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Integrating Genetics in Glaucoma Screening

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Précis: As additional glaucoma genes are identified and classified, polygenic risk scores will be refined, facilitating early diagnosis and treatment. Ensuring genetic research is equitable to prevent glaucoma blindness worldwide is crucial.

Purpose: To review the progress in glaucoma genetics over the past 25 years, including the identification of genes with varying contributions to the disease and the development of polygenic risk scores.

Methods/Results: Over the last 2 and a half decades, glaucoma genetics has evolved from identifying genes with Mendelian inheritance patterns, such as *myocilin* and *CYP1B1*, to the discovery of hundreds of genes associated with the disease. Polygenic risk scores have been developed, primarily based on research in Northern European populations, and efforts to refine these scores are ongoing. However, there is a question regarding their applicability to other ethnic groups, especially those at higher risk of primary open angle glaucoma, like individuals of African ancestry. Glaucoma is highly heritable and family history can be used for cascade clinical screening programs, but these will not be feasible in all populations. Thus, cascade genetic testing using well-established genes such as *myocilin* may help improve glaucoma diagnosis. In addition, ongoing investigations seek to identify pathogenic genetic variants within genes like *myocilin*.

Conclusions: The expanding availability of genetic testing for various diseases and early access to genetic risk information necessitates further research to determine when and how to act on specific genetic results. Polygenic risk scores involving multiple genes with subtle effects will require continuous refinement to improve clinical utility. This is crucial for effectively interpreting an individual's risk of developing glaucoma and preventing blindness.

Key Words: glaucoma, genetics, *myocilin*, polygenic risk score

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GLAUCOMA GENETICS ARE COMPLEX

Discovery of the glaucoma genes *myocilin*[1] and *CYP1B1*[2] led to a renaissance in the field of glaucoma genetics. However, a full decade later, these 2 genes were explaining only ~5% and 20% of primary open angle glaucoma (POAG) and primary congenital glaucoma (PCG), respectively. With the era of genome-wide association studies (GWAS), glaucoma genetics research accelerated, with the identification of the *LOXL1* gene[3] found to be associated with exfoliation, the *CAV1/CAV2* genes[4], and the *TMCO1* and *CDKN2BAS* genes found to be associated with POAG.[5] Identifying additional glaucoma genes forced a change from thinking of glaucoma as solely a monogenic (Mendelian) disease caused by a single gene mutation with a major effect to realizing most forms of glaucoma are polygenic. Polygenic diseases arise from the sum of many gene mutations with small effects combined to have a major effect. An analogy is that a Mendelian disease is like possessing a dollar bill, whereas a polygenic disease is akin to having a lot of coins (of different values) that, in total, add up to a dollar.

Mendelian genes for glaucoma have been known for over 25 years, and there are some recent good reviews[6,7] on the topic. New genes are being identified as further populations are studied, and some very rare pediatric syndromes with PCG have been described. These include the *SH3PXD2B* gene causing Frank-Ter Haar syndrome[8] and *GLIS3*, which may cause congenital[9] as well as adult glaucoma.[10] Populations with high rates of PCG have been studied most intensively, such as in Saudi Arabia,[11] where many patients' disease is explained by a single gene, *CYP1B1*. In other countries with lower rates of congenital glaucoma, such as Australia's 1/30,000[12], the majority of patients do not yet have a genetic explanation[13], even with intensive laboratory investigation.

Numerous GWAS have been conducted in POAG, with several major meta-analyses completed by the International Glaucoma Genetics Consortium facilitating the development of polygenic risk scores (PRS).[14–17] These studies have grown from including thousands of people with glaucoma and identifying a couple of genes to hundreds of thousands identifying hundreds of gene locations or Single Nucleotide Polymorphisms (SNPs). Work needs to continue; the largest GWAS meta-analysis to date (focusing on height) with the GIANT (*G*enetic *I*nvestigation of *AN*thropometric *T*raits) consortium felt that saturation had been reached with 5.5 million participants.[18] With glaucoma GWAS, there is a long way to go to achieve those numbers. Moreover, although these glaucoma GWAS have involved different ethnic groups, most participants have been Northern European in origin, and thus, the results may not be broadly accurate for glaucoma.

Ethnic Diversity in GWAS is Key

Africans have a higher clinical risk of POAG, but paradoxically, fewer of these individuals have been included in

glaucoma genetics research.[19] This is partly a function of limited funding for wide-scale genetics research in lesser-resourced populations and a problem that is relevant to all genetics research.[20] Efforts are being made to improve this situation.[21]

Studying ethnically diverse populations is also better for science in that it allows true mutations to be recognized. The 2 SNPs in LOXL1 that were found to be associated with exfoliation glaucoma illustrate this well.[3] Subsequent research in Asian populations showed that one of the SNPs was not associated with exfoliation and was protective against the condition.[22] Further studies in African populations showed that both SNPs were significantly associated with protection from exfoliation.[23,24] In combination, these studies showed that the 2 SNPs, while linked markers for risk in their specific populations of origin, were not the pathogenic mutations causing disease but were merely linked to the true, as yet unidentified mutations. Without this knowledge, we would be targeting research on these specific SNP changes when the SNPs are not directly involved.

Most cities and glaucoma clinics that service them are ethnically diverse. We conducted an audit of ethnicity in Australia's largest glaucoma clinic, located at the Royal Victorian Eye and Ear Hospital (RVEEH) in Melbourne, Victoria. Although most patients were of Anglo-Celtic origin, other ethnicities such as Chinese, Greek, Italian, Indian, German, Croatian, and Dutch were represented, and individuals with this heritage have been involved in some glaucoma GWAS. However, other minorities seen— Vietnamese, Maltese, Filipino, Sinhalese, Macedonian, Arab, Spanish, Hispanic, Tigrinya, Turkish, Polish, and Serb—have not participated extensively in glaucoma genetic studies. (Fig. 1) Thus, when offering genetic testing to these minorities, we cannot be sure that the results from international meta-analyses, which are predominantly derived from Northern European populations, will be applicable. A similar challenge will exist in other glaucoma clinics in cities with different proportions of these and other minority populations.

To rectify this challenge of understanding ethnic diversity and risk for glaucoma, we need to at least validate the PRS in these minority populations. In Australia, we have been funded to test and validate the PRS in many of the ethnic populations listed above. Moreover, GWAS from these populations will help strengthen the international meta-analyses.

Although these minorities can be recruited and tested in countries with good research funding, identifying and providing appropriate language translation of ethics/IRB consent and including normal controls for these minority groups is more challenging. It would be much easier to collect DNA from several hundred patients with glaucoma of Filipino or Vietnamese heritage in a glaucoma clinic in the Philippines or Vietnam, respectively. However, funding and appropriate ethics/IRB approval can be more difficult to obtain, and there may be restrictions on sending DNA out of the country. Despite these obstacles, we need to continue to build our datasets of genetically studied patients with glaucoma from different origins around the globe.

How will we Incorporate PRS into Clinical Care?

Current practices of clinical screening for glaucoma vary from country to country. Most guidelines, such as the 2022 US Preventive Services Task Force (USPSTF), do not recommend screening the general population, but glaucoma can be detected as an incidental finding during a routine eye examination (https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/primary-open-angle-glaucoma-screening). However, although targeted clinical screening of individuals with a history of glaucoma in a first-degree relative[25] and people with a myocilin mutation[26] may be useful, there are no clear consensus guidelines.

Potential Uses for PRS

A PRS can have significant utility by stratifying screening intensity according to one's risk. For example, 80% of first-degree relatives are not at high risk of glaucoma and could be discharged, with efforts and resources focused on carefully following the remaining 20% who are at high risk. In the case of people who are considered "glaucoma suspects," a PRS may provide insights as to who requires more intensive screening.

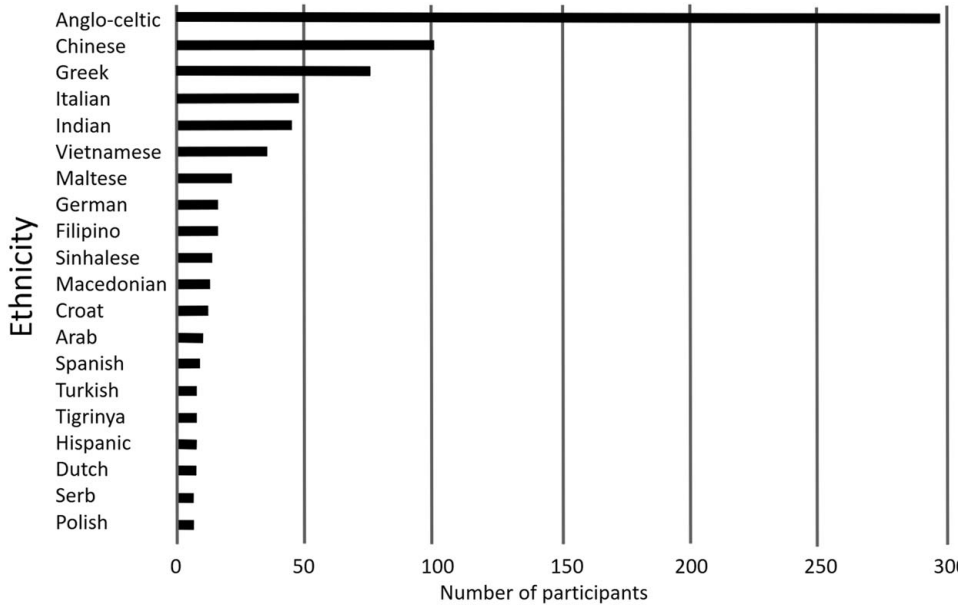

FIGURE 1. Representation of ethnicities for patients with glaucoma attending the glaucoma clinic at the RVEEH.

Outpatient clinic waiting lists are notoriously long, thus a PRS may facilitate efficient and effective triage of the patients most likely to develop glaucoma blindness. Alternatively, a PRS for glaucoma may temper or heighten the significance of incidental findings from genetic testing for other eye or non-eye-related diseases. Finally, in the future, population-wide testing could also utilize a glaucoma PRS to inform surveillance.

When do we Test, and When do we act on the Result?

Currently, newborn babies can be tested at, or even before, birth for genetic conditions. This will become much more common in the future, and this genetic data can be used to identify risks for many diseases, including glaucoma.

For those diseases that are actionable, such as glaucoma, for which clinical screening can be conducted and treatment commenced, this information is likely to be disclosed to the baby's family at some stage.

Thus, if a baby has a high risk of developing adult-onset POAG, when should the family be told, and when should the baby commence regular clinical testing for POAG? To answer this question, we need to be assured the PRS is accurate for POAG and confident it is valid for the child's ethnic background. We would also need to determine the optimal age to commence screening for a disease that typically has an onset in adulthood, as well as consider whether we should examine the parents of a child with a high PRS. In providing the relevance of and implications for genetic testing, health literacy is also a critical factor in either accepting the PRS or knowing how to respond or act on the information.

Family History in the Management of Glaucoma

Family history is just a proxy for a person's genetic risk. Glaucoma[27,28] and its related biometric traits[29] are highly heritable, and thus, an emphasis on being aware of a family history of glaucoma is an important tool in preventing glaucoma blindness. The Rotterdam Study found that the lifetime risk of first-degree relatives of patients with glaucoma developing the disease was 22.0% versus 2.3% in relatives of controls[30]; the Glaucoma Inheritance Study in Tasmania found that 40% of people with glaucoma have an affected first-degree relative.[31] Thus, cascade clinical screening for glaucoma can be an effective strategy to detect undiagnosed glaucoma.

In the Tasmanian targeted familial screening study, the number needed to screen was 19 to detect 1 new undiagnosed case.[25] This compared favorably with the population-based Blue Mountains Eye Study, where the number needed to screen was 68 people. Patients with glaucoma in the Glaucoma Inheritance Study in Tasmania were very willing to involve their families in a glaucoma screening study,[25] and promoting cascade clinical screening in families has led to a large increase in glaucoma examinations in Tasmania.[32]

Although family models had worked well in Tasmania[25], this may not always be the case. The Australian and New Zealand Registry of Advanced Glaucoma (ANZRAG)[33] was developed as a research tool to identify genes causing glaucoma by recruiting patients with severe or early-onset glaucoma and those with a family history of glaucoma. A further extension study of ANZRAG was Targeting At-Risk Relatives of Glaucoma cases for Early Treatment (TARRGET)[34], 1 arm of which investigated cascade clinical screening with the Lions Outback Vision Service in Western Australia. Uptake for cascade clinical screening was not as successful in remote Western Australia, possibly because smaller mining communities may not have the same family networks as rural farming towns. Similarly, cascade screening for glaucoma in Afro-Caribbean populations in South London reported poor participation.[35] The failure cited in this study was largely because affected individuals were typically retirees and were out of the country and not contactable or considered their families were too busy to attend the screening.

Improving Management in Myocilin Glaucoma

In genetic research, the most severely affected families are the first studied, and this may lead to a disease being construed as being more severe than it actually is. As more individuals are identified and confirmed with genetic testing, the phenotype usually broadens as mildly and unaffected people are identified, thereby altering the measured penetrance calculations. This has been illustrated very well over the last 25 years with the *MYOC* Gln368Ter (Gln368STOP), where the calculated risk of penetrance dropped as we moved from studies of severely affected families through to the general population. In 1998, Alward et al stated[36] that carriage of these mutations conveyed a significant risk of glaucoma; Craig JE et al, 2001,[37] with families from the Glaucoma Inheritance Study in Tasmania, reported the age-related penetrance for ocular hypertension, or POAG, was 72% at 40 years of age and 82% at 65 years of age; Han X et al, 2019,[38] with families from the ANZRAG, reported a penetrance of 56.1%; and Zebardast N et al, 2021,[39] using data from the UK Biobank, reported a penetrance of 25%.

Investigating the optic nerve appearances in younger adults within high-penetrance myocilin pedigrees suggested that glaucomatous optic neuropathy did not start until people developed elevated intraocular pressure. Thus, clinical screening for *MYOC* glaucoma incorporates monitoring intraocular pressure.[40] Within MYOC glaucoma pedigrees, not everyone who carries the genetic mutation develops glaucoma; moreover, not everyone in the family who has

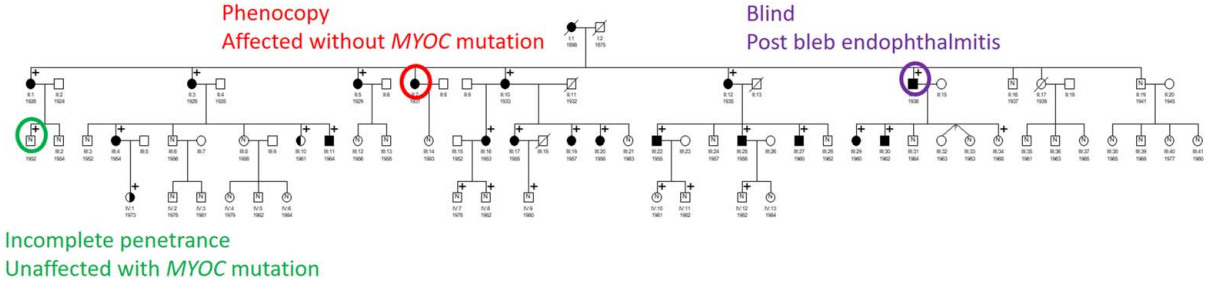

FIGURE 2. Myocilin Thr377Met pedigree showing 3 extreme variant individuals with incomplete penetrance, a phenocopy, and blindness secondary to complications of treatment.

glaucoma will have a MYOC mutation. These are examples of incomplete penetrance and phenocopies.[41] (Fig. 2).

Community Attitudes to Genetic Testing

Understanding the attitudes of the community is essential when considering genetic testing to aid disease diagnosis. An early study explored the attitudes to predictive genetic testing for myocilin glaucoma in a large Australian family.[42] Most participants wished to know their results after genetic counseling, and 26/27 (96%) agreed the counseling session was necessary. Of the 43 participants surveyed 5 years after their initial counseling session, none reported any problems relating to the predictive testing, although 2 had been asked about DNA testing by insurance companies. However, 5/24 (21%) who had been informed they did not carry the mutation were unsure if they carried the mutation 5 years after their counseling, while all 19 mutation carriers, who were being examined annually, correctly recalled their mutation status. Thus, while the uptake of genetic testing was positive, retention of information may require a different approach to the initial disclosure of the results. Health literacy could also be an important factor in the understanding and retention of health information.[43]

A further study investigated attitudes towards PRS in people with glaucoma recruited through ANZRAG.[39] Here, 1169/2369 (49%) responded, where 69.4% of individuals (798/1150) indicated a keenness to being tested before a diagnosis had it been available. Moreover, people who were interested in testing were more likely to change their eye health-seeking intentions and to recommend testing to family members and others, as well as to undergo testing for prognostication.[44]

Can we be Certain That a Mutation is Pathogenic?

The National Institutes of Health in the United States have created the Clinical Genome Resource (ClinGen) for which Variant Curation Expert Panels (VCEP) are using guidelines from the American College of Medical Genetic and Genomics (ACMG) and the Association for Molecular Pathology (AMP). Genetic variants are classified as pathogenic, likely pathogenic, variant of unknown significance (VUS), likely benign, and benign. The original attempt at classifying variants in Myocilin as pathogenic and benign was published in 1998. With respect to the Gly364Val, Gln368STOP, Thr377Met, Tyr437His, and Ile477Asn mutations, we believe that enough patients have been studied to indicate that the penetrance is sufficiently high to state that carriage of these mutations conveys a significant risk of glaucoma.[36] The recent re-evaluation of myocilin variants by the VCEP has confirmed that these variants are pathogenic[45] (Fig. 3).

Alward et al 1998 classification		Variant	VCEP classification
Probable disease-causing		Gln19His	Likely benign
		Arg82Cys	Likely benign
		Trp286Arg	VUS
		Thr293Lys	Likely benign
		Pro361Ser	VUS
	#	Gly364Val	Likely pathogenic
	#	Gln368Ter	Pathogenic
	#	Thr377Met	Pathogenic
		Asp380Gly	VUS
		396INS397 (Glu396dup)	Likely pathogenic
		Arg422His	VUS
	#	Tyr437His	Pathogenic
		Ala445Val	Likely benign
		Arg470Cys	VUS
	#	Ile477Asn	Likely pathogenic
		Lys500Arg	Likely benign
Unlikely to be disease-causing		bp -83 (G>A)	N/A
		Cys9Ser	VUS
		Asn73Ser	VUS
		Arg76Lys	Benign
		Ser203Phe	VUS
		Glu352Lys	Benign
		Lys398Arg	Likely benign
		Arg422Cys	VUS
		Ser425Pro	VUS
		Tyr473Cys	VUS
		Val495Ile	VUS
Synonymous - unlikely to be disease-causing		Pro13Pro	Benign
		Gly122Gly	Likely benign
		Leu159Leu	Benign
		Thr204Thr	Benign
		Lys266Lys	VUS
		Thr285Thr	Benign
		Thr325Thr	Benign
		Val329Val	N/A
		Tyr347Tyr	Benign
		Glu396Glu	Benign
		Val439Val	Likely benign

FIGURE 3. List of myocilin variants showing original Alward 1998[36] classification with pathogenic mutations marked # on the left with VCEP classification on the right.[45]

The Future…is Bright, if Uncertain

Is routine, universal, genetic testing for glaucoma with PRS inevitable? The answer is "very likely". Genetics will help us identify who to clinically screen, who to follow, who to treat, and when to begin treatment.

But is it better not to know? "*Primum non nocere*" (first, do no harm). If we over-treat someone with a spurious genetic result, this may cause harm from treatment. If we falsely reassure someone that they do not have a specific genetic risk when they may have other genetic risk factors, they could miss being diagnosed. Another major research question remains: "Do we treat a person with a mild increase in intraocular pressure but with a high genetic risk?" This could be done with a milder agent to lower intraocular pressure (eg, timolol or Selective Laser Trabeculoplasty [SLT]). Or might long-term protection of the optic nerve with a simple agent (eg, oral niacin) prevent glaucoma?

Our understanding of glaucoma genetics is proceeding at an incredibly swift pace. While there is evidence genetic testing and PRS may support a stratified approach to screening, facilitating early diagnosis of disease and mitigating glaucoma blindness, there is much we still need to know. Identifying strategies to implement efficient and cost-effective methods to diagnose glaucoma at its earliest is critical to reducing the burden of glaucoma blindness. Equitable access globally to these strategies is essential.

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