Predicting the genetic risk of glaucoma

Ayub Qassim and Owen M Siggs (Flinders University, Australia)

Glucoma is the leading cause of irreversible blindness globally and is one of the most heritable human diseases. Labelled the ‘silent thief of sight’, primary open angle glaucoma is a progressive neurodegenerative disease of the retinal ganglion cells that can be treated by reducing intraocular pressure. Treatment is highly effective in preventing glaucoma vision loss; however, as it is asymptomatic in its early stages, many individuals with glaucoma are diagnosed only after a considerable amount of vision has already been lost. Given the high heritability of glaucoma, genetic risk profiling is now being explored as a way to identify individuals at the highest risk of developing glaucoma and those who will require the most intense treatment. Combining rare glaucoma-causing variants in single genes with more common genetic risk variants across many genes means that clinicians may soon be able to effectively stratify glaucoma risk across whole populations. This promises to maximize the efficiency of healthcare spending by prioritizing surveillance of high-risk individuals and reducing irreversible vision loss through early commencement of vision-saving treatments.

Glaucoma is a leading cause of blindness

Glucoma is a progressive neurodegenerative disease of the optic nerve that results from the accelerated death of retinal ganglion cells. This leads to a progressive and irreversible loss of peripheral vision that advances centrally if left untreated, ultimately leading to blindness. Glaucoma is the leading cause of irreversible blindness globally, with epidemiological studies estimating that over 60 million people are affected worldwide. This number is expected to double over the next two decades, primarily due to an ageing population, since old age is the single biggest glaucoma risk factor.

Clinically, glaucoma is an umbrella term: it encompasses a group of optic neuropathies that clinically present with a characteristic ‘cupping’ of the optic nerve head, often with an elevated intraocular pressure (IOP) (Figure 1). The enlarged optic cup seen clinically is a direct visualization of lost retinal ganglion cell axons as they traverse posteriorly to the occipital cortex in the brain. Although the pathogenesis of glaucoma is not fully understood, IOP-mediated optic nerve injury is a key mechanism in disease onset and progression. It is widely accepted that elevated IOP causes mechanical stress and strain on retinal ganglion cell axons and surrounding support structures, disrupting their axonal transport system ultimately leading to cell death via apoptosis.

An important anatomical structure in glaucoma pathogenesis is the drainage angle, where the aqueous humour produced behind the iris drains out of the eye and into the venous network. Narrowing or closure of this drainage angle can lead to angle closure glaucoma, where acute increases in IOP can cause pain and visual symptoms. But raised IOP and glaucoma can also occur in the presence of an open drain angle — this is the hallmark of primary open angle glaucoma (POAG), the most common type of glaucoma worldwide. Unlike acute angle closure where pain and vision disturbance are often the presenting complaints, POAG is often asymptomatic until the disease becomes advanced and severe vision loss is noticed.

Glucoma is readily diagnosed by examining the optic disc by slit-lamp microscopy, measuring IOP and performing visual field testing using automated perimetry. Once diagnosed, treatment is widely available and highly effective. IOP-lowering treatment options include topical eye drops (typically by reducing aqueous humour production, increasing outflow or both), laser therapy or incisional surgery (to open the drainage angle and increase outflow) and surgically implantable drainage devices. The often slowly progressive and asymptomatic nature of the disease, combined with safe and effective treatment options, means that early diagnosis of POAG is the key to saving vision, which would otherwise be irreversibly lost.

Monogenic and polygenic risk in glaucoma

First-degree relatives of individuals with POAG have an approximately ninefold greater risk of glaucoma than the general population. Heritability studies have shown that glaucoma is one of the most heritable common diseases, more so than other common diseases such as...
cardiovascular disease or breast cancer. This high genetic contribution, combined with the ease of diagnosis and good treatment outcomes, makes glaucoma an ideal disease target for genetic risk prediction studies.

Family-based genetic linkage analysis has identified at least three monogenic causes of POAG (MYOC, TBK1, OPTN), with pathogenic variants in the myocilin gene (MYOC) being the most common. Heterozygous pathogenic variants in MYOC typically cause a characteristically high-pressure glaucoma at a young age, while heterozygous pathogenic variants in TBK1 or OPTN cause normal-pressure glaucoma where progressive vision loss occurs despite IOP remaining within normal limits. Rare, heterozygous, pathogenic variants in all of these genes are widely used in glaucoma risk prediction, in particular for counselling, testing and surveillance of family members. If found to be a carrier, regular screening of at-risk family members can lead to earlier glaucoma diagnosis and reduced glaucoma vision loss.

Despite this, these known monogenic causes explain less than 5% of all POAG cases. We now know that most of the genetic contribution to POAG risk and other ocular traits associated with POAG (such as optic disc morphology and high IOP) is polygenic: that is, the high heritability of these traits is due to many hundreds or thousands of genetic variants, each with a much smaller impact (or effect size) than their monogenic counterparts (Figure 2). The combined effect of these variants helps explain how POAG can cluster in families, but without following a defined pattern of Mendelian inheritance. This polygenic architecture is similar to other complex genetic traits such as height, or common diseases such as coronary artery disease.

The study of polygenic risk factors for many diseases and traits (including POAG, IOP and optic disc morphology) has rapidly accelerated with the development of population-scale biobanks, where clinical and genetic data are collected in parallel. Genome-wide association studies of over a 100,000 people with ocular phenotypic data have allowed the discovery of over a hundred common genetic variants associated with POAG, IOP or vertical optic cup-to-disc ratio (a quantitative measure of optic disc cupping).

**Predicting genetic risk in glaucoma**

A polygenic risk score (PRS) is a quantitative summary of an individual’s genetic risk for a particular trait. When a person is genotyped or has their genome sequenced, the resulting output is typically a list of genetic variants (or differences from a gold-standard ‘reference’ genome) that this person harbours. This list of genetic variants can then be compared to a list of disease-associated variants discovered by large genetic association studies. In its simplest form, a PRS is the sum of disease-associated variants an individual is carrying. Often, however, each variant is weighted by its relative impact (or ‘effect size’), such that risk variants with higher effect sizes are...
assigned higher scores than risk variants with lower effect sizes. In some cases, a PRS can be calculated using the risk scores for millions of genetic variants. This score is then expressed as a percentile risk relative to a reference population to allow clinical interpretation and communication (Figure 3).

The application of PRS in predicting POAG risk has been a major success in the study of common complex diseases. Taking advantage of other heritable ocular traits strongly associated with glaucoma, a multitrait glaucoma PRS was developed encompassing risk alleles associated with elevated IOP, optic cup morphology and glaucoma diagnosis. This approach harnesses the powers of large genetic association studies from multiple cohorts across multiple glaucoma-related traits.

The glaucoma PRS is highly informative of the risk of developing POAG, with people in the highest risk decile of the PRS having a 15-fold higher risk of developing advanced glaucoma relative to the lowest decile. Furthermore, the PRS is strongly associated with higher IOP, a younger age at glaucoma diagnosis, a higher number of affected family members and a higher likelihood of requiring incisional surgery for glaucoma management. Importantly, carriers of one of the most common pathogenic monogenic variants (MYOC Gln368Ter), who also inherit a high glaucoma PRS, have a higher risk of developing glaucoma than MYOC variant carriers with a low PRS — in other words, common risk variants included in a glaucoma PRS can influence the penetrance of rarer ‘monogenic’ variants.

In summary, PRS can be used to inform the risk of developing glaucoma, and disease severity in the long term, and can be combined with known demographic, genetic and clinical risk factors to further improve risk stratification (Figure 4).
The future of glaucoma genetic risk prediction

Combining genetic and clinical information to make evidence-based, individualized treatment decisions has been a holy grail of personalized medicine. The development of genetic risk scores has been a key step in translating the results of genome-wide association studies into clinically meaningful risk prediction tools. POAG is an ideal case to apply genetic risk prediction as it is highly heritable, asymptomatic until its late stages, has a progressive and irreversible natural history and has effective and safe treatment options that prevent vision loss.

Genetic risk stratification for glaucoma can be implemented as a tool to guide glaucoma screening. Previously, community-based screening protocols for glaucoma were not cost-effective due to a high false-positive rate with the screening modalities used. However, incorporating genetic risk stratification is a promising means of identifying individuals at the highest risk of developing glaucoma for screening. This will improve pre-test probabilities and detection rates and, thus, cost-effectiveness, of glaucoma population screening.

Current efforts to identify the earliest stages of glaucoma have led to many individuals to be diagnosed as ‘glaucoma suspects’. These individuals require regular follow-up to establish if they will ultimately develop glaucoma. Increased access to advanced retinal imaging in community optometry practices, combined with an ageing population, has resulted in a large influx of glaucoma suspect referrals to specialist glaucoma clinics. Often, these individuals are monitored for years with only limited clinical insight into their likely disease trajectory. Genetic risk scores may help identify individuals who warrant more urgent or more regular reviews, and possibly also earlier intervention, allowing finite healthcare resources to be focussed on higher-risk individuals and minimizing unnecessary interventions or intensive monitoring of lower-risk individuals.

Genetic testing for glaucoma risk prediction could conceivably be implemented in at least three different contexts: in specialist glaucoma clinics (as described above), primary care (optometry or general practice) or even in a direct-to-consumer setting. Once a person has been genotyped or had their genome sequenced for any reason, a PRS can readily be calculated in silico using this data for any number of diseases or traits and recalculated as these scores are refined and improved over time. Because germline genetic variation is stable throughout life, raw genotyping data can be generated once from a single blood or saliva sample (and perhaps embedded in an individual’s medical record), and then be used for a whole range of diseases and genetic risk predictions over that individual’s lifetime. Genetic prediction can be informative at both the community and tertiary clinician levels to inform the risk of disease and provide deeper insight into disease phenotype.
Nevertheless, although genetic risk prediction has made enormous progress over the last decade, barriers to its clinical application remain. A disproportionate number of genome-wide association studies have been conducted on populations of European ancestry, limiting the utility of genetic risk prediction tools derived from them in other ancestries. Mixed ancestry biobanks are being established to fill this gap, which will allow larger cross-ancestry genetic association studies. Education is also needed to enable treating clinicians to interpret, communicate and apply this information for improving health outcomes. Finally, high-quality evidence from randomized controlled trials is needed to support the clinical utility of genetic risk prediction in glaucoma to improve clinical care.

Further reading

- Sugrue, L.P. and Desikan, R.S., 2019. What are polygenic scores and why are they important? JAMA, 321(18), pp.1820–1821.

Ayub Qassim is a clinician-scientist, currently finishing his PhD on novel clinical and genetic risk factors for glaucoma progression at Flinders University under the supervision of Professor Jamie Craig. Email: ayub.qassim@flinders.edu.au

Owen Siggs is an early-career clinician-scientist and a Practitioner Fellow in the Department of Ophthalmology at Flinders University, with a research focus on the clinical impact of genetic variation. Email: owen.siggs@flinders.edu.au