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Underlying genetic mechanisms of hereditary dystrophies in retina and cornea

Frida Jonsson

Akademisk avhandling

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Avhandlingen kommer att försvaras på engelska.

Fakultetsopponent: PhD, Carlo Rivolta,

Department of Computational Biology, University of Lausanne, Switzerland

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Author Frida Jonsson

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Abstract

Inherited retinal and corneal dystrophies represent a group of disorders with great genetic heterogeneity. Over 250 genes are associated with retinal diseases and 16 genes are causative of corneal dystrophies. This thesis is focused on finding the genetic causes of corneal dystrophy, Leber congenital amaurosis (LCA), Stargardt disease and retinitis pigmentosa in families from northern Sweden. By whole exome sequencing a novel mutation, c.2816C>T, p.Thr939Ile, in Collagen Type XVII, Alpha 1 chain, *COL17A1*, gene was identified in several families with epithelial recurrent erosion dystrophy (ERED). We showed that the COL17A1 protein is expressed in the basement membrane of the cornea, explaining the mutation involvement in the corneal symptoms. We could link all the families in this study to a couple born in the late 1700s confirming a founder mutation in northern Sweden. Our finding highlights role of COL17A1 in ERED and suggests screening of this gene in patients with similar phenotype worldwide.

Furthermore the genetic causes in several retinal degenerations were identified. In one family with two recessive disorders, LCA and Stargardt disease, a novel stop mutation, c.2557C>T, p.Gln853Stop, was detected in all LCA patients. In the Stargardt patients two intronic variants, the novel c.4773+3A>G and c.5461-10T>C, were detected in the *ABCA4* gene. One individual was homozygous for the known variant c.5461-10T>C and the other one was compound heterozygote with both variants present. Both variants, c.4773+3A>G and c.5461-10T>C caused exon skipping in HEK293T cells demonstrated by *in vitro* splice assay, proving their pathogenicity in Stargardt disease. Finally, in recessive retinitis pigmentosa, Bothnia Dystrophy (BD), we identified a second mutation in the *RLBP1* gene, c.677T>A, p.Met226Lys. Thus, BD is caused not only by common c.700C>T variant but also by homozygosity of c.677T>A or compound heterozygosity. Notably, known variant, c.40C>T, p.R14W in the *CAIV* gene associated with a dominant retinal dystrophy RP17 was detected in one of the compound BD heterozygote and his unaffected mother. This variant appears to be a benign variant in the population of northern Sweden.

In conclusion, novel genetic causes of retinal dystrophies in northern Sweden were found demonstrating the heterogeneity and complexity of retinal diseases. Identification of the genetic defect in *COL17A1* in the corneal dystrophy contributes to understanding ERED pathogenesis and encourages refinement of IC3D classification. Our results provide valuable information for future molecular testing and genetic counselling of the families.

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