagram of the predicted primary structure of human WNT10A (signal peptide (SP); N-terminal domain (NTD) with Helix E, Thumb hairpin containing the O-acylation site (in red) and Helix F; interface motif containing the linker region; and C-terminal domain (CTD) with Helix G and Index finger hairpin) based on the crystal structure of human WNT3 (Kantaputra and Sripathomsawat, 2011).

elements that may act as activator and inhibitors, respectively, hence interceding the signaling pathway (Qurrat Ul et al., 2011). This is in line with studies that suggest that SOX9 antagonizes WNT signaling either by promoting β-catenin degradation or by inhibiting β-catenin transcriptional activity (Akiyama et al., 2004).

### 2.3. Protein modifications, functional domains, and structure

The functional protein WNT10A consists of a signal peptide (amino acid position 1–59) and the WNT domain (amino acid position 60–417), which can be further subdivided (Fig. 1 and below) (Kantaputra and Sripathomsawat, 2011). Post-translational modifications of WNT domain include multiple N-glycosylations and the coordination of a series of disulfide bonds (Coudreuse and Korswagen, 2007; Willert and Nusse, 2012), as well as O-acylation at a specific Ser residue (Ser268 in human WNT10A) (Kantaputra and Sripathomsawat, 2011) (Fig. 1C). The latter is performed in the endoplasmic reticulum (ER) by porcupine (PORCN) to generate palmitoleic acid- or palmitate-modified WNT (PAM WNT). This modification is necessary for the PAM WNT-WNTLESS interaction responsible for transport through the Golgi to the cell surface. Intercellular trafficking of PAM WNT from producing to receiving cells during paracrine WNT signaling most likely occurs via cytonemes and extracellular vesicles/exosomes, with the WNT protein remaining tethered to the cellular and vesicular membranes via its PAM moiety (Routledge and Scholpp, 2019). This moiety is also critical to form the PAM WNT–Frizzled (FZD) complex on the surface of WNT target cells for WNT signal transduction (Nile and Hannoush, 2016).

WNT palmitoylation has complicated the production and purification of recombinant material because it is insoluble in the absence of detergents (Nile and Hannoush, 2016; Willert, 2008). Therefore, relatively few detailed structure-function studies of WNTs have been carried out that shed light on their protein structure and how WNTs engage FZD complex formation with its transmembrane receptor (Janda et al., 2012). Both the crystal structures of human WNT3 in complex with mouse Frizzled 8 Cys-rich domain (CRD) and the cryo-EM structure of a ternary initiation complex of an affinity-matured XWnt8–Frizzled8–LRP6 complex have previously been solved (Hirai et al., 2019; Tsutsumi et al., 2023). Wnt3 grabs the receptor in a manner very similar to that found in Xenopus Wnt8 complexed with the same receptor (Tsutsumi et al., 2023). The hWNT10A protein structure has been predicted by using both the known the Xenopus Wnt8 structure (Yuan et al., 2017) and the hWNT3 structure (Adachi et al., 2023; Kantaputra and Sripathomsawat, 2011), presented in this review (Fig. 1C) (Yuan et al., 2017), as templates. The amino acid sequences of WNT10A and WNT3 are highly conserved (Adachi et al., 2023), especially the arrangement of cysteine residues in the C-terminus, suggesting that they share the same higher-order structure and, consequently, the same biological function. This model predicts that the signal sequence (SP aa 1–59) is followed by the N-terminal domain (NTD aa 59–296) containing Helix E and Helix F, and the thumb hairpin; the interface motif (296–340) containing the linker region; and the C-terminal domain (CTD aa 341–417) containing helix G and index finger consisting of a 2-stranded β-sheet hairpin. The NTD comprises a 6-helix core and 2 protruding β-hairpins, one of which is acylated with a fatty acid, while the CTD index finger, which contains the 24 conserved cysteine residues of WNT10A, constitutes a disulfide-bond-stabilized cytokine-like hairpin loop. Both the fatty acyl group of the NTD protruding β-hairpin (the thumb hairpin) and the CTD β-hairpin (index finger structure) interact with FZD (Bazan and de Sauvage, 2009; Hirai et al., 2019; Janda et al., 2012), resembling the thumb and index finger of a hand grasping FZD at two distinct binding sites (Janda et al., 2012; Kerekes et al., 2015), while the linker between the NTD and the cysteine-rich CTD of WNT10A is required for binding to the co-receptor lipoprotein receptor-related protein 6 (LRP6) (Chu et al., 2013; Kantaputra and Sripathomsawat, 2011). Binding of WNT proteins to FZD and LRP6 or its paralog LRP5 then initiates the intracellular WNT/β-catenin signal transduction pathway (Janda et al., 2012; Willert and Nusse, 2012). The index finger structure is also responsible for binding of WNT10A to WNTLESS, the membrane protein that binds lipid-acylated WNT proteins to carry them from the endoplasmatic reticulum to the cell surface (Kantaputra and Sripathomsawat, 2011; Nile and Hannoush, 2016; Nygaard et al., 2021; Zhong et al., 2021).

An important structure-function study providing information on the predicted protein folding and/or stabilization of WNT10A and its binding affinity to FZD5 was performed with bioinformatic and functional characterization analysis of *WNT10A* variants (Zeng et al., 2021). Thirteen tooth agenesis (TA)-associated *WNT10A* variants were used to perform functional characterization experiments. Most *WNT10A* variants lead to a truncated protein that perturbs or fails to activate WNT signaling. Variants with predicted ability to destabilize disulfide bonds or disrupt proper disulfide bond formation due to a cysteine exchange at the C-terminal end of the protein, displayed significantly decreased FZD5 binding in co-immunoprecipitation experiments, correlated with dysregulated expression of genes involved in tooth and skeletal development, morphogenesis, and pattern specification. Similarly, in silico prediction of variant function of all *WNT10A* missense variants reported in the Exome Aggregation Consortium database was performed based on *Xenopus laevis* WNT8 as a template. Most of the tooth TA-associated variants, including the frequently observed missense mutation p.Phe228Ile, had deleterious scores by potentially destabilizing or preventing disulfide bond formation, thereby impacting proper folding and function of the protein (Dinckan et al., 2018; Du et al., 2018).

Together, these protein models of WNT10A are important to understand how pathogenic variants in *WNT10A* appear to cause variant-specific changes in protein folding or stabilization leading to improper WNT signaling or dysregulated expression of additional genes.

## 3. *WNT10A* expression

In this section we explore the expression patterns of *WNT10A* in different animal models and in human, subdivided into mesenchymal and/or epithelial expression where possible, and touch on its correlated roles revealed in functional studies in according cell culture and/or animal systems. The overall organismal defects resulting from the loss of Wnt10a function in the animal models mouse and zebrafish are summarized below in Tables 1 and 2, and will be described in more detail in Section 4, while human disorders associated with pathogenic variants of *WNT10A* or altered levels of *WNT10A* expression will be discussed in more detail in Section 5.

*WNT10A* is predominantly (but not exclusively) expressed in tissues and processes involving epithelial-mesenchymal interactions, no matter whether the particular cell types are of ectodermal, endodermal or mesenchymal origin (Ribatti and Santoiemma, 2014). To elucidate the (usually paracrine) intercellular WNT10A signaling underlying such epithelial-mesenchymal interactions, it is necessary to combine analyses of WNT10A production (e.g. via *in situ* hybridization detecting intracellular *WNT10A* transcripts) with analyses of WNT10A signal reception (e.g. via immunodetection of nuclear β-catenin or with transgene-encoded TCF/LEF reporters) (see (Benard et al., 2023; Xu et al., 2017) for examples). Yet, such combined studies at cellular resolutions are rather rare and usually restricted to animal models, so that definitive conclusions about WNT10A-driven epithelial-mesenchymal interactions remain difficult, also because WNT10A could in principle signal in an autocrine, self-stimulatory fashion. This is observed for other canonical WNT signals, in particular in the context of cancer, and with monotypic cell culture systems (see for instance (Schlange et al., 2007)).

### 3.1. WNT10A expression and function in dental epithelium and mesenchyme during tooth development

The *Wnt10a* expression pattern during tooth development in mice is well documented in the literature and considering that *WNT10A* is the

**Table 1**
*Wnt10a* mutant mice and their phenotypes.

| Mutant | Phenotype | Reference |
|---|---|---|
| CRISPR/Cas mediated | | |
| *Wnt10a*−/− (CRISPR/Cas disruption middle region exon 2 to middle region exon 3) | severe root or enamel hypoplasia | Yoshinaga et al. (2023) |
| **Endonuclease-mediated (inducible, recombinase)** | | |
| Wnt10a$^{em1(cre/ERT2)Amc}$ /Wnt10a-CE/ Wnt10aCRE-ERT2 (reporter strain) | Not published | Wegner et al. (2017) |
| Wnt10a$^{em1Smoc}$ | Not published | The Jackson Laboratory (2017) |
| *K14-Cre;Wnt10a*$^{fl/fl}$ | enlarged pulp chamber and apical displacement of the root furcation of multi-rooted teeth | (Sun et al., 2024; Yu et al., 2020) |
| **Allele type: Targeted mutation (Targeted, Null/knockout, Reporter)** | | |
| **Mutations: Insertion, Intragenic deletion** | | |
| Wnt10atm1.1(KOMP) Vlcg (Deletion Wnt10a coding region, Null/ knockout, Reporter) | adipose, craniofacial, supernumerary ectopic fourth molar and crown malformations, growth/size/ body, integument, limbs/ digits/tail, pigmentation, skeleton | Yang et al. (2015) |
| Wnt10a$^{tm1(KOMP)Vlcg}$ (Null/knockout, Reporter) | hyperlucent areas in the bone, severe kyphosis, overt alopecia, female infertility, delayed wound healing, increased number beige adipocytes in subcutaneous fat, hippocampal neurodegeneration, and memory deficit | (Tsukamoto et al., 2019; Wang et al., 2018; Zhang et al., 2022a, 2022b) |
| Wnt10a$^{tm1.1Smr}$ Wnt10a$^{KO}$ (Null, knockout) | behavior, craniofacial, supernumerary ectopic fourth molar and crown malformations, digestive/ alimentary, endocrine/ exocrine, growth/size/body, integument, skeleton, taste/ olfaction | Xu et al. (2017) |
| Wnt10a$^{tm1Smr}$ Wnt10$^{fl}$ (Conditional ready) | cellular, craniofacial, digestive/alimentary, endocrine/exocrine, growth/ size/body, integument, skeleton, taste/olfaction | Xu et al. (2017) |
| Wnt10a$^{tm1a(EUCOMM)Wtsi}$ (Conditional ready, Null/knockout, Reporter) (Cell line) | Not published | Skarnes et al. (2011) |

**Table 2**
*wnt10a* mutant and knockdown zebrafish and their phenotypes.

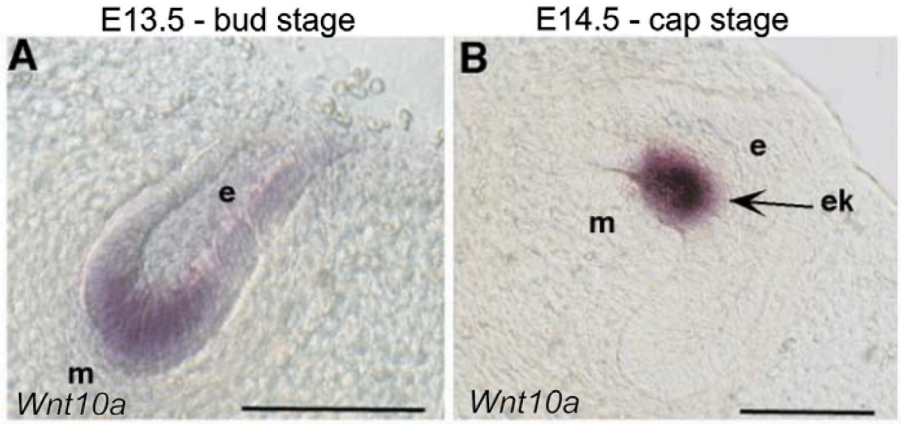
| Mutant/knockdown | Phenotype | Reference |
|---|---|---|
| *wnt10a*$^{t30922}$ mutant | Abnormal embryonic tooth development, no adult teeth, underdeveloped adult ceratobranchial 5 arch, collapse of the minor and major lobes of the median fin fold from 48 hours post fertilization (hpf) onwards, abnormal adult fins (either absent or containing only few lepidotrichia). | Benard et al. (2023) |
| MO1-*wnt10a*, morpholino 5′-TTTGATTTGATCGCTTACCCCTGCT -3′ knockdown | Collapse of the minor and major lobes of the median fin fold from 48 hpf onwards | Benard et al. (2023) |
| MO1-*wnt10a*, morpholino '5-GTCGTGAGAGCTCATTCATGGAATC-3' knockdown | Abnormal cranial cartilage morphology, odontogenesis arrested | Yuan et al. (2017) |
| MO2-*wnt10a*, morpholino '5-CTGTTTGATTTGATCGCTTACCCCT-3' knockdown | Odontogenesis arrested, ceratobranchial 5 tooth absent, abnormal cranial cartilage morphology | Yuan et al. (2017) |
| CRISPR1-*wnt10a* (46 ins, Z001495) and CRISPR2-*wnt10a* (Z001496) | Not published | Pei et al. (2018) |

most commonly mutated gene in human non-syndromic selective agenesis of permanent teeth (Mues et al., 2014; van den Boogaard et al., 2012), it is not surprising that *WNT10A* was later found to be expressed in developing human teeth as well (Kornsuthisopon et al., 2022). During early stages of mouse tooth development, *Wnt10a* expression is restricted to the epithelium of the tooth bud (Dassule and McMahon, 1998; Miletich and Sharpe, 2003; Raju et al., 2023). At bud stage (embryonic day 13.5; E13.5), *Wnt10a* is most strongly expressed at the tip of the invaginating epithelium (Fig. 2A), at the cap stage (E14.5), it is strongly expressed in the enamel knot (Fig. 2B). Expression of *Wnt10a* then shifts from the epithelium to the dental mesenchyme at E15.5 (Raju et al., 2023; Suomalainen and Thesleff, 2010; Yamashiro et al., 2007) where it contributes to or initiates odontoblast differentiation, possibly through the up-regulation of *dentin sialophosphoprotein* (*Dspp*) expression (Yamashiro et al., 2007). By postnatal day 0 (P0), *Wnt10a* expression is observed in both terminally differentiating and secreting odontoblasts lining dentin of molars and incisors and in fully differentiated ameloblasts (ectoderm-derived epithelial cells responsible for orchestrating the formation and mineralization of dental enamel (Bei, 2009)) at the developing cusp tip of both molars and incisors (Dassule and McMahon, 1998; Raju et al., 2023; Yamashiro et al., 2007). This indicates that W*nt10a* potentially functions during dentin and root development and crown patterning (Dassule and McMahon, 1998; Yang et al., 2015). At P7 and 14, after the dentin and enamel has been mineralized, *Wnt10a* was expressed in odontoblasts (derived from the neural crest-derived mesenchymal cells) and in ameloblasts and odontoblasts towards the proximal end of incisors, near the cervical loop (Raju et al., 2023).

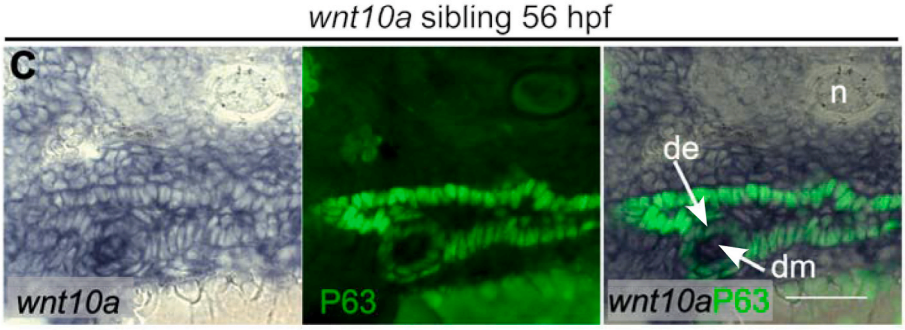
Also, during zebrafish embryogenesis, *wnt10a* is expressed at critical time points for tooth development (Yuan et al., 2017). Strong *wnt10a* expression can be found in the dental mesenchyme and weaker *wnt10a* expression in the surrounding p63-positive dental epithelium at 56 hours post fertilization (hpf) (Fig. 2C) (Benard et al., 2023). Antisense morpholino oligonucleotide-mediated knockdown of *wnt10a* (Yuan et al., 2017) as well as genetic loss of *wnt10a* (Benard et al., 2023) resulted in impaired normal tooth development at 5 days post fertilization (dpf), while as adults, *wnt10a* mutants lack teeth completely (Benard et al., 2023).

### 3.2. *Epithelial and mesenchymal Wnt10a expression during hair follicle development*

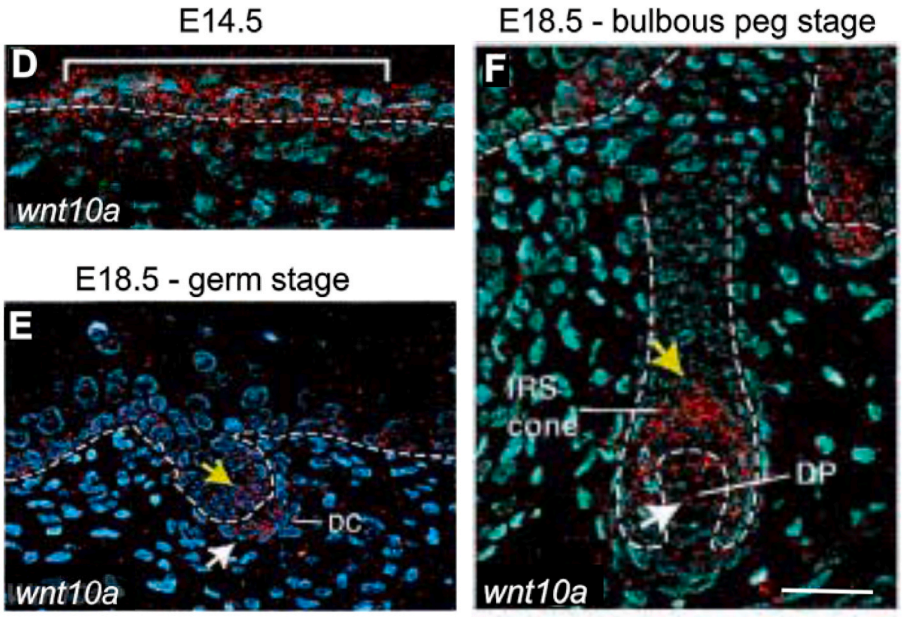
There is substantial evidence that WNT signaling is important in skin morphogenesis and homeostasis (Maretto et al., 2003; Merrill et al., 2001). Embryonic hair follicle induction and formation are regulated by mesenchymal-epithelial interactions between specialized dermal (mesenchymal) cells and epidermal (epithelial) stem cells that switch to a hair fate (Sennett and Rendl, 2012). Similarly, during postnatal hair growth, communication between mesenchymal dermal papilla cells and surrounding epithelial matrix cells coordinates hair shaft production (Sennett and Rendl, 2012). *Wnt10a* is highly expressed in epidermal cells (epithelia) of the developing mouse skin (Wang and Shackleford, 1996), in particular in the placodes of the embryonic hair follicles (HF) anlagen (Fig. 2D–F), where it is even further up-regulated compared to interfollicular epidermis during the placode stage (Reddy et al., 2001). Subsequently, during germ and peg stages, epithelial *Wnt10a* expression becomes restricted to follicular cells immediately adjacent to the dermal




Dassule and MacMahon 1998




Benard et al., 2023




Reddy et al., 2001

(caption on next page)

**Fig. 2.** Expression patterns of mouse and zebrafish *Wnt10a*.
Expression pattern of *Wnt10a* at bud and cap stages of tooth development in mice. Frontal sections through E13.5 and E14.5 M. **A.** *Wnt10a* is expressed at the tip of the epithelial bud. **B.** *Wnt10a* is expressed in the enamel knot. e, epithelium; ek, enamel knot; m, mesenchyme; Scale bars 0.1 mm. **A and B.** Reproduced/adapted (Dassule and McMahon, 1998) with permission from Elsevier. **C.** Expression pattern of zebrafish *wnt10a* at 56 hpf in the developing tooth. Transverse cryosection of 56 hpf wild-type zebrafish embryo after *wnt10a in situ* hybridization and p63 immunostaining, revealing strong *wnt10a* expression in the dental mesenchyme (dm; white arrow) and weak *wnt10a* expression in the surrounding p63-positive dental epithelium (de; white arrow). de, dental epithelium; dm, dental mesenchyme; n, notochord; Scale bar 20 μm. Reproduced/adapted (Benard et al., 2023) with permission from Wiley Periodicals LLC on behalf of American Association for Anatomy. **D-F.** Expression of *Wnt10a* during mouse hair follicle morphogenesis. *Wnt10a in situ* hybridization at E14.5 (**D**) and E18.5 (**E and F**). The dermal–epithelial junction is indicated by a dashed white line in each panel. Hair follicle placode in panel **D** is indicated by white brackets. Hybridization appears as red grains and nuclei are counterstained with Hoechst dye and appear blue. **D.** The expression of *Wnt10a* is slightly upregulated in the placode compared with adjacent epidermis. **E.** At germ stage, *Wnt10a* is expressed in follicular epithelial cells immediately adjacent to the dermal condensate (yellow arrows) and in the dermal condensate itself (white arrows). **F.** At the bulbous peg stage, *Wnt10a* expression decreases in the dermal papilla (white arrows) and concentrates in inner root sheath precursors (yellow arrows). The photographs in panels **D-F** were taken at the same magnification. A scale bar representing 20 μm is shown in panel **F**. DC, dermal condensate; DP, dermal papilla; IRS, inner root sheath. **D-F.** Reproduced/adapted (Reddy et al., 2001) with permission from Elsevier.

condensate (consisting of mesenchymal cells), and will be initiated in the dermal condensate itself. Once the dermal papilla forms, *Wnt10a* expression decreases in the dermal component of the follicle and concentrates in inner root sheath precursor cells (Reddy et al., 2001). In adult mice it, *Wnt10a* is expressed in the interfollicular epidermis, as well as in HF epithelial cells at the beginning of a new cycle of hair growth (Choi et al., 2013; Cui et al., 2014; Liu et al., 2007; Reddy et al., 2001). Also for human, *WNT10A* has been reported to be expressed in anagen and, to a lower level, in (early) catagen hair follicles (Hochfeld et al., 2021), although it is not clear whether it is specifically expressed in the hair follicle epithelium and/or the mesenchyme.

### 3.3. Epithelial expression of Wnt10a in specialized skin regions: palmoplantar epidermis, sweat glands and taste buds

Plantar skin is the specialized hairless skin region of human palms, soles and ventral wrist, and the mouse footpad. It is generally believed that positional skin identity is regulated by epithelial (keratinocytes) and mesenchymal (fibroblasts) interactions (Driskell et al., 2013). *Keratin 9* (*KRT9*) is exclusively expressed in suprabasal keratinocytes of palmoplantar epidermis where it provides structural support for palmoplantar skin (Kim et al., 2016). In mouse, *Wnt10a* was found to be expressed in footpad epidermis skin at similar levels to those in haired skin epidermis (Xu et al., 2017). Deletion of *WNT10A* resulted in reduction of *KRT9* mRNA and protein levels in mouse footpad epidermis (Xu et al., 2017). In humans, decreased WNT/β-catenin signaling caused by the genetic loss of WNT10A activity often results in hyperkeratosis of the palms and soles (Adaimy et al., 2007; Petrof et al., 2011).

Mouse *Wnt10a* is also localized to sweat gland myoepithelial cells, but was not detectable in sweat gland mesenchyme (Xu et al., 2017). Interestingly, embryonic development of sweat gland germs is not affected by the genetic loss of *Wnt10a*. At later stages, however, the sweat gland ducts fail to extend, most likely due to a decrease in sweat duct basal cell proliferation (Xu et al., 2017). Human *WNT10A* variants sometimes display either palmoplantar hypohidrosis or hyperhidrosis, most likely depending on variable compensatory mechanisms (Xu et al., 2017).

Mouse *Wnt10a* expression was also found in the filiform and fungiform papillae of the tongue (Xu et al., 2017). The filiform papillae predominantly have a keratinized stratified squamous epithelium and are the only papillae without taste buds while the fungiform papillae contain taste buds and are raised lingual structures with a densely vascularized core that is protected by a stratified squamous non-keratinized epithelium (Kobayashi et al., 1994). *Wnt10a* deletion did not grossly affect embryonic development of filiform or fungiform papillae, however, it did result in progressively abnormal filiform and fungiform papilla structures later on, causing a flattened tongue surface (Xu et al., 2017), resembling the smooth tongue with marked reduction of fungiform and filiform papillae found in individuals with *WNT10A* variants associated with OODD (Adaimy et al., 2007).

### 3.4. Mesenchymal and epithelial expression of Wnt10a in regenerating skin

Only in later stages of life, non-dental anomalies such as palmoplantar keratoderma, thinning hair, sweat gland abnormalities, and a smooth tongue surface usually become apparent in some human individuals with *WNT10A* mutations (Granger et al., 2013; Tziotzios et al., 2014), suggesting possible roles for *WNT10A* in epithelial regeneration and self-renewal, rather than initial epidermal development (Liu et al., 2013; Xu et al., 2017). This notion is supported by findings in both mouse and zebrafish that *Wnt10a* is essential for proper wound healing and fin regeneration (see Section 4). The epidermis greatly contributes to post-trauma healing by engaging in re-epithelialization and activating epithelial-mesenchymal transition (EMT). In mouse, *Wnt10a* is highly upregulated at 14 and 21 days post wounding in all layers of the neo-epidermis, as well as in the dermal compartment (a connective tissue layer of mesenchymal origin), possibly contributing to maturation of the extracellular matrix during the early phases of tissue remodeling and fibrosis (Bukowska et al., 2021). Indeed, it has been shown to be essential for proper wound repair by regulating collagen expression/-synthesis (Wang et al., 2018). *wnt10a* is also upregulated during fin regeneration in zebrafish. In regenerating embryonic tail fins, it is expressed in the cells neighboring the “notochord bead”, a cluster of former notochordal cells that forms upon fin amputation and that organizes the regeneration process (Romero et al., 2018), while in regenerating adult tail fins it is expressed at the distal tip of the blastema (Poss et al., 2000; Stoick-Cooper et al., 2007; Wehner et al., 2014). The blastema is a cluster of undifferentiated and proliferating mesenchymal cells, thereby accounting for tail re-growth, that is covered by a wound epidermis above the amputation plane. Some of these blastema mesenchymal cells are obtained by a de-differentiation of osteoblasts, which later re-differentiate to osteoblasts again, accounting for the re-growth of the bony elements of the regenerating fin. *wnt10a* was found to be particularly highly expressed in cells of distal and lateral regions of the blastema adjacent to such de- or re-differentiating osteoblasts (Stewart et al., 2014). In developing zebrafish, we failed to detect *wnt10a* expression in regular skin except for a specific subset of dermal fibroblasts located in the developing median fin folds, which signal to distal-most epidermal cells of the folds (Benard et al., 2023) to control proper fold morphogenesis. Human *WNT10A* expression was specifically observed in keloid dermal myofibroblasts of skin scars, characterized by co-expression of α-smooth muscle actin (α-SMA), as well as in stromal fibroblasts of skin tumors, but not in normal skin dermal fibrocytes (Yasuniwa et al., 2010), pointing to a possible role of WNT10A in fibrosis, stromagenesis and tumor progression (Beacham and Cukierman, 2005) (see Section 5).

### 3.5. Wnt10a expression in tissues of the central nervous system

A comprehensive assessment of *WNT10A* expression in the developing central nervous system is not yet delineated. *WNT10A* expression

is detected in the basal ganglia, cerebral cortex, hippocampal formation, thalamus and to lesser levels in the amygdala, hypothalamus, midbrain, pons, cerebellum, medulla oblongata, spinal cord, white matter, and choroid plexus (as derived from a consensus dataset combining transcriptomic data from The Human Protein Atlas (HPA, version 23.0) and The Genotype-Tissue Expression (GTEx) project). In the mouse central nervous system, *Wnt10a* is expressed in the pituitary gland, basal ganglia, cerebral cortex, hippocampal formation, hypothalamus, amygdala, midbrain, and spinal cord (Mammalian Organogenesis Cell Atlas, https://oncoscape.v3.sttrcancer.org/atlas.gs.washington.edu.mouse.rna/genes (Cao et al., 2019). *Wnt10a*$^{-/-}$ mice exhibit significantly decreased protein expressions of β-catenin, brain-derived neurotrophic factor, and doublecortin, accompanied by increased numbers of activated microglia (innate immune cells of the brain), microglia-associated neuroinflammation, amyloid-β accumulation and synaptic dysfunction. These morphological alterations related to impaired special memory and anxiety-like behavior (Zhang et al., 2022b). *wnt10a* is also found to be expressed in the central nervous system of developing zebrafish (Kelly et al., 1993). In adult zebrafish, *wnt10a* has been reported to be expressed in the retina. However expression levels decrease upon optic nerve injury. For axon growth to proceed in lower vertebrates, it is thought that small GTPases, such as CDC42 and Rac1, need to be activated, whereas RhoA must be inactivated. Accordingly, the decreased expression of *wnt10a* after optic nerve injury was associated with a reduction in nuclear β-catenin levels, which in turn caused a drop in RhoA activity, thereby promoting optic nerve regeneration (Matsukawa et al., 2018).

### 3.6. Epithelial Wnt10a expression in urogenital sinus and urothelium

The urogenital sinus is an endoderm-derived embryonic structure giving rise to the epithelium of the urinary bladder, all of the female urethra, and most of the male urethra (Thomas, 2020). Mouse *Wnt10a* mRNA is selectively expressed in a subset of basal epithelial cells within the female and male urogenital sinus, including prostatic ductal bud epithelium in males (Mehta et al., 2013). Also in human, *WNT10A* is expressed in the native urothelium (a protective barrier of specialized stratified epithelium that lines the inside of the urinary bladder (Jafari and Rohn, 2022)) and in the regenerating urothelium during the regenerative program following bladder augmentation (Sharma et al., 2013).

### 3.7. Epithelial Wnt10a expression in the liver

Hepatocytes, along with biliary epithelial cells, are derived from the embryonic endoderm and are of epithelial character, while the stromal cells of the liver are of mesenchymal character and are derived from the embryonic mesoderm. Mouse *Wnt10a* has been shown to be expressed in the developing liver during embryogenesis (Wang and Shackleford, 1996), as well as postnatal stages (Fan et al., 2017). However, to our knowledge, no studies discriminating between the different cell types of the developing liver have been reported. In hepatocyte progenitor cell cultures, *Wnt10a* was shown to inhibit cell proliferation and promote hepatic differentiation (Fan et al., 2017), somehow contrasting its reported oncogenic effects identified in our contexts (see Section 5.3). Furthermore, *Wnt10a* was found to be expressed in cholangiocytes (the epithelial cells lining the bile ducts) and in a few hepatocytes in the periportal area of adult mice after injury induced by feeding with the biliary toxin, 3,5-diethoxycarbonyl-1,4-dihydrocollidine (Okabe et al., 2016), and was shown to regulate, in β-catenin-dependent and -independent manners, hepatobiliary repair by inducing the trans-differentiation of hepatocytes to bile duct cells and the proliferation of such small cholangiocytes, respectively (Okabe et al., 2016; Russell and Monga, 2018).

### 3.8. Expression of WNT10A in epithelial esophageal cells

Mouse *WNT10A* is expressed in epithelial cells of the developing esophagus, a derivative of the embryonic endoderm, peaking at embryonic day 18.5, but diminishing substantially postnatally (Long et al., 2015). Yet, in adults, *WNT10A* expression is re-activated upon esophageal carcinogenesis, as observed in both a mouse model of esophageal epithelial dysplasia as well as in human esophageal squamous cell carcinoma, suggesting that *WNT10A* may serve as an oncofetal factor on epithelial cells of the esophagus (Long et al., 2015). In line with this, *WNT10A* overexpression *in vitro* promotes an invasive and self-renewing phenotype in esophageal squamous cell carcinoma cells (Long et al., 2015).

### 3.9. Wnt10a expression in kidney fibroblasts and renal epithelial cells

Development of kidney tissue, which is of mesodermal origin, also involves striking and well-characterized epithelial-mesenchymal interactions (Little and McMahon, 2012). As in the dermis, *WNT10A* is expressed in (mesenchymal) kidney fibroblasts co-expressing α-smooth muscle actin (α-SMA) (Yasuniwa et al., 2010; Kuma et al., 2014), as characteristic for myofibroblasts involved in dermal fibrosis and scarring upon cutaneous wound healing (Hinz, 2016). Strikingly, *Wnt10A* overexpression in COS1 cells, a monkey kidney fibroblast cell line, increased the expression levels of fibronectin and other markers of early-stage fibrosis, while increased *WNT10A* expression levels in human kidney biopsies correlated with kidney dysfunction in patients with acute interstitial nephritis (Kuma et al., 2014). Similarly, in a mouse model studying acute injury induced by either ischemia or nephrotoxins, renal expression of multiple Wnts, including *Wnt10a*, and β-catenin were upregulated, and the magnitude of their induction was tightly associated with the severity of ischemia-reperfusion injury (Xiao et al., 2016). Together, this points to a profibrotic effect of WNT10A in kidney fibroblasts similar to that during cutaneous wound healing.

*WNT10A* expression was also identified in proximal tubule epithelial cell of human kidneys, and was found to be - in contrast to all other canonical *WNT* genes - significantly increased in renal cell carcinoma (RCC) tissues (Hsu et al., 2012). Forced *WNT10A* expression in renal epithelial cell line models induced RCC cell proliferation and aggressiveness, including higher chemoresistance, cell migration, invasiveness, and cell transformation, due to the activation of β-catenin-dependent signaling, whereas *WNT10A* siRNA knockdown decreased these traits (Hsu et al., 2012), indicating that *WNT10A* plays an oncogenic role in renal cell carcinoma (Hsu et al., 2012; Niida et al., 2004).

### 3.10. Mesenchymal expression of WNT10A and its role in adipocytes and osteoblasts

Both adipocytes and osteoblasts derive from the embryonic mesoderm or, later in life, from mesenchymal stem cells (Gregoire et al., 1998; Rangwala and Lazar, 2000). Research has established Wnt/β-catenin signaling as a key determinant between adipogenic and osteoblastogenic fates of the shared progenitor cells (Cawthorn et al., 2012; Ross et al., 2000). *WNT10A* is found to be expressed within white adipose tissue (WAT), however its expression is decreased in adipocyte relative to stromovascular (preadipocyte-containing) fractions of WAT (Cawthorn et al., 2012). *In vitro* experiments show that *WNT10A* is capable of inhibiting adipogenesis by suppressing the expression of adipocyte genes, while strongly stimulating osteoblastogenesis in a β-catenin dependent manner (Cawthorn et al., 2012). Later it was discovered that the switch from adipogenesis to osteoblastogenesis induced by pharmacological inhibition of DNA methylation is exclusively due to a demethylation of the *Wnt10a* locus and the corresponding upregulation of its expression (Chen et al., 2016). Consistent with this bone-promoting function in mouse, human individuals with pathogenic

variants of *WNT10A* associated with tooth agenesis (discussed in Section 5) sometimes present decreased jaw and alveolar bone growth (Vink et al., 2014). A recent study implied that the reduction in bone mineral density observed in a proband with *WNT10A* variant could be caused by a significant decrease in proliferation and osteogenic differentiation capacities of alveolar bone mesenchymal stem cells (Lin et al., 2024). In zebrafish, knockdown of *wnt10a* in embryos results in some cartilage abnormalities (Yuan et al., 2017) and adult *wnt10a* mutant zebrafish have underdeveloped ceratobranchial 5 bones (Benard et al., 2023).

Other organs and tissues with *WNT10A* expression, such as the cornea, the lung, the colon, and the ovaries will be referred to, together with the corresponding phenotypes, in Sections 4 and 5.

## 4. WNT10A mutants and phenotypes in animal models

Studies of mouse and zebrafish mutants have been helpful for delineating the diverse roles of WNT10A, as summarized in Tables 1 and 2 and below.

### 4.1. Phenotypes of Wnt10a knock-out mice

Although there are multiple *Wnt10a* mutants available (see Table 1), we will, in chronological order, focus on the three most deeply characterized alleles. The first represents a global and full *Wnt10a* knockout (Wnt10atm1.1(KOMP)Vlcg) generated via gene-targeted embryonic stem cells with a deletion of 11,515 bp comprising the entire *Wnt10a* coding region (Yang et al., 2015). Since human *WNT10A* mutations cause tooth agenesis, it was unexpected that the *Wnt10a* null mice had a complete dentition. This is most likely due to partial functional redundancy with other *Wnt* genes, as evidenced by more recent work on *Wnt10a/b* double mutants generated with CRISPR/Cas9-technology, which display a loss of at least some (incisors and third molars of both jaws), but not all teeth (Yoshinaga et al., 2023). In contrast, *Wnt10a* single mutants have supernumerary mandibular fourth molars, and smaller molars with abnormal cusp patterning and root taurodontism, while incisors show distinctive apical–lingual wedge-shaped defects (Yang et al., 2015).

The second represents a conditional floxed allele with *loxP* sites flanking exons 3 and 4 of the *Wnt10a* gene, allowing the deletion of a large part of the C-terminal domain of the protein that contains 20 of the 24 conserved, functionally important cysteine residues. *Wnt10a*$^{fl/fl}$ mice were crossed with *CMV-Cre* mice to generate global null mutants. In addition, *Wnt10a*$^{fl/fl}$ mice were crossed to *Krt5-rtTA tetO-Cre* or *Krt14-Cre* mice to obtain temporally inducible *Krt5-rtTA tetO-Cre Wnt10a*$^{fl/fl}$ or epidermis-specific *Krt14-Cre Wnt10a*$^{fl/fl}$ mutants. Similar to the first allele, these mutants developed loosely anchored ectopic fourth molars (Fig. 3A), while the maxillary and mandibular molar teeth had flattened cusps, reduced size and defective root bifurcation and extension (Fig. 3B). By 1 year of age, molar teeth were frequently exfoliated and lost (Fig. 3B). Further examinations revealed that *Wnt10a* not only plays a role in activation of the proliferative potential of mesenchymal odontogenic progenitors during early tooth development (in line with formerly published data showing that siRNA-mediated down-regulation of *Wnt10a* in dental mesenchymal calls impairs odontogenesis and cell proliferation (Liu et al., 2013)), but also in the induction and maintenance of primary and secondary enamel nodes (Xu et al., 2017). Of note, *Wnt10a* deletion does not grossly affect embryonic development of the primary and secondary hair follicle (HF) placodes (Xu et al., 2017).

The situation changes during later life, since both the global and tissue-specific *Wnt10a* mutants display progressively sparse hair with age (Fig. 3C), in line with data from genome-wide associated studies that indicate association of a *WNT10A* variant with androgenetic alopecia in men (Cesarato et al., 2023; Heilmann-Heimbach et al., 2016; Heilmann et al., 2013; Nuwaihyd et al., 2014), pointing to a role of *WNT10A* in stem-cell activation during the hair cycle (Hawkshaw et al., 2020). In addition, mutants display later defects in nail growth, consistent with onychodystrophy in humans (Xu et al., 2017), and, from postnatal day (P)7 onwards and despite their initially normal development, progressive defects in tongue papillae structure (Fig. 3D) and sweat gland ducts extension (Fig. 3E), in line with the palmoplantar hypohidrosis seen in some individuals with *WNT10A* mutations (Tziotzios et al., 2014; Xu et al., 2017; Zeng et al., 2016). In addition, as potential targets of Wnt10a signaling that are downregulated in mouse mutants and human patients and that could account for at least some of these later region-specific differentiation defects, hard keratin genes such as *KRT9* were identified (Xu et al., 2017). This is in line with former *in vitro* studies suggesting that Wnt/β-catenin signaling enhances *KRT9* expression (Kim et al., 2016; Rinn et al., 2008), and that palmoplantar skin defects of *KRT9* mouse mutants and humans with mutations in *KRT9* (Fu et al., 2014) overlap with those of the *WNT10A* counterparts (Xu et al., 2017).

The third allele, Wnt10atm1(KOMP)Vlcg, again represents a global and full *Wnt10a* knockout generated via gene-targeted embryonic stem cells with an even larger deletion of 12,663 bp removing the entire *Wnt10a* coding region. For these mice, more phenotypes in addition to the teeth, hair, nails, and skin symptoms of the aforementioned other alleles were described (which of course does not necessarily mean that these "new" phenotypic traits are not displayed by the other alleles as well). Adult Wnt10atm1(KOMP)Vlcg$^{/tm1(KOMP)Vlcg}$ mice are smaller in size and display spine curvature and many hyperlucent areas in the bone resulting from reduced osteogenic activity and bone mineralization, as well as a reduction of white fat mass (driven by a conversion of white to beige adipocytes) and female infertility (no or markedly fewer ovarian follicles, thinner endometria, lower serum estrogen levels and higher testosterone and progesterone levels) (Wang et al., 2018; Zhang et al., 2022a). In addition, they display numerous neuronal defects, such as decreased neurogenesis and impaired synaptic function as well as hippocampal neuroinflammation, eventually leading to hippocampal neurodegeneration and memory deficit (Zhang et al., 2022b).

Of note, this allele was also used to investigate the role of Wnt10a during skin regeneration and malignancy. Interestingly, adult mutants displayed reduced scarring upon cutaneous wound healing, associated with reduced collagen expression and production/stromagenesis especially by fibroblasts/myofibroblasts (Wang et al., 2018; Zhang et al., 2022a). Similarly, upon xenografting of malignant tumor cells, *Wnt10a* mutants displayed reduced malignant skin tumor growth, associated with less collagen expression and thereby less fibrosis and fewer microvessels in the *Wnt10a*-deficient tumor microenvironment (Kumagai et al., 2019). This is in line with previous data demonstrating that *WNT10A* overexpression significantly promoted the proliferation of microvascular endothelial cells and fibroblasts/myofibroblasts in nude mouse xenograft models with injection of HeLa cells (Yasuniwa et al., 2010). Together, this indicates that in addition to the exhaustively studied oncogenic effects of canonical WNT signaling in cancer cells themselves (Jung and Park, 2020; Werner et al., 2023), WNT10a can promote tumor progression via fibroblast-dependent stromagenesis and conditioning of the extracellular tumor microenvironment, thus applying mechanisms similar to those during regular development and tissue repair/scarring/fibrosis in non-transformed conditions.

### 4.2. Phenotypes of wnt10a zebrafish mutant and morphants

There is one published genetic zebrafish *wnt10a* null mutant described to date, the *wnt10a*$^{t30922}$ allele, while other loss-of-function studies were performed with morpholino antisense oligonucleotide knock-down technology (see Table 2). The genetic mutant was isolated during a phenotype-based forward genetics screen after mutagenesis with ethylnitrosourea (ENU) and has a point mutation in the splice acceptor site in front of exon 4 of *wnt10a*, leading to false transcript splicing and, ultimately, to the loss of the C-terminal 165 amino acid residues of the Wnt10a protein including large parts of the conserved Wnt domain. This mutant has impaired embryonic tooth development,

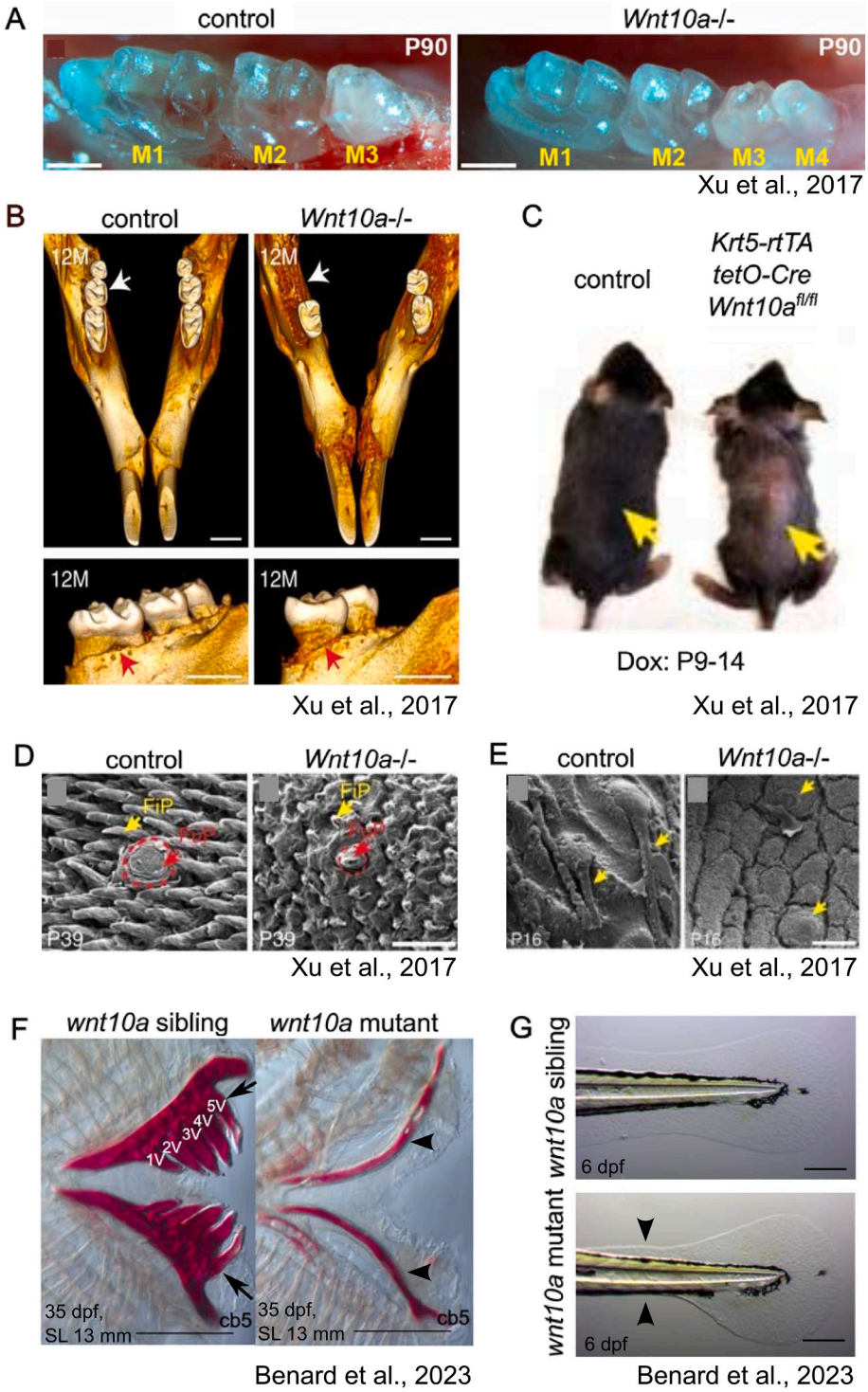



**Fig. 3.** Mutant phenotypes in *Wnt10a* mutant mice and zebrafish.
**A.** *Wnt10a*−/− mice have smaller molar teeth with blunted cusp formation, and presence of an ectopic molar M4 compared with control mandible at P90 (molar numbers (M#) written in yellow). **B.** Micro-CT analysis of mandibles from control and *Wnt10a*$^{-/-}$ mice at 12 months old. Maxillary and mandibular molar teeth had flattened cusps, reduced size and defective root bifurcation and extension compared with littermate controls. *Wnt10a*$^{-/-}$ mice had frequently missing molar teeth. **C.** Accelerated catagen following epithelial *Wnt10a* deletion from P9 (embryonic anagen) (photographed at P14 after hair clipping) in *Krt5-rtTA tetO-Cre Wnt10a*$^{fl/fl}$ mice. **D.** Scanning electron microscope (SEM) shows fungiform (FuP, written in red letters) and filiform (FiP, written in yellow letters) papilla defects in adult global *Wnt10a* mutants. **E.** SEM reveals failure of postnatal sweat duct development in P16 *Wnt10a*$^{-/-}$ mutant footpad. **A-E.** Reproduced/adapted (Xu et al., 2017) with permission from Springer Nature Limited. **F.** At 35 dpf (SL 13 mm), dissected ceratobranchial 5 (cb5) of zebrafish controls have fully formed alizarin red-stained mineralized teeth (only 1V, 2V, 3V, 4V, and 5V are visible in this view) while the *wnt10a* mutants have no teeth and an underdeveloped cb5. Arrows indicate regular teeth, arrowheads compromised or absent teeth. **G.** At 6 dpf, the zebrafish embryo median fin fold (MFF) of the sibling has extended while most of the mutant MFF has collapsed (arrowheads). **F-G.** Reproduced/adapted (Benard et al., 2023) with permission from Wiley Periodicals LLC on behalf of American Association for Anatomy. Scale bar, 50 μm (**E**), 100 μm (**D**, **F**), 200 μm (**G**), 500 μm (**A**) and 1 mm (**B**).

lack of all adult teeth, and an underdeveloped adult ceratobranchial 5 arch (Fig. 3F) (Benard et al., 2023). Knockdown of *wnt10a* in zebrafish embryos also impaired normal tooth development, arrested tooth development at 5 dpf and decreased the expression levels of additional tooth development genes like *msx1*, *dlx2b*, *eda*, and *axin2* at 2 dpf (Yuan et al., 2017). Interestingly, upon *wnt10a* overexpression, adult zebrafish have increased tooth replacement rates (Square et al., 2023) and 2 dpf zebrafish embryos have increased expression levels of *msx1*, *dlx2b*, *eda* and *axin2* (Yuan et al., 2017), confirming its function during tooth development. It seems that tooth regeneration is modulated in a similar fashion as hair (both epithelial appendages) with respect to the known opposing roles of the Wnt and BMP pathways. Both developmental processes are under elaborate control of multiple families of signaling molecules, including bone morphogenetic proteins (BMPs), fibroblast growth factors (FGFs), Shh and Wnt proteins (Tummers and Thesleff, 2009).

In addition to tooth development, the *wnt10a*$^{t30922}$ zebrafish mutant also demonstrates that *wnt10a* is required for maintaining embryonic median fin fold structure. Mutant embryos display a progressive shrinkage of actinotrichia, thick collagenous fibers of the

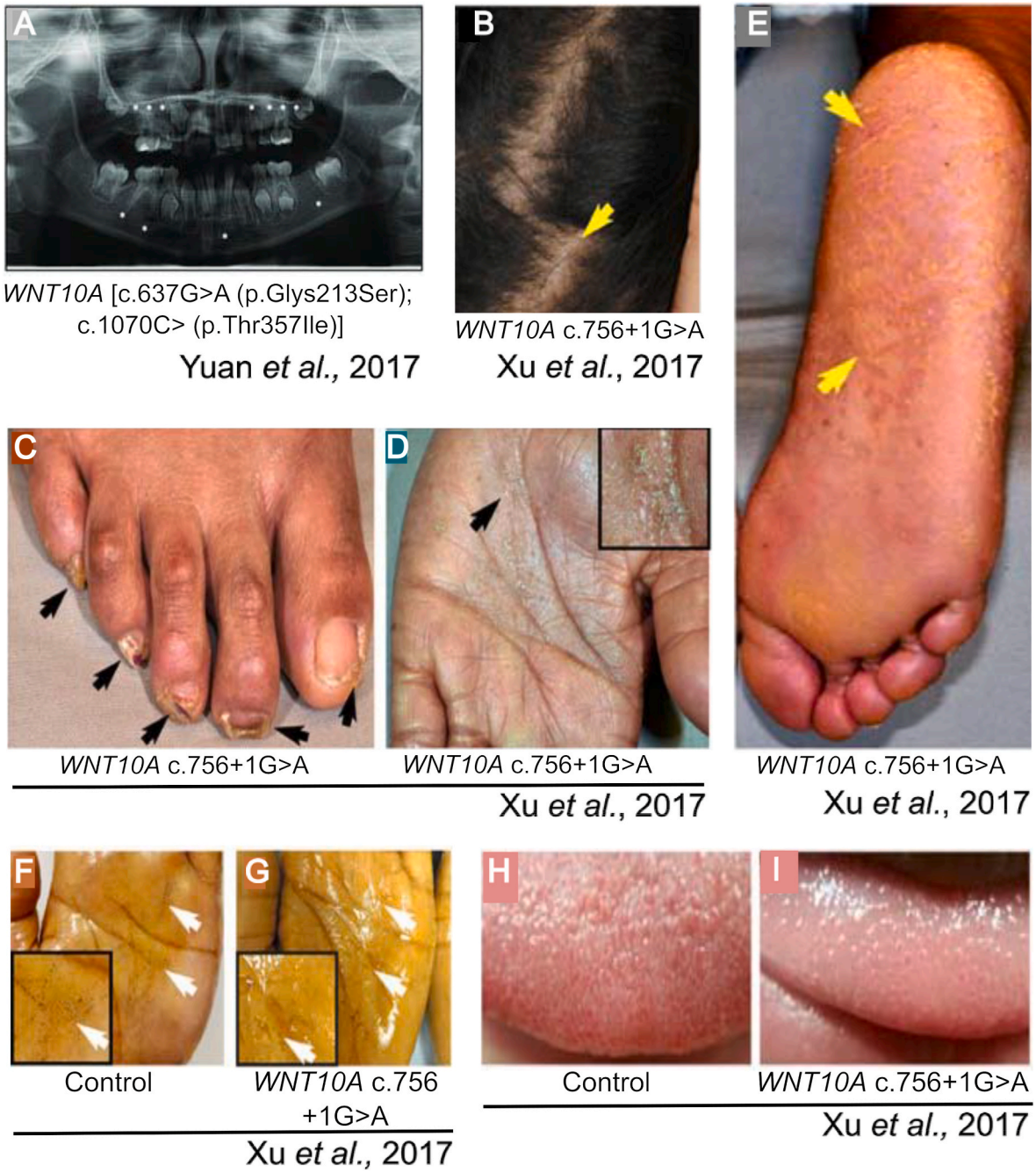



**Fig. 4.** Clinical features associated with human *WNT10A* mutation.
**A**. Panoramic radiograph of proband with oligodontia. Radiograph shows a mixed dentition stage with the presence of deciduous teeth and some permanent teeth erupted. Stars denote absence of tooth buds for teeth # 3, 4, 5, 11, 12, 13, 14, 19, 24, 29, and 30. **B.** Thinning hair. **C.** Nail dystrophy. **D and E.** Fissures and scaling on palms and soles. **F and G.** Starch-iodine sweat testing. Note brown grains on control palm indicating sweat production, and decreased sweating in patient (arrows). Insets show higher magnification of areas indicated by the lower arrow in each photograph. **H and I.** Smooth tongue surface **A.** Reproduced/adapted (Yuan et al., 2017). **B-I.** Reproduced/adapted (Xu et al., 2017) with permission from Springer Nature Limited.

interepithelial/dermal space of the embryonic fin folds (Fig. 3G). In addition, they display compromised formation of adult body fins during metamorphosis, a timepoint when lepidotrichia, the dermal bone components of the fin rays, start to form (Benard et al., 2023). The embryonic median fin fold defects point to a formerly unknown function of Wnt10a in determining distal-most cell identities in epithelial folds to assure the formation of specific subcellular structures ("fibripositors", initially described in mammalian tendons (Canty et al., 2006)) controlling proper anchorage, linear growth and/or stability of higher-order collagenous structures. The exact targets of Wnt10a signaling mediating this function, however, and its relevance in mammals, for instance for proper tendon functionality and healing, which does involve WNT10A up-regulation (Schulze-Tanzil et al., 2022), remain to be identified. One crucial zebrafish Wnt10a target seems to be the collagen gene *col1a1*, which normally is strongly expressed in distal-most epithelial cells of the median fin fold, but which is expressed there at much lower levels in *wnt10a* mutants (Benard et al., 2023), consistent with the reported positive effect of Wnt10a on *Col1a1a* expression in human corneal epithelial cells (Foster et al., 2021). However, additional targets must be involved to account for the complex processes of actinotrichia and dermal extracellular matrix morphogenesis.

## 5. Human *WNT10A* disorders and diseases

As mentioned above, *WNT10A* is vital for embryonic and postnatal development as well as tissue homeostasis and repair and regeneration not only in various animal models, but also in human beings. The most striking features of individuals with *WNT10A* variants (summarized in recently published *WNT10A* reviews (Doolan et al., 2021; Williams and Letra, 2018)), are isolated/non-syndromic tooth agenesis (affecting solely dentition) or syndromic tooth agenesis (affecting not only dentition, but also other organs or tissues) (Yu et al., 2019). Both disorders present variable phenotypes and genotypes, including homozygous, compound heterozygous and heterozygous mutations (Bergendal et al., 2016; Dinckan et al., 2018; Kantaputra and Sripathomsawat, 2011; Mostowska et al., 2012; Nagy et al., 2010; Nawaz et al., 2009; van den Boogaard et al., 2012) most likely because these ectodermal structures specifically use WNT10A as a critical (and possibly sole canonical WNT) ligand controlling cell proliferation and/or differentiation (Xu et al., 2017). These disorders are described in more detail below.

### 5.1. Non-syndromic tooth agenesis (NSTA)

NSTA, also known as selective tooth agenesis or isolated tooth agenesis (Fig. 4A), is divided into three types: hypodontia, defined as agenesis of less than 6 teeth, oligodontia, defined as agenesis of 6 or more permanent teeth, and anodontia, defined as complete lack of all primary and permanent teeth (Polder et al., 2004; Yin and Bian, 2015). The numbers used for the definition hypodontia and agenesis do not include absence of third molars (wisdom teeth). Although the genetic etiology of tooth agenesis is heterogenous (non-syndromic tooth agenesis has been associated with more than a dozen genes) (Du et al., 2018), population-based studies have shown that 28%–62% of tooth agenesis patients have *WNT10A* variants (Arzoo et al., 2014; Mostowska et al., 2012; van den Boogaard et al., 2012). Heterogenous, homozygous, and compound heterozygous forms of *WNT10A* mutations were associated with non-syndromic tooth agenesis with phenotypic heterogeneity (Kanchanasevee et al., 2020; Yuan et al., 2017).

### 5.2. Syndromic tooth agenesis

Syndromic tooth agenesis is most often encountered as part of an ectodermal dysplasia (ED) phenotype, such as Tooth agenesis, selective, 4 (STHAG4; Online Mendelian Inheritance in Man (OMIM) #150400), Odonto-oncho-dermal dysplasia (OODD, OMIM #257980), and Schöpf–Schulz–Passarge syndrome (SSPS; OMIM #224750).

In STHAG4, the upper lateral incisors are absent or peg-shaped. Some syndromic STHAG4 patients manifest mild features of ED, including sparse hair, sparse eyebrows, short eyelashes, abnormalities of the nails, sweating anomalies, and dry skin. STHAG4 inheritance is heterozygous, homozygous, compound heterozygous with missense or compound heterozygous with nonsense (Bohring et al., 2009; Dinckan et al., 2018; Kantaputra et al., 2014; Kantaputra and Sripathomsawat, 2011; Song et al., 2014; van den Boogaard et al., 2012). An overview of selected known and novel *WNT10A* variants identified in associated with STHAG4 are presented in (Du et al., 2018).

OODD is caused by homozygous or compound heterozygous mutation in the *WNT10A* gene and is a rare autosomal recessive ED characterized by oligodontia (Fig. 4A), dry and thinning hair (Fig. 4B), onychodysplasia (Fig. 4C), hyperkeratosis of the palms (Fig. 4D) and soles (Fig. 4E), hyper- and hypohidrosis (Fig. 4F and G) of the skin, smooth tongue with marked reduction of fungiform and filiform papillae (Fig. 4H and I), and atrophic patches on the face (Adaimy et al., 2007; Xu et al., 2017; Yu et al., 2020). Although many patients had previously been diagnosed with OODD, it was not until 2007 that mutations in *WNT10A* had been associated with the disease in homozygosity mapping studies, which was the first form of an ED syndrome to be shown to be caused by altered WNT signaling (Adaimy et al., 2007).

SPS is caused by homozygous mutations in *WNT10A* and is described as a rare ED, characterized by a constellation of multiple cysts of the eyelid margins, hypodontia (the absence of one to five teeth), hypotrichosis, palmoplantar hyperkeratosis, and onychodystrophy (nail dystrophy) (Mallaiah and Dickinson, 2001). Multiple eyelid apocrine hidrocystomas (benign cystic lesions) are the hallmark of this condition, although they usually appear in adulthood (Castori et al., 2008). The concomitant presence of eccrine syringofibroadenoma in most patients and of other adnexal skin tumors in some affected subjects indicates that SSPS is a genodermatosis with skin appendage neoplasms (Castori et al., 2008). Homozygosity for a proven nonsense mutation in *WNT10A* causing SSPS was first published in 2009 (Bohring et al., 2009). During this study, homozygous or compound heterozygous *WNT10A* mutations were also found in 8 patients with OODD but devoid of eyelid cysts.

Of all the identified *WNT10A* mutations in the above mentioned syndromes, there are two missense mutations leading to specific amino acid exchanges that are most frequently seen in each population studied: p.Cys107Ter (Reference SNP cluster ID (rs)121908119) and p.Phe228Ile (rs121908120) (Jonsson et al., 2018). Both mutations collectively account for ~ 20% of the total *WNT10A* pathology in these forms of ED, although neither have been reported in cases of hypohidrotic/anhidrotic ED (Doolan et al., 2021). Bioinformatic and functional characterization analysis of *WNT10A* variants in a dental cell model system has now shown that *WNT10A* variants deemed pathogenic for tooth agenesis likely affect protein folding and/or stabilization, leading to decreased WNT signaling and concomitant dysregulated expression of relevant genes (Zeng et al., 2021).

*WNT10A* ED manifests variably between the sexes and depends on patient age (Granger et al., 2013; Tziotzios et al., 2014). Similarly, strengths of developmental dental defects (including microdontia of primary teeth, defective root and molar cusp formation, and complete absence of secondary dentition) strongly vary between individual patients (Bohring et al., 2009; Mues et al., 2014), pointing to a strong impact of the genetic background on the penetrance of the *WNT10A* mutation.

This observation that (hypomorphic) loss-of-function mutations of *WNT10A* at least in SSPS can lead to neoplastic conditions, pointing to a tumor-suppressive role of WNT10A, is in striking contrast to other findings according to which multiple types of carcinoma are correlated, and most likely caused by WNT10A gain-of-function alterations, pointing to oncogenic effects (see Section 3 and below/Section 5.3). However, it is in line with contrasting *in vitro* data pointing to anti- or pro-proliferative effects of WNT10A (see for instance (Fan et al., 2017)), suggesting that effects of WNT10A function can differ fundamentally,

dependent on the particular tissues and molecular and cellular contexts.

### 5.3. Fibrosis and carcinogenesis correlated with increased WNT10A expression

In addition to the described pathologies caused by, or at least correlated with, genetic loss-of-function alteration in the WNT10A protein, human pathologies with no specific loss-of-function *WNT10A* mutation, but with correlating reductions in *WNT10A* expression levels, have been described. One example is Keratoconus, a progressive thinning and outwards-bulging of the cornea, a stratified (5–6 layers thick) non-keratinized squamous epithelium. Keratoconus patients display reductions in *WNT10A* expression that positively correlate with the Keratoconus severity (Foster et al., 2021).

The human syndromes and disorders described above all constitute WNT10A loss-of-function scenarios. Yet, there are multiple examples that gain of WNT10A function, whether genetically inherited or of epigenetic nature, can also be detrimental for human health. Most striking conditions already touched upon in the corresponding parts of Section 3 are fibrosis, which means excessive fibroblast (mesenchymal) activity leading to the uncontrolled replacement of parenchymal by connective tissue, and carcinogenesis, which means the transformation and uncontrolled proliferation of epithelial cells.

For example, increased *WNT10A* expression levels in human kidney fibroblasts are correlated with kidney fibrosis and dysfunction in human acute interstitial nephritis (Kuma et al., 2014). Similarly, higher *WNT10A* expression levels in lung fibroblasts obtained from biopsies of patients with idiopathic pulmonary fibrosis were found to be correlated with a poorer prognosis of the patients (Oda et al., 2016). Furthermore, increased *WNT10A* expression levels compared to normal skin were found in dermal (myo)fibroblasts of skin keloid scars and skin tumors, pointing to a possible role of WNT10A in fibroblasts to promote fibrosis per se as well as stromagenesis, supplying a microenvironment to promote keratinocyte (thus epithelial) overgrowth and malignancy (Yasuniwa et al., 2010). The latter is consistent with *Wnt10a* loss-of-function data obtained in mouse according to which genetic depletion of *Wnt10a* prevents melanoma growth by suppressing collagen expression (Kumagai et al., 2019). In addition, carcinogenesis has been reported to be linked to, and possibly caused by, *WNT10A* overexpression in epithelia-derived cancer cells themselves. For instance, *WNT10A* overexpression in kidney proximal tubule cells has been shown to be strongly correlated with renal cell carcinoma formation, while complementary cell culture studies indicate that this overexpression - and the resulting enhancement of autocrine signaling - is both sufficient and necessary for the oncogenic effects (Hsu et al., 2012). Similar correlations and oncogenic effects of elevated *WNT10* expression and nuclear β-catenin levels have been reported for epithelial ovarian cancer cells during ovarian carcinogenesis (Li et al., 2017) and for epithelial colorectal cancer cells during colorectal carcinogenesis (Li et al., 2019). Other reports implicate *WNT10A* upregulation with gastric carcinogenesis, with early and late stages of esophageal carcinogenesis, promoting epithelial cancer cell proliferation, motility, invasiveness and self-renewal (Kirikoshi et al., 2001a; Long et al., 2015), as well as with cholangiocarcinogenesis, the second most common hepatobiliary liver cancer (Boulter et al., 2015; Vaquero et al., 2017), although in these cases it has not been distinguished whether *WNT10A* is primarily up-regulated in the tumor cells themselves (which are of epithelial origin), or in cells of the tumor microenvironment, for instance cancer-associated fibroblasts.

These findings, together with the exclusive up-regulation of *WNT10A*, but no other canonical WNT genes in at least some of the investigated carcinomas (Hsu et al., 2012), and with the comparably rare reports on late-onset diseases correlated with reduced *WNT10A* expression (Foster et al., 2021), point to *WNT10A* gene products as potential targets for the treatment of multiple frequently occurring types of carcinogenesis.

## 6. Summary

This primer review summarizes current knowledge of *WNT10A* expression and function in different models and during different processes of development and regeneration, including and high-lighting its impact on extracellular matrix formation, maturation and remodeling that has been studied in more recent animal models; it describes how genetic variants in *WNT10A* underlie human disorders such as selective tooth agenesis, and ED syndromes OODD and SSPS, and how *WNT10A* overexpression might contribute to fibrosis and carcinogenesis, including its effects on conditioning the collagenous extracellular tumor microenvironment. Understanding *WNT10A* function, regulation, downstream signaling and its regenerative properties will help to improve treatment of patients with ED, STHAG4 and other linked disorders, including fibrotic and malignant conditions.

## CRediT authorship contribution statement

**Erica L. Benard:** Writing – review & editing, Writing – original draft, Conceptualization. **Matthias Hammerschmidt:** Writing – review & editing, Funding acquisition, Conceptualization.

## Funding

NIH/NIGMS R01 GM063904 to M.H.

DFG Research Project Grant No. 453407124 and FOR 2722 (Project number 384170921) to M.H.

## Conflict of interest

The authors declare no conflicts of interest.

## References

Adachi, J., Aoki, Y., Izumi, H., Nishiyama, T., Nakayama, A., Sana, M., Morimoto, K., Kaetsu, A., Shirozu, T., Osumi, E., Matsuoka, M., Hayakawa, E., Maeda, N., Machida, J., Nagao, T., Tokita, Y., 2023. Novel WNT10A variant in a Japanese case of nonsyndromic oligodontia. Hum Genome Var 10, 3.

Adaimy, L., Chouery, E., Megarbane, H., Mroueh, S., Delague, V., Nicolas, E., Belguith, H., de Mazancourt, P., Megarbane, A., 2007. Mutation in WNT10A is associated with an autosomal recessive ectodermal dysplasia: the odonto-onycho-dermal dysplasia. Am. J. Hum. Genet. 81, 821–828.

Akiyama, H., Lyons, J.P., Mori-Akiyama, Y., Yang, X., Zhang, R., Zhang, Z., Deng, J.M., Taketo, M.M., Nakamura, T., Behringer, R.R., McCrea, P.D., de Crombrugghe, B., 2004. Interactions between Sox9 and beta-catenin control chondrocyte differentiation. Genes Dev. 18, 1072–1087.

Arzoo, P.S., Klar, J., Bergendal, B., Norderyd, J., Dahl, N., 2014. WNT10A mutations account for (1/4) of population-based isolated oligodontia and show phenotypic correlations. Am. J. Med. Genet. 164A, 353–359.

Bazan, J.F., de Sauvage, F.J., 2009. Structural ties between cholesterol transport and morphogen signaling. Cell 138, 1055–1056.

Beacham, D.A., Cukierman, E., 2005. Stromagenesis: the changing face of fibroblastic microenvironments during tumor progression. Semin. Cancer Biol. 15, 329–341.

Beaty, T.H., Hetmanski, J.B., Fallin, M.D., Park, J.W., Sull, J.W., McIntosh, I., Liang, K.Y., Vanderkolk, C.A., Redett, R.J., Boyadjiev, S.A., Jabs, E.W., Chong, S.S., Cheah, F.S., Wu-Chou, Y.H., Chen, P.K., Chiu, Y.F., Yeow, V., Ng, I.S., Cheng, J., Huang, S., Ye, X., Wang, H., Ingersoll, R., Scott, A.F., 2006. Analysis of candidate genes on chromosome 2 in oral cleft case-parent trios from three populations. Hum. Genet. 120, 501–518.

Bei, M., 2009. Molecular genetics of ameloblast cell lineage. J. Exp. Zool. B Mol. Dev. Evol. 312B, 437–444.

Benard, E.L., Kucukaylak, I., Hatzold, J., Berendes, K.U.W., Carney, T.J., Beleggia, F., Hammerschmidt, M., 2023. wnt10a is required for zebrafish median fin fold maintenance and adult unpaired fin metamorphosis. Dev Dyn.

Bergendal, B., Norderyd, J., Zhou, X., Klar, J., Dahl, N., 2016. Abnormal primary and permanent dentitions with ectodermal symptoms predict WNT10A deficiency. BMC Med. Genet. 17, 88.

Bohring, A., Stamm, T., Spaich, C., Haase, C., Spree, K., Hehr, U., Hoffmann, M., Ledig, S., Sel, S., Wieacker, P., Ropke, A., 2009. WNT10A mutations are a frequent cause of a broad spectrum of ectodermal dysplasias with sex-biased manifestation pattern in heterozygotes. Am. J. Hum. Genet. 85, 97–105.

Bonczek, O., Krejci, P., Izakovicova-Holla, L., Cernochova, P., Kiss, I., Vojtesek, B., 2021. Tooth agenesis: what do we know and is there a connection to cancer? Clin. Genet. 99, 493–502.

Boulter, L., Guest, R.V., Kendall, T.J., Wilson, D.H., Wojtacha, D., Robson, A.J., Ridgway, R.A., Samuel, K., Van Rooijen, N., Barry, S.T., Wigmore, S.J., Sansom, O.J.,

Forbes, S.J., 2015. WNT signaling drives cholangiocarcinoma growth and can be pharmacologically inhibited. J. Clin. Invest. 125, 1269–1285.
Bukowska, J., Walendzik, K., Kopcewicz, M., Cierniak, P., Gawronska-Kozak, B., 2021. Wnt signaling and the transcription factor Foxn1 contribute to cutaneous wound repair in mice. Connect. Tissue Res. 62, 238–248.
Canty, E.G., Starborg, T., Lu, Y., Humphries, S.M., Holmes, D.F., Meadows, R.S., Huffman, A., O'Toole, E.T., Kadler, K.E., 2006. Actin filaments are required for fibripositor-mediated collagen fibril alignment in tendon. J. Biol. Chem. 281, 38592–38598.
Cao, J., Spielmann, M., Qiu, X., Huang, X., Ibrahim, D.M., Hill, A.J., Zhang, F., Mundlos, S., Christiansen, L., Steemers, F.J., Trapnell, C., Shendure, J., 2019. The single-cell transcriptional landscape of mammalian organogenesis. Nature 566, 496–502.
Castori, M., Ruggieri, S., Giannetti, L., Annessi, G., Zambruno, G., 2008. Schopf-Schulz-Passarge syndrome: further delineation of the phenotype and genetic considerations. Acta Derm. Venereol. 88, 607–612.
Caubit, X., Nicolas, S., Shi, D.L., Le Parco, Y., 1997. Reactivation and graded axial expression pattern of Wnt-10a gene during early regeneration stages of adult tail in amphibian urodele Pleurodeles waltl. Dev Dyn 208, 139–148.
Cawthorn, W.P., Bree, A.J., Yao, Y., Du, B., Hemati, N., Martinez-Santibanez, G., MacDougald, O.A., 2012. Wnt6, Wnt10a and Wnt10b inhibit adipogenesis and stimulate osteoblastogenesis through a beta-catenin-dependent mechanism. Bone 50, 477–489.
Cesarato, N., Schwieger-Briel, A., Gossmann, Y., Henne, S.K., Hillmann, K., Frommherz, L.H., Wehner, M., Xiong, X., Thiele, H., Oji, V., Milani, D., Tantcheva-Poor, I., Giehl, K., Folster-Holst, R., Teichler, A., Braeckmans, D., Hoeger, P.H., Jones, G., Frank, J., Weibel, L., Blume-Peytavi, U., Hamm, H., Nothen, M.M., Geyer, M., Heilmann-Heimbach, S., Basmanav, F.B., Betz, R.C., 2023. Short anagen hair syndrome: association with mono- and biallelic variants in WNT10A and a genetic overlap with male pattern hair loss. Br. J. Dermatol. 189, 741–749.
Chen, Y.S., Wu, R., Yang, X., Kou, S., MacDougald, O.A., Yu, L., Shi, H., Xue, B., 2016. Inhibiting DNA methylation switches adipogenesis to osteoblastogenesis by activating Wnt10a. Sci. Rep. 6, 25283.
Choi, Y.S., Zhang, Y., Xu, M., Yang, Y., Ito, M., Peng, T., Cui, Z., Nagy, A., Hadjantonakis, A.K., Lang, R.A., Cotsarelis, G., Andl, T., Morrisey, E.E., Millar, S.E., 2013. Distinct functions for Wnt/beta-catenin in hair follicle stem cell proliferation and survival and interfollicular epidermal homeostasis. Cell Stem Cell 13, 720–733.
Chu, M.L., Ahn, V.E., Choi, H.J., Daniels, D.L., Nusse, R., Weis, W.I., 2013. Structural Studies of Wnts and identification of an LRP6 binding site. Structure 21, 1235–1242.
Clauss, F., Waltmann, E., Barriere, P., Hadj-Rabia, S., Maniere, M.C., Schmittbuhl, M., 2014. Dento-maxillo-facial phenotype and implants-based oral rehabilitation in Ectodermal Dysplasia with WNT10A gene mutation: report of a case and literature review. J. Cranio-Maxillo-Fac. Surg. 42, e346–e351.
Coudreuse, D., Korswagen, H.C., 2007. The making of Wnt: new insights into Wnt maturation, sorting and secretion. Development 134, 3–12.
Cui, C.Y., Yin, M., Sima, J., Childress, V., Michel, M., Piao, Y., Schlessinger, D., 2014. Involvement of Wnt, Eda and Shh at defined stages of sweat gland development. Development 141, 3752–3760.
Dassule, H.R., McMahon, A.P., 1998. Analysis of epithelial-mesenchymal interactions in the initial morphogenesis of the mammalian tooth. Dev. Biol. 202, 215–227.
Dinckan, N., Du, R., Petty, L.E., Coban-Akdemir, Z., Jhangiani, S.N., Paine, I., Baugh, E. H., Erdem, A.P., Kayserili, H., Doddapaneni, H., Hu, J., Muzny, D.M., Boerwinkle, E., Gibbs, R.A., Lupski, J.R., Uyguner, Z.O., Below, J.E., Letra, A., 2018. Whole-exome sequencing identifies novel variants for tooth agenesis. J. Dent. Res. 97, 49–59.
Doolan, B.J., Onoufriadis, A., Kantaputra, P., McGrath, J.A., 2021. WNT10A, dermatology and dentistry. Br. J. Dermatol. 185, 1105–1111.
Driskell, R.R., Lichtenberger, B.M., Hoste, E., Kretzschmar, K., Simons, B.D., Charalambous, M., Ferron, S.R., Herault, Y., Pavlovic, G., Ferguson-Smith, A.C., Watt, F.M., 2013. Distinct fibroblast lineages determine dermal architecture in skin development and repair. Nature 504, 277–281.
Du, R., Dinckan, N., Song, X., Coban-Akdemir, Z., Jhangiani, S.N., Guven, Y., Aktoren, O., Kayserili, H., Petty, L.E., Muzny, D.M., Below, J.E., Boerwinkle, E., Wu, N., Gibbs, R.A., Posey, J.E., Lupski, J.R., Letra, A., Uyguner, Z.O., 2018. Identification of likely pathogenic and known variants in TSPEAR, LAMB3, BCOR, and WNT10A in four Turkish families with tooth agenesis. Hum. Genet. 137, 689–703.
Fan, J., Wei, Q., Liao, J., Zou, Y., Song, D., Xiong, D., Ma, C., Hu, X., Qu, X., Chen, L., Li, L., Yu, Y., Yu, X., Zhang, Z., Zhao, C., Zeng, Z., Zhang, R., Yan, S., Wu, T., Wu, X., Shu, Y., Lei, J., Li, Y., Zhang, W., Haydon, R.C., Luu, H.H., Huang, A., He, T.C., Tang, H., 2017. Noncanonical Wnt signaling plays an important role in modulating canonical Wnt-regulated stemness, proliferation and terminal differentiation of hepatic progenitors. Oncotarget 8, 27105–27119.
Foster, J.W., Parikh, R.N., Wang, J., Bower, K.S., Matthaei, M., Chakravarti, S., Jun, A.S., Eberhart, C.G., Soiberman, U.S., 2021. Transcriptomic and immunohistochemical analysis of progressive Keratoconus reveal altered WNT10A in epithelium and bowman's layer. Invest. Ophthalmol. Vis. Sci. 62, 16.
Fu, D.J., Thomson, C., Lunny, D.P., Dopping-Hepenstal, P.J., McGrath, J.A., Smith, F.J. D., Irwin McLean, W.H., Leslie Pedrioli, D.M., 2014. Keratin 9 is required for the structural integrity and terminal differentiation of the palmoplantar epidermis. J. Invest. Dermatol. 134, 754–763.
Granger, R.H., Marshman, G., Liu, L., McGrath, J.A., 2013. Late diagnosis of ectodermal dysplasia syndrome. Australas. J. Dermatol. 54, 46–48.
Gregoire, F.M., Smas, C.M., Sul, H.S., 1998. Understanding adipocyte differentiation. Physiol. Rev. 78, 783–809.
Hawkshaw, N.J., Hardman, J.A., Alam, M., Jimenez, F., Paus, R., 2020. Deciphering the molecular morphology of the human hair cycle: wnt signalling during the telogen-anagen transformation. Br. J. Dermatol. 182, 1184–1193.
Heilmann-Heimbach, S., Hochfeld, L.M., Paus, R., Nothen, M.M., 2016. Hunting the genes in male-pattern alopecia: how important are they, how close are we and what will they tell us? Exp. Dermatol. 25, 251–257.
Heilmann, S., Kiefer, A.K., Fricker, N., Drichel, D., Hillmer, A.M., Herold, C., Tung, J.Y., Eriksson, N., Redler, S., Betz, R.C., Li, R., Karason, A., Nyholt, D.R., Song, K., Vermeulen, S.H., Kanoni, S., Dedoussis, G., Martin, N.G., Kiemeney, L.A., Mooser, V., Stefansson, K., Richards, J.B., Becker, T., Brockschmidt, F.F., Hinds, D.A., Nothen, M. M., 2013. Androgenetic alopecia: identification of four genetic risk loci and evidence for the contribution of WNT signaling to its etiology. J. Invest. Dermatol. 133, 1489–1496.
Hinz, B., 2016. The role of myofibroblasts in wound healing. Curr Res Transl Med 64, 171–177.
Hirai, H., Matoba, K., Mihara, E., Arimori, T., Takagi, J., 2019. Crystal structure of a mammalian Wnt-frizzled complex. Nat. Struct. Mol. Biol. 26, 372–379.
Hochfeld, L.M., Bertolini, M., Broadley, D., Botchkareva, N.V., Betz, R.C., Schoch, S., Nothen, M.M., Heilmann-Heimbach, S., 2021. Evidence for a functional interaction of WNT10A and EBF1 in male-pattern baldness. PLoS One 16, e0256846.
Hsu, R.J., Ho, J.Y., Cha, T.L., Yu, D.S., Wu, C.L., Huang, W.P., Chu, P., Chen, Y.H., Chen, J.T., Yu, C.P., 2012. WNT10A plays an oncogenic role in renal cell carcinoma by activating WNT/beta-catenin pathway. PLoS One 7, e47649.
Jafari, N.V., Rohn, J.L., 2022. The urothelium: a multi-faceted barrier against a harsh environment. Mucosal Immunol. 15, 1127–1142.
Janda, C.Y., Waghray, D., Levin, A.M., Thomas, C., Garcia, K.C., 2012. Structural basis of wnt recognition by frizzled. Science 337, 59–64.
Jonsson, L., Magnusson, T.E., Thordarson, A., Jonsson, T., Geller, F., Feenstra, B., Melbye, M., Nohr, E.A., Vucic, S., Dhamo, B., Rivadeneira, F., Ongkosuwito, E.M., Wolvius, E.B., Leslie, E.J., Marazita, M.L., Howe, B.J., Moreno Uribe, L.M., Alonso, I., Santos, M., Pinho, T., Jonsson, R., Audolfsson, G., Gudmundsson, L., Nawaz, M.S., Olafsson, S., Gustafsson, O., Ingason, A., Unnsteinsdottir, U., Bjornsdottir, G., Walters, G.B., Zervas, M., Oddsson, A., Gudbjartsson, D.F., Steinberg, S., Stefansson, H., Stefansson, K., 2018. Rare and common variants conferring risk of tooth agenesis. J. Dent. Res. 97, 515–522.
Jung, Y.S., Park, J.I., 2020. Wnt signaling in cancer: therapeutic targeting of Wnt signaling beyond beta-catenin and the destruction complex. Exp. Mol. Med. 52, 183–191.
Kanchanasevee, C., Sriwattanapong, K., Theerapanon, T., Thaweesapphithak, S., Chetruengchai, W., Porntaveetus, T., Shotelersuk, V., 2020. Phenotypic and genotypic features of Thai patients with nonsyndromic tooth agenesis and WNT10A variants. Front. Physiol. 11, 573214.
Kantaputra, P., Kaewgahya, M., Kantaputra, W., 2014. WNT10A mutations also associated with agenesis of the maxillary permanent canines, a separate entity. Am. J. Med. Genet. 164A, 360–363.
Kantaputra, P., Sripathomsawat, W., 2011. WNT10A and isolated hypodontia. Am. J. Med. Genet. 155A, 1119–1122.
Katoh, M., 2002. WNT and FGF gene clusters. Int. J. Oncol. 21, 1269–1273 (review).
Kelly, G.M., Lai, C.J., Moon, R.T., 1993. Expression of wnt10a in the central nervous system of developing zebrafish. Dev. Biol. 158, 113–121.
Kerekes, K., Banyai, L., Patthy, L., 2015. Wnts grasp the WIF domain of Wnt Inhibitory Factor 1 at two distinct binding sites. FEBS Lett. 589, 3044–3051.
Kim, D., Hossain, M.Z., Nieves, A., Gu, L., Ratliff, T.S., Mi Oh, S., Park, A., Han, S., Yang, N.B., Qi, J., Taube, J.M., Kang, S., Garza, L.A., 2016. To control site-specific skin gene expression, autocrine mimics paracrine canonical wnt signaling and is activated ectopically in skin disease. Am. J. Pathol. 186, 1140–1150.
Kirikoshi, H., Inoue, S., Sekihara, H., Katoh, M., 2001a. Expression of WNT10A in human cancer. Int. J. Oncol. 19, 997–1001.
Kirikoshi, H., Sekihara, H., Katoh, M., 2001b. WNT10A and WNT6, clustered in human chromosome 2q35 region with head-to-tail manner, are strongly coexpressed in SW480 cells. Biochem. Biophys. Res. Commun. 283, 798–805.
Kobayashi, K., Kumakura, M., Shinkai, H., Ishii, K., 1994. Three-dimensional fine structure of the lingual papillae and their connective tissue cores in the human tongue. Kaibogaku Zasshi 69, 624–635.
Kornsuthisopon, C., Photichailert, S., Nowwarote, N., Tompkins, K.A., Osathanon, T., 2022. Wnt signaling in dental pulp homeostasis and dentin regeneration. Arch. Oral Biol. 134, 105322.
Kuma, A., Yamada, S., Wang, K.Y., Kitamura, N., Yamaguchi, T., Iwai, Y., Izumi, H., Tamura, M., Otsuji, Y., Kohno, K., 2014. Role of WNT10A-expressing kidney fibroblasts in acute interstitial nephritis. PLoS One 9, e103240.
Kumagai, M., Guo, X., Wang, K.Y., Izumi, H., Tsukamoto, M., Nakashima, T., Tasaki, T., Kurose, N., Uramoto, H., Sasaguri, Y., Kohno, K., Yamada, S., 2019. Depletion of WNT10A prevents tumor growth by suppressing microvessels and collagen expression. Int. J. Med. Sci. 16, 416–423.
Lan, R., Wu, Y., Dai, Q., Wang, F., 2023. Gene mutations and chromosomal abnormalities in syndromes with tooth agenesis. Oral Dis. 29, 2401–2408.
Letra, A., 2022. Rethinking the genetic etiology of nonsyndromic tooth agenesis. Curr. Osteoporos. Rep. 20, 389–397.
Li, J., Zhang, Z., Wang, L., Zhang, Y., 2019. The oncogenic role of Wnt10a in colorectal cancer through activation of canonical Wnt/beta-catenin signaling. Oncol. Lett. 17, 3657–3664.
Li, P., Liu, W., Xu, Q., Wang, C., 2017. Clinical significance and biological role of Wnt10a in ovarian cancer. Oncol. Lett. 14, 6611–6617.
Lin, B., Liu, H., Liu, H., Su, L., Sun, K., Feng, H., Liu, Y., Yu, M., Han, D., 2024. A novel WNT10A variant impairs the homeostasis of alveolar bone mesenchymal stem cells. Oral Dis.

Little, M.H., McMahon, A.P., 2012. Mammalian kidney development: principles, progress, and projections. Cold Spring Harb Perspect Biol 4.
Liu, F., Thirumangalathu, S., Gallant, N.M., Yang, S.H., Stoick-Cooper, C.L., Reddy, S.T., Andl, T., Taketo, M.M., Dlugosz, A.A., Moon, R.T., Barlow, L.A., Millar, S.E., 2007. Wnt-beta-catenin signaling initiates taste papilla development. Nat. Genet. 39, 106–112.
Liu, Y., Han, D., Wang, L., Feng, H., 2013. Down-regulation of Wnt10a affects odontogenesis and proliferation in mesenchymal cells. Biochem. Biophys. Res. Commun. 434, 717–721.
Long, A., Giroux, V., Whelan, K.A., Hamilton, K.E., Tetreault, M.P., Tanaka, K., Lee, J.S., Klein-Szanto, A.J., Nakagawa, H., Rustgi, A.K., 2015. WNT10A promotes an invasive and self-renewing phenotype in esophageal squamous cell carcinoma. Carcinogenesis 36, 598–606.
Mallaiah, U., Dickinson, J., 2001. Photo essay: bilateral multiple eyelid apocrine hidrocystomas and ectodermal dysplasia. Arch. Ophthalmol. 119, 1866–1867.
Maretto, S., Cordenonsi, M., Dupont, S., Braghetta, P., Broccoli, V., Hassan, A.B., Volpin, D., Bressan, G.M., Piccolo, S., 2003. Mapping Wnt/beta-catenin signaling during mouse development and in colorectal tumors. Proc Natl Acad Sci U S A 100, 3299–3304.
Matsukawa, T., Morita, K., Omizu, S., Kato, S., Koriyama, Y., 2018. Mechanisms of RhoA inactivation and CDC42 and Rac1 activation during zebrafish optic nerve regeneration. Neurochem. Int. 112, 71–80.
Mehta, V., Schmitz, C.T., Keil, K.P., Joshi, P.S., Abler, L.L., Lin, T.M., Taketo, M.M., Sun, X., Vezina, C.M., 2013. Beta-catenin (CTNNB1) induces Bmp expression in urogenital sinus epithelium and participates in prostatic bud initiation and patterning. Dev. Biol. 376, 125–135.
Merrill, B.J., Gat, U., DasGupta, R., Fuchs, E., 2001. Tcf3 and Lef1 regulate lineage differentiation of multipotent stem cells in skin. Genes Dev. 15, 1688–1705.
Miletich, I., Sharpe, P.T., 2003. Normal and abnormal dental development. Hum. Mol. Genet. 12 (Spec No 1), R69–R73.
Mostowska, A., Hozyasz, K.K., Biedziak, B., Wojcicki, P., Lianeri, M., Jagodzinski, P.P., 2012. Genotype and haplotype analysis of WNT genes in non-syndromic cleft lip with or without cleft palate. Eur. J. Oral Sci. 120, 1–8.
Mues, G., Bonds, J., Xiang, L., Vieira, A.R., Seymen, F., Klein, O., D'Souza, R.N., 2014. The WNT10A gene in ectodermal dysplasias and selective tooth agenesis. Am. J. Med. Genet. 164A, 2455–2460.
Nagy, N., Wedgeworth, E., Hamada, T., White, J.M., Hashimoto, T., McGrath, J.A., 2010. Schopf-Schulz-Passarge syndrome resulting from a homozygous nonsense mutation in WNT10A. J. Dermatol. Sci. 58, 220–222.
Narita, T., Sasaoka, S., Udagawa, K., Ohyama, T., Wada, N., Nishimatsu, S., Takada, S., Nohno, T., 2005. Wnt10a is involved in AER formation during chick limb development. Dev Dyn 233, 282–287.
Nawaz, S., Klar, J., Wajid, M., Aslam, M., Tariq, M., Schuster, J., Baig, S.M., Dahl, N., 2009. WNT10A missense mutation associated with a complete odonto-onycho-dermal dysplasia syndrome. Eur. J. Hum. Genet. 17, 1600–1605.
Nie, X., Liu, H., Liu, L., Wang, Y.D., Chen, W.D., 2020. Emerging roles of wnt ligands in human colorectal cancer. Front. Oncol. 10, 1341.
Niida, A., Hiroko, T., Kasai, M., Furukawa, Y., Nakamura, Y., Suzuki, Y., Sugano, S., Akiyama, T., 2004. DKK1, a negative regulator of Wnt signaling, is a target of the beta-catenin/TCF pathway. Oncogene 23, 8520–8526.
Nile, A.H., Hannoush, R.N., 2016. Fatty acylation of Wnt proteins. Nat. Chem. Biol. 12, 60–69.
Nusse, R., 2001. An ancient cluster of Wnt paralogues. Trends Genet. 17, 443.
Nuwaihyd, R., Redler, S., Heilmann, S., Drichel, D., Wolf, S., Birch, P., Dobson, K., Lutz, G., Giehl, K.A., Kruse, R., Tazi-Ahnini, R., Hanneken, S., Bohm, M., Miesel, A., Fischer, T., Wolff, H., Becker, T., Garcia-Bartels, N., Blume-Peytavi, U., Nothen, M. M., Messenger, A.G., Betz, R.C., 2014. Investigation of four novel male androgenetic alopecia susceptibility loci: no association with female pattern hair loss. Arch. Dermatol. Res. 306, 413–418.
Nygaard, R., Yu, J., Kim, J., Ross, D.R., Parisi, G., Clarke, O.B., Virshup, D.M., Mancia, F., 2021. Structural basis of WLS/Evi-Mediated wnt transport and secretion. Cell 184, 194-206 e114.
Oda, K., Yatera, K., Izumi, H., Ishimoto, H., Yamada, S., Nakao, H., Hanaka, T., Ogoshi, T., Noguchi, S., Mukae, H., 2016. Profibrotic role of WNT10A via TGF-beta signaling in idiopathic pulmonary fibrosis. Respir. Res. 17, 39.
Okabe, H., Yang, J., Sylakowski, K., Yovchev, M., Miyagawa, Y., Nagarajan, S., Chikina, M., Thompson, M., Oertel, M., Baba, H., Monga, S.P., Nejak-Bowen, K.N., 2016. Wnt signaling regulates hepatobiliary repair following cholestatic liver injury in mice. Hepatology 64, 1652–1666.
Pei, W., Xu, L., Huang, S.C., Pettie, K., Idol, J., Rissone, A., Jimenez, E., Sinclair, J.W., Slevin, C., Varshney, G.K., Jones, M., Carrington, B., Bishop, K., Huang, H., Sood, R., Lin, S., Burgess, S.M., 2018. Guided genetic screen to identify genes essential in the regeneration of hair cells and other tissues. NPJ Regen. Med. 3, 11.
Petrof, G., Fong, K., Lai-Cheong, J.E., Cockayne, S.E., McGrath, J.A., 2011. Schopf-Schulz-Passarge syndrome resulting from a homozygous nonsense mutation, p. Cys107X, in WNT10A. Australas. J. Dermatol. 52, 224–226.
Polder, B.J., Van't Hof, M.A., Van der Linden, F.P., Kuijpers-Jagtman, A.M., 2004. A meta-analysis of the prevalence of dental agenesis of permanent teeth. Community Dent. Oral Epidemiol. 32, 217–226.
Poss, K.D., Shen, J., Keating, M.T., 2000. Induction of lef1 during zebrafish fin regeneration. Dev Dyn 219, 282–286.
Qurrat Ul, A., Seemab, U., Nawaz, S., Rashid, S., 2011. Integrative analyses of conserved WNT clusters and their co-operative behaviour in human breast cancer. Bioinformation 7, 339–346.
Raju, R., Pina, J.O., Roth, D.M., Chattaraj, P., Kidwai, F.K., Faucz, F.R., Iben, J., Fridell, G., Dale, R.K., D'Souza, R.N., 2023. Profiles of Wnt pathway gene expression during tooth morphogenesis. Front. Physiol. 14, 1316635.
Rangwala, S.M., Lazar, M.A., 2000. Transcriptional control of adipogenesis. Annu. Rev. Nutr. 20, 535–559.
Reddy, S., Andl, T., Bagasra, A., Lu, M.M., Epstein, D.J., Morrisey, E.E., Millar, S.E., 2001. Characterization of Wnt gene expression in developing and postnatal hair follicles and identification of Wnt5a as a target of Sonic hedgehog in hair follicle morphogenesis. Mech. Dev. 107, 69–82.
Ribatti, D., Santoiemma, M., 2014. Epithelial-mesenchymal interactions: a fundamental Developmental Biology mechanism. Int. J. Dev. Biol. 58, 303–306.
Rinn, J.L., Wang, J.K., Allen, N., Brugmann, S.A., Mikels, A.J., Liu, H., Ridky, T.W., Stadler, H.S., Nusse, R., Helms, J.A., Chang, H.Y., 2008. A dermal HOX transcriptional program regulates site-specific epidermal fate. Genes Dev. 22, 303–307.
Romero, M.M.G., McCathie, G., Jankun, P., Roehl, H.H., 2018. Damage-induced reactive oxygen species enable zebrafish tail regeneration by repositioning of Hedgehog expressing cells. Nat. Commun. 9, 4010.
Ross, S.E., Hemati, N., Longo, K.A., Bennett, C.N., Lucas, P.C., Erickson, R.L., MacDougald, O.A., 2000. Inhibition of adipogenesis by Wnt signaling. Science 289, 950–953.
Routledge, D., Scholpp, S., 2019. Mechanisms of intercellular Wnt transport. Development 146.
Russell, J.O., Monga, S.P., 2018. Wnt/beta-Catenin signaling in liver development, homeostasis, and pathobiology. Annu. Rev. Pathol. 13, 351–378.
Schlange, T., Matsuda, Y., Lienhard, S., Huber, A., Hynes, N.E., 2007. Autocrine WNT signaling contributes to breast cancer cell proliferation via the canonical WNT pathway and EGFR transactivation. Breast Cancer Res. 9, R63.
Schulze-Tanzil, G.G., Delgado-Calcares, M., Stange, R., Wildemann, B., Docheva, D., 2022. Tendon healing: a concise review on cellular and molecular mechanisms with a particular focus on the Achilles tendon. Bone Joint Res 11, 561–574.
Sennett, R., Rendl, M., 2012. Mesenchymal-epithelial interactions during hair follicle morphogenesis and cycling. Semin. Cell Dev. Biol. 23, 917–927.
Sharma, A.K., Bury, M.I., Fuller, N.J., Marks, A.J., Kollhoff, D.M., Rao, M.V., Hota, P.V., Matoka, D.J., Edassery, S.L., Thaker, H., Sarwark, J.F., Janicki, J.A., Ameer, G.A., Cheng, E.Y., 2013. Cotransplantation with specific populations of spina bifida bone marrow stem/progenitor cells enhances urinary bladder regeneration. Proc Natl Acad Sci U S A 110, 4003–4008.
Sidow, A., 1992. Diversification of the Wnt gene family on the ancestral lineage of vertebrates. Proc Natl Acad Sci U S A 89, 5098–5102.
Skarnes, W.C., Rosen, B., West, A.P., Koutsourakis, M., Bushell, W., Iyer, V., Mujica, A.O., Thomas, M., Harrow, J., Cox, T., Jackson, D., Severin, J., Biggs, P., Fu, J., Nefedov, M., de Jong, P.J., Stewart, A.F., Bradley, A., 2011. A conditional knockout resource for the genome-wide study of mouse gene function. Nature 474, 337–342.
Song, S., Zhao, R., He, H., Zhang, J., Feng, H., Lin, L., 2014. WNT10A variants are associated with non-syndromic tooth agenesis in the general population. Hum. Genet. 133, 117–124.
Square, T.A., Mackey, E.J., Sundaram, S., Weksler, N.C., Chen, Z.Z., Narayanan, S.N., Miller, C.T., 2023. Modulation of tooth regeneration through opposing responses to Wnt and BMP signals in teleosts. Development 150.
Stewart, S., Gomez, A.W., Armstrong, B.E., Henner, A., Stankunas, K., 2014. Sequential and opposing activities of Wnt and BMP coordinate zebrafish bone regeneration. Cell Rep. 6, 482–498.
Stoick-Cooper, C.L., Weidinger, G., Riehle, K.J., Hubbert, C., Major, M.B., Fausto, N., Moon, R.T., 2007. Distinct Wnt signaling pathways have opposing roles in appendage regeneration. Development 134, 479–489.
Sun, K., Yu, M., Wang, J., Zhao, H., Liu, H., Feng, H., Liu, Y., Han, D., 2024. A Wnt10a-Notch signaling axis controls Hertwig's epithelial root sheath cell behaviors during root furcation patterning. Int. J. Oral Sci. 16, 25.
Suomalainen, M., Thesleff, I., 2010. Patterns of Wnt pathway activity in the mouse incisor indicate absence of Wnt/beta-catenin signaling in the epithelial stem cells. Dev Dyn 239, 364–372.
Teiken, K., Kuehnel, M., Rehkaemper, J., Kreipe, H., Laenger, F., Hussein, K., Jonigk, D., 2018. Non-canonical WNT6/WNT10A signal factor expression in EBV+ post-transplant smooth muscle tumors. Clin. Sarcoma Res. 8, 10.
The Jackson Laboratory, 2017. Mouse genome database (MGD), at the mouse genome informatics website. MGI, 7293181, 2017 ed, Bar Harbor, Maine.
Thomas, D.F.M., 2020. The embryology of persistent cloaca and urogenital sinus malformations. Asian J. Androl. 22, 124–128.
Tsukamoto, M., Wang, K.Y., Tasaki, T., Murata, Y., Okada, Y., Yamanaka, Y., Nakamura, E., Yamada, S., Izumi, H., Zhou, Q., Azuma, K., Sasaguri, Y., Kohno, K., Sakai, A., 2019. Findings as a starting point to unravel the underlying mechanisms of in vivo interactions involving Wnt10a in bone, fat and muscle. Bone 120, 75–84.
Tsutsumi, N., Hwang, S., Waghray, D., Hansen, S., Jude, K.M., Wang, N., Miao, Y., Glassman, C.R., Caveney, N.A., Janda, C.Y., Hannoush, R.N., Garcia, K.C., 2023. Structure of the Wnt-Frizzled-LRP6 initiation complex reveals the basis for coreceptor discrimination. Proc Natl Acad Sci U S A 120, e2218238120.
Tummers, M., Thesleff, I., 2009. The importance of signal pathway modulation in all aspects of tooth development. J. Exp. Zool. B Mol. Dev. Evol. 312B, 309–319.
Tziotzios, C., Petrof, G., Liu, L., Verma, A., Wedgeworth, E.K., Mellerio, J.E., McGrath, J. A., 2014. Clinical features and WNT10A mutations in seven unrelated cases of Schopf-Schulz-Passarge syndrome. Br. J. Dermatol. 171, 1211–1214.
van den Boogaard, M.J., Creton, M., Bronkhorst, Y., van der Hout, A., Hennekam, E., Lindhout, D., Cune, M., Ploos van Amstel, H.K., 2012. Mutations in WNT10A are present in more than half of isolated hypodontia cases. J. Med. Genet. 49, 327–331.

Vaquero, J., Guedj, N., Claperon, A., Nguyen Ho-Bouldoires, T.H., Paradis, V., Fouassier, L., 2017. Epithelial-mesenchymal transition in cholangiocarcinoma: from clinical evidence to regulatory networks. J. Hepatol. 66, 424–441.
Vink, C.P., Ockeloen, C.W., ten Kate, S., Koolen, D.A., Ploos van Amstel, J.K., Kuijpers-Jagtman, A.M., van Heumen, C.C., Kleefstra, T., Carels, C.E., 2014. Variability in dentofacial phenotypes in four families with WNT10A mutations. Eur. J. Hum. Genet. 22, 1063–1070.
Wang, J., Shackleford, G.M., 1996. Murine Wnt10a and Wnt10b: cloning and expression in developing limbs, face and skin of embryos and in adults. Oncogene 13, 1537–1544.
Wang, K.Y., Yamada, S., Izumi, H., Tsukamoto, M., Nakashima, T., Tasaki, T., Guo, X., Uramoto, H., Sasaguri, Y., Kohno, K., 2018. Critical in vivo roles of WNT10A in wound healing by regulating collagen expression/synthesis in WNT10A-deficient mice. PLoS One 13, e0195156.
Wegner, K.A., Cadena, M.T., Trevena, R., Turco, A.E., Gottschalk, A., Halberg, R.B., Guo, J., McMahon, J.A., McMahon, A.P., Vezina, C.M., 2017. An immunohistochemical identification key for cell types in adult mouse prostatic and urethral tissue sections. PLoS One 12, e0188413.
Wehner, D., Cizelsky, W., Vasudevaro, M.D., Ozhan, G., Haase, C., Kagermeier-Schenk, B., Roder, A., Dorsky, R.I., Moro, E., Argenton, F., Kuhl, M., Weidinger, G., 2014. Wnt/beta-catenin signaling defines organizing centers that orchestrate growth and differentiation of the regenerating zebrafish caudal fin. Cell Rep. 6, 467–481.
Werner, J., Boonekamp, K.E., Zhan, T., Boutros, M., 2023. The roles of secreted wnt ligands in cancer. Int. J. Mol. Sci. 24.
Willert, K., Nusse, R., 2012. Wnt proteins. Cold Spring Harb Perspect Biol 4, a007864.
Willert, K.H., 2008. Isolation and application of bioactive Wnt proteins. Methods Mol. Biol. 468, 17–29.
Williams, M.A., Letra, A., 2018. The changing landscape in the genetic etiology of human tooth agenesis. Genes 9.
Wright, J.T., Grange, D.K., Fete, M., 1993. Hypohidrotic ectodermal dysplasia. In: Adam, M.P., Feldman, J., Mirzaa, G.M., Pagon, R.A., Wallace, S.E., Bean, L.J.H., Gripp, K.W., Amemiya, A. (Eds.), GeneReviews((R)), Seattle (WA).
Xiao, L., Zhou, D., Tan, R.J., Fu, H., Zhou, L., Hou, F.F., Liu, Y., 2016. Sustained activation of wnt/beta-catenin signaling drives AKI to CKD progression. J. Am. Soc. Nephrol. 27, 1727–1740.
Xu, M., Horrell, J., Snitow, M., Cui, J., Gochnauer, H., Syrett, C.M., Kallish, S., Seykora, J. T., Liu, F., Gaillard, D., Katz, J.P., Kaestner, K.H., Levin, B., Mansfield, C., Douglas, J. E., Cowart, B.J., Tordoff, M., Liu, F., Zhu, X., Barlow, L.A., Rubin, A.I., McGrath, J.A., Morrisey, E.E., Chu, E.Y., Millar, S.E., 2017. WNT10A mutation causes ectodermal dysplasia by impairing progenitor cell proliferation and KLF4-mediated differentiation. Nat. Commun. 8, 15397.
Yamashiro, T., Zheng, L., Shitaku, Y., Saito, M., Tsubakimoto, T., Takada, K., Takano-Yamamoto, T., Thesleff, I., 2007. Wnt10a regulates dentin sialophosphoprotein mRNA expression and possibly links odontoblast differentiation and tooth morphogenesis. Differentiation 75, 452–462.
Yang, J., Wang, S.K., Choi, M., Reid, B.M., Hu, Y., Lee, Y.L., Herzog, C.R., Kim-Berman, H., Lee, M., Benke, P.J., Lloyd, K.C., Simmer, J.P., Hu, J.C., 2015. Taurodontism, variations in tooth number, and misshapened crowns in Wnt10a null mice and human kindreds. Mol Genet Genomic Med 3, 40–58.
Yasuniwa, Y., Izumi, H., Wang, K.Y., Shimajiri, S., Sasaguri, Y., Kawai, K., Kasai, H., Shimada, T., Miyake, K., Kashiwagi, E., Hirano, G., Kidani, A., Akiyama, M., Han, B., Wu, Y., Ieiri, I., Higuchi, S., Kohno, K., 2010. Circadian disruption accelerates tumor growth and angio/stromagenesis through a Wnt signaling pathway. PLoS One 5, e15330.
Yin, W., Bian, Z., 2015. The gene network underlying hypodontia. J. Dent. Res. 94, 878–885.
Yoshinaga, K., Yasue, A., Mitsui, S.N., Minegishi, Y., Oyadomari, S., Imoto, I., Tanaka, E., 2023. Effects of Wnt10a and Wnt10b double mutations on tooth development. Genes 14.
Yu, M., Liu, Y., Wang, Y., Wong, S.W., Wu, J., Liu, H., Feng, H., Han, D., 2020. Epithelial Wnt10a is essential for tooth root furcation morphogenesis. J. Dent. Res. 99, 311–319.
Yu, M., Wong, S.W., Han, D., Cai, T., 2019. Genetic analysis: wnt and other pathways in nonsyndromic tooth agenesis. Oral Dis. 25, 646–651.
Yuan, Q., Zhao, M., Tandon, B., Maili, L., Liu, X., Zhang, A., Baugh, E.H., Tran, T., Silva, R.M., Hecht, J.T., Swindell, E.C., Wagner, D.S., Letra, A., 2017. Role of WNT10A in failure of tooth development in humans and zebrafish. Mol Genet Genomic Med 5, 730–741.
Zeng, B., Xiao, X., Li, S., Lu, H., Lu, J., Zhu, L., Yu, D., Zhao, W., 2016. Eight mutations of three genes (EDA, EDAR, and WNT10A) identified in seven hypohidrotic ectodermal dysplasia patients. Genes 7.
Zeng, Y., Baugh, E., Akyalcin, S., Letra, A., 2021. Functional effects of WNT10A rare variants associated with tooth agenesis. J. Dent. Res. 100, 302–309.
Zhang, J.H., Tasaki, T., Tsukamoto, M., Wang, K.Y., Azuma, K., 2022a. Deficiency of Wnt10a causes female infertility via the beta-catenin/Cyp19a1 pathway in mice. Int. J. Med. Sci. 19, 701–710.
Zhang, J.H., Tasaki, T., Tsukamoto, M., Wang, K.Y., Kubo, K.Y., Azuma, K., 2022b. Deletion of Wnt10a is implicated in hippocampal neurodegeneration in mice. Biomedicines 10.
Zhong, Q., Zhao, Y., Ye, F., Xiao, Z., Huang, G., Xu, M., Zhang, Y., Zhan, X., Sun, K., Wang, Z., Cheng, S., Feng, S., Zhao, X., Zhang, J., Lu, P., Xu, W., Zhou, Q., Ma, D., 2021. Cryo-EM structure of human Wntless in complex with Wnt3a. Nat. Commun. 12, 4541.