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Hypomyelination with tooth and bone involvement: New insights

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Summary

Hypomyelinating leukodystrophies are a group of diseases with large variability in their genetic background, less so in their clinical and radiological features. MRI pattern recognition and advances in genetic testing are now able to classify most hypomyelinating leukodystrophies. However, the phenotypic differences can be considerable even in a single hypomyelinating leukodystrophy, such as 4H syndrome. This thesis explores the radiological and genetic differences of hypomyelinating leukodystrophies, particularly 4H leukodystrophy, as described in **Chapter 2**, and describes a novel intriguing hypomyelinating leukodystrophy with unique involvement of bone tissue (hypomyelination with spondylometaphyseal dysplasia, H-SMD) in **Chapter 3**. It also validates an *in vitro* model of direct transdifferentiation of fibroblasts to osteoblast-like cells to investigate bone involvement.

MRI in hypomyelination leukodystrophies

Chapter 2.1 describes the importance of pattern recognition in 4H leukodystrophy. Without typical 4H leukodystrophy MRI findings, direct genetic testing of *POLR3* genes is not recommended. Instead, alternative diagnoses of other hypomyelinating leukodystrophies and utilization of whole exome sequencing (WES) should be considered. **Chapter 2.2** explores the utilization of MRI not only as diagnostic tool, but also as a tool correlating to clinical disease severity. This MRI scoring system, based on the degree of hypomyelination and atrophy in 4H leukodystrophy, can be simply applied for future studies such as to monitor diseases progression in clinical trials or be adapted as biomarker for other hypomyelinating leukodystrophies.

Chapter 2.3 provides new MRI features of 4H leukodystrophy which are clearly visible on 3T MRI: myelin islets, closed eye sign and cyst-like lesion in the splenium. On the other hand, diffuse hypomyelination is no longer an obligatory MRI feature for 4H leukodystrophy as described in **Chapter 2.4**. Six patients with *POLR3A* mutations and two patients with *POLR3B* mutations all had either partial hypomyelination or

adequate myelination, but two distinct patterns: specific involvement of corticospinal tracts in four out of six patients with *POLR3A* mutations and cerebellar atrophy in absence of diffuse hypomyelination in patients with either *POLR3A* or *POLR3B* mutations. Other classical clinical criteria – hypodontia and hypogonadotropic hypogonadism – may still suggest the correct diagnosis, even when the cardinal MRI features are lacking.

Bone involvement in hypomyelinating leukodystrophies

Chapter 3.1 explores the non-neurological involvement in a unique hypomyelination leukodystrophy, H-SMD. Diffuse hypomyelination accompanied by bone abnormalities, spondylometaphyseal dysplasia, in a group of 12 patients led to identification of mutations in or near exon 7 of the *AIFM1* gene, within a region of 70 base pairs. When analyzing WES data, these mutations were initially overlooked as some of them were intronic or synonymous, and also because *AIFM1* mutations were previously associated with other distinct clinical presentations without bone abnormalities. By using an *in vitro* model, which mimics the involved tissue, the effect of the mutations, namely a reduced expression of *AIFM1* on mRNA and protein level only in osteoblasts without affecting the fibroblasts, could be confirmed although the specific mechanism still needs to be elucidated.

An *in vitro* model applied for H-SMD was validated in **Chapter 3.2**. Highly efficient platelet lysate-based transdifferentiation of skin-derived fibroblasts to osteoblasts-like cells was characterized on functional, protein and mRNA level. Positive staining of mineralization assays, positive immunofluorescence staining of osteoblast-specific proteins and significantly increased mRNA expression of osteoblast-specific markers confirmed the properties of transdifferentiated osteoblasts. RNA-seq supported the successful transdifferentiation by clustering transdifferentiated cells separately from fibroblasts and showed significant upregulation of two important pathways in bone differentiation involving WNT and BMP.

