The understanding of bone formation processes during development and bone remodeling has been substantially improved in the last years by the identification of novel genes underlying monogenic forms of bone diseases. The present PhD thesis focussed on the molecular identification of novel disease causing genes and on the uncovering of the underlying pathophysiological mechanisms in rare, monogenic bone disorders including osteogenesis imperfecta (OI), inherited early-onset osteoporosis, and congenital forms of craniosynostosis.

In this context, through the application of next generation sequencing technology and effective bioinformatic data analysis, we succeeded in identifying pathogenic mutations in a total of four novel bone-disease causing genes. Subsequent molecular and functional studies unravelled the role of these genes as important key players involved in evolutionarily conserved pathways of bone formation physiology.

In detail, we identified causative mutations in (i) *BMP1* and (ii) *WNT1* as the molecular causes of autosomal recessive OI and *WNT1* mutations as a cause for autosomal dominantly inherited osteoporosis as well as (iii) mutations in *IFITM5* in patients with autosomal dominant OI and (iv) recessive *IL11RA* mutations in patients with congenital syndromic and non-syndromic craniosynostoses. Moreover, to gain further insights into the molecular pathogenesis of these bone formation defects, the molecular consequences of protein alterations at the cellular level were studied with distinct *in vitro* and *in vivo* approaches.

In the course of the PhD project, we discovered that reduced BMP1 activity results in severely disturbed collagen I processing and fibrillogenesis leading to impaired bone matrix formation and mineralization. Thus, we confirmed that the role in collagen I biology is the main contribution of BMP1 during osteogenesis. As a further result, we ascertained that hypofunctional *WNT1* mutations with a reduced potential to activate LRP5-mediated WNT/β-catenin signaling are a novel and frequent cause in different types of bone fragility disorders leading to recessively inherited OI or dominantly inherited early-onset osteoporosis. Further experiments showed severely impaired collagen I secretion in fibroblast cell lines harbouring *WNT1* mutations and thus indicated an interesting correlation between WNT1 signaling and collagen I regulation. These findings revealed the remarkable relevance of WNT1 activity in bone formation physiology and provided the first evidence for a novel mechanism of canonical WNT-signaling in collagen I biosynthesis and bone matrix formation. Furthermore, we identified a nucleotide substitution within the 5' UTR of *IFITM5* as the first molecular cause of dominant OI type V. Subsequent molecular and functional analysis determined that this mutation generates a second in frame start codon upstream of the reference start codon, resulting in a pathogenic protein-extension of the N-terminus of IFITM5. The exact role of

IFITM5 as well as the pathophysiology of the altered protein is not explained yet. Another distinct bone formation process is the development of the cranial vault, which is still poorly understood. Here, we demonstrated that impaired IL11RA activity leads to reduced STAT3-mediated intracellular downstream signaling, which results in premature suture fusion. Subsequent molecular and functional analyses suggested IL11RA as a crucial main regulator in the course of cranial development in particular involved in suture patency.

Taken together our data provide new and fascinating insights into the heterogeneity of the complex physiology and pathophysiology of bone formation and shed new light on crucial key regulators in different aspects of bone biology.