GHENT UNIVERSITY

FACULTY OF MEDICINE AND HEALTH SCIENCES

CIL-EYE

Functional characterization of potential ciliary genes involved in syndromic inherited retinal diseases

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SUMMARY

Inherited retinal diseases (IRDs) are a group of diseases that are caused by dysfunction or loss of photoreceptors or retinal pigment epithelium. They are amongst the most frequent causes of early-onset blindness and account for 5% of blindness worldwide. However, still 30-50% of patients diagnosed with IRD have an incomplete molecular diagnosis. The latter becomes increasingly important given the era of therapies for IRD. Moreover, apart from a molecular diagnosis, insight into the underlying pathogenic mechanisms is highly needed.

The general aim of this doctoral work was to identify and functionally characterize new genes and variants involved in syndromic and non-syndromic IRD.

First, autozygosity mapping combined with whole exome sequencing (WES) in a consanguineous family with syndromic IRD revealed a homozygous missense variant in *RCBTB1*. Further data mining of WES data revealed four additional homozygous missense variants in five unrelated families with non-syndromic and syndromic IRD. Overall, this study allowed to put forward *RCBTB1* as new gene for autosomal recessive IRD (**Paper 1**). A stable knockout model of *rcbtb1* was generated in *Xenopus tropicalis*, a diploid amphibian, to study the pathogenesis of *RCBTB1*-associated IRD. In the CRISPR/Cas9-mediated knockout model the effects of *rcbtb1* loss-of-function on retinal structures were evaluated and compared with the retinal features of *RCBTB1*-associated IRD in human. In addition, stress response was studied *in vivo* and *in vitro* using an *RCBTB1* knock-down human cellular model. This study resulted in **Paper 2**.

A third study focused on *CEP78*, a gene in which inactivating variants have recently been found to cause cone-rod dystrophy with hearing loss (CRDHL). We identified and functionally characterized the first *CEP78* missense variant in three unrelated CRDHL families, to evaluate if a 'milder allele' in *CEP78* could underlie the same phenotype so far only associated with inactivating variants. This study resulted in **Paper 3**.

Given the occurrence of a complex structural variant (SV) of the *CEP78* region in a patient with CRDHL, we further investigated the role of SVs in unsolved CRDHL patients. In two unrelated individuals we identified a total and partial gene deletion in a heterozygous and homozygous state, respectively. This study emphasized the importance of SV identification and characterization in Mendelian diseases and resulted in **Paper 4**.

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