Université franco-allemande
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- Thesis -

Identification and Validation of novel genes implicated in Neurosensory and Neurological Diseases

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Summary

Worldwide, about 5-10 % of the population suffer from rare genetic diseases. Although the interest in rare diseases has grown in recent years, there are often no therapies available. The reason for this, is especially that the genes responsible for rare diseases are still unknown. In order to get a better understanding of the molecular processes behind those diseases and to be able to find new therapeutic targets, it is very important to identify these yet unknown genes. During my thesis, I was particularly interested in the identification of disease genes associated with neurodevelopmental and neurosensory diseases. The strategy I used to identify new disease-causing genes is based primarily on the analysis of high-throughput sequencing data from patients, the confirmation of variants by Sanger sequencing and the performance of functional experiments using patients' cells and the zebrafish model to proof the pathogenicity of the novel gene mutations. Using this strategy, I was able to contribute to the identification of three novel disease genes.

In **project 1**, I report on 13 individuals with an Intellectual Disability (ID) syndrome caused by variations in one of the protein arginine methyltransferase genes. Beside ID, patients present mainly a global developmental delay, autism, epilepsy and hypotonia. By performing transcriptomic analysis, I was able to show that genes associated with ID and autism are differentially expressed in patients' fibroblasts. Moreover, a longer primary cilium length as well as differentially expressed cilia genes in patients' cells suggest a potential role of the protein arginine methyltransferase protein during ciliogenesis.

In **project 2**, I contributed to the identification of a heterozygous missense mutation in one of the non-muscle myosin genes in three family members with autosomal dominant eyeball malformations, including coloboma, ptosis and craniofacial features. Given the symptoms a Baraitser-Winter cerebro-fronto-facial syndrome (BWCFF) was suggested. Interestingly, the protein of interest is thought to interact with the only known BWCFF proteins, ACTB and ACTG1 and has been shown previously to be involved in the reorganization of the actin cytoskeleton. Indeed, in patients' cells, we observed an abnormal actin network. In zebrafish, a reduced expression of the gene of interest resulted in eye and muscle anomalies.

In **project 3**, Whole-genome sequencing was performed on patients with severe deafness and early-onset cataracts as part of a neurological, sensorial and cutaneous novel syndrome. A unique homozygous variant in intron 10 of the *PSMC3* gene, encoding the 26S proteasome ATPase ring subunit 5, was identified with a predicted local splice effect as a new donor site. Functional experiments in patients' fibroblasts indicated that these cells are unable to

compensate for proteotoxic stress. Two different *PSMC3* loss of function studies in zebrafish led to inner ear development anomalies as well as cataracts similar to the phenotype observed in patients.

This new finding can be an important step towards a better understanding of the pathophysiology of neurodevelopmental disorders and could possibly aid the search for therapeutic targets and pathways.