You have your mother's eyes:

The genetics of open-angle glaucoma in Finland

Perttu Johannes Liuska
Dept. of Ophthalmology, University of Helsinki; Eye Genetics Group, Folkhälsan Research Center

On December 1, 2023, Perttu Johannes Liuska defended his thesis, "Myocilin and the genetics of open-angle glaucoma in Finland," at the Dept. of Ophthalmology, University of Helsinki. The PhD project was conducted at the Dept. of Ophthalmology, Helsinki University Hospital and Eye Genetics Group, Folkhälsan Research Center. The supervisors were docent Joni A. Turunen, MD, and assistant Prof. Mika Harju, MD, Dept. of Ophthalmology, University of Helsinki, and Helsinki University Hospital.

Key points:

- Myocilin, the most frequent monogenic glaucoma gene, was population-associated, with its most common risk variant, p.(Gln368Ter), enriched in the Finnish population.
- The myocilin p.(Gln368Ter) variant was associated with glaucoma subtypes with elevated IOP in the Finnish population, including exfoliation glaucoma.
- *APOE ε4* demonstrated a protective effect against glaucoma in the Finnish population but with a weaker effect than for AMD

Glaucoma is characterized by progressive optic neuropathy that may lead to distinct patterns of visual field loss, and genetics can influence the risk of its development. Adult-onset forms tend to have a complex pattern of inheritance, whereas early-onset glaucoma, typically diagnosed before the age of 40 years, often exhibits a Mendelian inheritance pattern, either autosomal-dominant or recessive.

Myocilin (*MYOC*) was the first gene discovered in families with autosomal-dominant glaucoma, and it has subsequently been identified mutated in 2–4% of individuals with adult-onset glaucoma and 6–36% of individuals with juvenile-onset open-angle glaucoma (JOAG). Several other monogenic genes linked to open-angle glaucoma have been reported. More recently, some genetic factors such as apolipoprotein E4 (*APOE4*) have shown a protective effect against glaucoma.

We first assessed the clinical relevance of published *MYOC* variants and estimated their prevalence in various populations. We found six likely pathogenic missense variants, which were most prevalent in Asian populations. Furthermore, we identified five nonsense variants, with p.(Gln368Ter) being the most common risk variant for glaucoma in individuals of European ancestry, and with the highest population prevalence in the Finnish population. Pathogenic and likely pathogenic *MYOC* variants appeared to be population-associated. The allelic heterogeneity of *MYOC* adds complexity to gene testing and interpreting the results.

We then examined the association and penetrance of the *MYOC* p.(Gln368Ter) variant with different types of glaucoma in the Finnish population, using data from the FinnGen study. We confirmed the earlier findings of its association with open-angle glaucoma but could not replicate the association with normal-tension glaucoma, supporting the hypothesis that myocilin mutations primarily contribute to glaucoma pathogenesis by increasing intraocular pressure. This was the first large-population cohort analysis to detect that the variant was also robustly associated with exfoliation glaucoma.

In the third study, we identified germline variants in *MYOC* and 28 other known monogenic glaucoma genes in Finnish individuals with JOAG. We included 53 Finnish patients with JOAG from 50 pedigrees treated. Five had probably pathogenic mutations in *MYOC*, including one with *MYOC* p.(Gln368Ter). Of these, four had a family history suggesting dominantly inherited JOAG. Furthermore, one mother–son pair had a novel loss-of-function variant in *FOXC1*, and one patient had a homozygous likely pathogenic variant in *LTBP2*. All variants, except the homozygous *LTBP2*, suggested a dominant inheritance pattern. The genetic variants explained 14 % of JOAG in our cohort, which was low compared to other populations studied.

APOE4, a known risk factor for late-onset Alzheimer's disease, has been associated with a reduced risk of primary open-angle glaucoma and age-related macular degeneration. In the fourth study, we systematically quantified the associations of *APOE* haplotypes with age-related ocular diseases, using genetic and registry data from the FinnGen study. We detected a protective effect of *APOEε4* against glaucoma in the Finnish population, but the effect was weaker than for age-related macular degeneration. We could not show an association with exfoliation glaucoma, supporting the hypothesis that APOE is involved in retinal ganglion cell degeneration rather than intraocular pressure.

This thesis illuminates the genetics of open-angle glaucoma and JOAG in a genetically unique and homogeneous Finnish population. Myocilin was markedly population-associated, with its most common glaucoma risk variant, p.(Gln368Ter), enriched in the Finnish population. It is associated with glaucoma subtypes with elevated intraocular pressure, including exfoliation glaucoma. The protective *APOEε4* allele also had a high prevalence, but the allele demonstrated a relatively weak protective effect.

Future directions:

- The unique genetics of Finns might enable the identification of new glaucoma genes.
- A better molecular understanding of the disease is needed for future drug development.

References

1. Liuska PJ, et al. Prevalence of *MYOC* risk variants for glaucoma in different populations. *Acta Ophthalmol*. 2021 Nov;99(7):e1090-e1097
2. Liuska, PJ, et al. Association of the *MYOC* p.(Gln368Ter) Variant With Glaucoma in a Finnish Population. *JAMA Ophthalmol*. 2021 Jul 1;139(7):762-768
3. Liuska PJ, et al. Analysis of glaucoma genes in Finnish patients with juvenile open-angle glaucoma. *Acta Ophthalmol*. 2023 Nov;101(7):797-806
4. Liuska PJ, et al. Association of *APOE* Haplotypes With Common Age-Related Ocular Diseases in 412,171 Individuals. *IOVS*. 2023 Nov 1;64(14):33