Rewriting the story of Inherited retinal diseases

Josephine Prener Holtan, MD, PhD
Institute of Clinical Medicine, Oslo University
Department of Ophthalmology, Oslo University Hospital

Key points:

- Inherited retinal diseases in Norway are both clinically and genetically heterogeneous.
- Phenotype–genotype characterization increases knowledge of prognosis and eligibility of treatment.
- ABCA4-retinal dystrophies should be classified into mild, moderate, and severe.

On June 10, 2021, Josephine Prener Holtan defended her thesis, "Inherited retinal diseases in Norway. Studies on phenotype and genotype characteristics," at the Institute of Clinical Medicine, University of Oslo (UiO). This project was conducted at the Department of Ophthalmology, Oslo University Hospital (OUH) under the supervision of Associate Professor Ragnheidur Bragadottir, Institute of Clinical Medicine, UiO, with co-supervisors Kaja Kristine Selmer MD, PhD, Department of Research and Innovation, Division of Clinical Neuroscience, OUH and the UiO, and Ketil Riddervold Heimdal, Department of Medical Genetics, OUH.

Inherited retinal diseases are a leading cause of vision loss in children and young adults. Most are currently untreatable and lead to irreversible retinal damage and blindness. Recent advances in the understanding of the underlying molecular causes have increased our knowledge about the diseases and have aided the development of the first gene therapy treatment. Inherited retinal diseases are a heterogeneous group; there are around 60 clinical diagnoses caused by monogenetic variants in over 270 genes. Consequently, the clinical expression, prognosis, and potential treatment targets vary significantly.

With the advent of gene therapy, understanding the clinical expression (phenotype) and molecular causes (genotype) of inherited retinal diseases is increasingly important. This thesis aimed to further investigate inherited retinal diseases in Norway by estimating the prevalence and providing a detailed analysis of the phenotypes and genotypes of these diseases. To achieve this, we developed a registry of patients with inherited retinal disease. The registry included detailed clinical and genetic data from 900 patients, and we conducted a population-based study of these data.

We estimated the prevalence of inherited retinal diseases in the southeast region of Norway to be at least 1:4000. The heterogeneous clinical spectrum included more than 40 different diagnoses. Non-syndromic retinitis pigmentosa was both the most common and the most genetically heterogenic diagnosis, associated with over 20 genes. The diagnostic yield of routine genetic testing from 2007 to 2018 was 32%. The most common disease-causing genes in this population were *ABCA4, USH2A, BEST1, RHO* and *RS1*. We performed additional descriptive studies on the clinical subgroups of autosomal dominant retinitis pigmentosa and ABCA4-retinal dystrophies. We identified and described a novel autosomal dominant retinitis pigmentosa phenotype named retinitis pigmentosa type 83 [MIM# 618173], caused by a pathogenic variant in *ARL3*.

Clinical Pearls:

- **Unsolved cases should be retested with high-throughput sequencing gene panels.**
- **Patients should be added to registries to ensure identification upon treatment eligibility.**
- **Follow-up data is warranted to increase knowledge of disease progression.**

The study of ABCA4-retinal dystrophies included 106 patients. We demonstrated that the clinical diagnosis of Stargardt disease did not correlate well with the prognosis of peripheral degeneration of the retina. Further, the study demonstrated a high carrier frequency for the loss of function splice variant c.5461-10T>C in the Norwegian population, compared to other studies of the *ABCA4* gene. A whole-genome analysis established a genetic diagnostic yield of 89%. In total, 15 new variants were identified, including a novel deletion and several rare deep intronic variants.

This was the first population-based study to include all inherited retinal disease diagnoses in Norway. Our findings greatly increase the understanding of this patient population and enable updated clinical recommendations for genetic diagnostics, better clinical follow-up regimes, and improved prognostic guidance.

Articles in the dissertation

1. Holtan JP, et al. Dominant ARL3-related retinitis pigmentosa. Ophthalmic Genet. 2019;40(2):124-128.
2. Holtan JP, et al. Inherited retinal disease in Norway - a characterization of current clinical and genetic knowledge. Acta Ophthalmol. 2020;98(3):286-295.
3. Holtan JP, Aukrust I, et al. Clinical features and molecular genetics of patients with ABCA4-retinal dystrophies. Acta Ophthalmol. 2021;99(5):e733-e746.