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Genetic Determinants of Intraocular Pressure

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Abstract

Intraocular pressure (IOP) is the cardinal and only modifiable risk factor for glaucoma, the leading cause of irreparable blindness worldwide. Twin and family studies estimate the heritability of IOP to be 40–70%, and linkage studies for IOP have identified numerous loci. Mutations in *MYOC* can cause markedly elevated IOP and aggressive glaucoma often requiring surgical intervention. However, the majority of the genetic basis for raised IOP and glaucoma in populations is complex, and recent large genome-wide association studies (GWASs) have identified over 100 common variants that contribute to IOP variation. In combination, these loci are predictive for primary open-angle glaucoma in independent populations, achieving an area under the receiver operating characteristic curve of 76% for high-pressure primary open-angle glaucoma; this suggests the possibility of targeted screening in the future. Additionally, GWAS findings have identified important biological pathways underlying IOP regulation, including lymphangiogenesis and lipid metabolism, providing novel targets for new therapies.

INTRODUCTION

IOP: intraocular pressure

AH: aqueous humor

TM: trabecular meshwork

SC: Schlemm's canal

RGC: retinal ganglion cell

POAG: primary open-angle glaucoma

Intraocular pressure (IOP) is an ocular trait reflecting the fluid pressure within the eye. The aqueous humor (AH) is a transparent fluid that fills both the anterior and posterior chambers of the anterior segment of the eye, providing nutrition and contributing to the homeostasis of avascular ocular tissues (Goel et al. 2010). The IOP is determined by the balance between AH secretion by the ciliary body and resistance against its outflow (De Groef et al. 2016). The majority of AH (more than 80% of total outflow) is drained through the trabecular meshwork (TM) and Schlemm's canal (SC), exiting into the episcleral veins and then into the systemic cardiovascular circulation (Carreon et al. 2017, Ho et al. 2019); this is known as the conventional outflow pathway. The TM, enclosed by trabecular cells, is made up of collagen beams. It is a lamellar structure that is surrounded by extracellular connective tissue matrices (Acott et al. 2014, Kaufman et al. 1999, Tamm et al. 2015). Adjacent to the TM, at the juxtacanalicular region, is the SC (Keller & Acott 2013). The SC encircles the eye and has a lymphatic-like phenotype and endothelial lining (Aspelund et al. 2014). The juxtacanalicular region, together with the SC and TM, is a major site of resistance to AH flow; pathology in this region can lead to increased IOP (Carreon et al. 2017). Alternatively, a proportion of AH leaves the eye through the unconventional outflow route, also termed the uveoscleral outflow pathway (Karpinich & Caron 2014); fluid passes through the interstitium of the ciliary body into the suprachoroidal space and then via the sclera into the orbit and is drained via the orbital vessels (Kaufman et al. 1999). The conventional outflow pathway is pressure dependent, whereas uveoscleral outflow is thought to be pressure independent (Alm & Nilsson 2009).

INTRAOCULAR PRESSURE AND ITS RELEVANCE TO GLAUCOMA

The homeostasis of IOP is important for ocular health. Raised IOP is the cardinal and only modifiable risk factor for glaucoma (Chan et al. 2017), the leading cause of irreversible blindness worldwide. Glaucoma is a chronic, progressive, degenerative disease of the optic nerve that is clinically distinguishable from other optic neuropathies by a characteristic optic nerve head appearance and pattern of visual field loss (Weinreb et al. 2014). Loss of vision in glaucoma is a functional consequence of the loss of retinal ganglion cells (RGCs) and, if left untreated, can lead to blindness. The loss of RGCs and supporting glial and vascular tissue results in the typical appearance of optic disc cupping; this is in contrast to other optic neuropathies, which usually result in optic atrophy (Weinreb et al. 2014). Glaucoma can be classified as either primary or secondary (depending on whether there is a discernible underlying cause such as pseudoexfoliation or uveitis) and as either open-angle or angle-closure (depending on whether there is obstruction of aqueous drainage at the iridocorneal angle by the iris) (Weinreb et al. 2014). The most common form of glaucoma is primary open-angle glaucoma (POAG).

Richard Banister, a seventeenth-century British ophthalmologist, was the first to link high IOP with glaucoma (Banister 1622); later, Adolf Weber and Albrecht von Graefe further advanced the theory that glaucoma was a disease of optic nerve excavation caused by elevated IOP (see Weber 1855). Advances in measurement of IOP facilitated the study of its role in health and disease. In particular, the principles of applanation (measurement of IOP through the application of force sufficient to flatten the cornea) were pioneered in the nineteenth century by Imbert (1885) and Fick (1888), which paved the way for the first modern applanation tonometer in the mid-twentieth century (Goldmann 1955).

Population-based studies have demonstrated that higher IOP is associated with both prevalent and incident POAG across different continents and ethnicities (Jiang et al. 2012, Le et al. 2003, Leske et al. 2008). It is not specifically raised IOP above the normal range (i.e.,

IOP > 21 mm Hg) that is associated with POAG; the increased risk is apparent across the entire range of IOP. Therefore, a person with an IOP of 14 mm Hg is at higher risk of developing POAG than a person with an IOP of 12 mm Hg, even though both people have relatively low IOP. Longitudinal studies have reported an increased risk of incident POAG of 10–18% per 1 mm Hg higher IOP at baseline (Jiang et al. 2012, Kim et al. 2011, Le et al. 2003, Leske et al. 2008, Sommer et al. 1991). There is evidence that the shape of the IOP–POAG relationship is exponential rather than linear; the increase in risk of POAG per 1 mm Hg increase in IOP is greater at higher levels of IOP (Jiang et al. 2012). The traditional definition for raised IOP, or ocular hypertension (OHT), is based on the observed mean IOP plus twice the standard deviation within a population. The cutoff value of 21 mm Hg was derived from two population-based studies using Schiotz (Leydhecker et al. 1958) and Goldmann applanation tonometry (Hollows & Graham 1966). The relative risk of developing POAG is much higher for a person with OHT compared to a person with IOP ≤ 21 mm Hg; however, since there are many more people with IOP ≤ 21 mm Hg than with OHT, the absolute numbers of people with POAG are not necessarily greater among those with baseline IOP > 21 mm Hg. In other words, the proportion of patients with POAG that are classified as normal-tension glaucoma (IOP ≤ 21 mm Hg) at diagnosis is not necessarily small and ranges from 20% to 90% depending on the population (Iwase et al. 2004).

OHT: ocular hypertension

THE ROLE OF INTRAOCULAR PRESSURE IN GLAUCOMA PATHOGENESIS

The pathological processes by which higher IOP causes glaucoma remain to be fully elucidated. The biomechanical theory of glaucoma proposes that IOP mechanically induces glaucomatous changes in the optic nerve (Burgoyne 2011). There is considerable evidence locating the primary site of RGC injury in glaucoma to the optic nerve head, and specifically to the level of the lamina cribrosa (Anderson & Hendrickson 1974, Quigley & Anderson 1976, Quigley et al. 1981). RBC axons pass through pores in the lamina cribrosa, and it is in this location that the axons are thought to be susceptible to mechanical forces from IOP. The physical response of the optic nerve head to IOP depends on the level of IOP, collagen fiber organization in the lamina cribrosa and surrounding sclera, the morphology of the optic nerve head, and the overall biomechanical properties of the 3D load-bearing connective tissue architecture of the optic nerve head (Strouthidis & Girard 2013). Depending on these factors in an individual, a threshold may be reached where higher IOP results in damage to RGCs; this may occur via interrupted axoplasmic flow and supply of nutrients, altered blood flow (physical compression of capillaries), or mechanotransduction (the conversion of mechanical stimuli to chemical signals at a cellular level) (Strouthidis & Girard 2013). Lowering of IOP, using medical, laser, or surgical treatment, is the only proven treatment strategy to prevent glaucoma in people with OHT (Kass et al. 2002) or to slow disease progression in patients with established glaucoma (Garway-Heath et al. 2015, Leske et al. 2003).

INTRAOCULAR PRESSURE AS AN ENDOPHENOTYPE FOR GLAUCOMA

Given the critical role of IOP in the development, progression, and treatment of glaucoma, it may be considered a mediating factor in addition to being a risk factor. Therefore, it is likely that understanding the factors that underlie IOP variation will in turn allow us to understand some of the pathophysiological processes underlying glaucoma. Numerous population-based studies have examined sociodemographic, systemic, and ocular associations with IOP (Khawaja et al. 2016). Independent associations with higher IOP have been observed in men and in people with higher

blood pressure (particularly systolic), higher body mass index, shorter height, and more myopic refraction (Foster et al. 2011, Khawaja et al. 2016). More recently, with the development of molecular genetic tools and the improvement of the computational methods, studies have examined the genetic determinants of glaucoma with considerable success. The studies reviewed in this article make it clear that IOP is a strong endophenotype for glaucoma. That is, a large proportion of the identified genetic causes of IOP are also associated with glaucoma in independent studies. The endophenotype approach of examining determinants of IOP to learn about glaucoma pathophysiology has distinct advantages. First, one can learn about the genetic determinants of IOP by examining large healthy cohorts, as IOP varies by more than twofold even in normal populations (Chan et al. 2016, 2017). Second, glaucoma case ascertainment is complex and can vary greatly according to the case definition used (Wolfs et al. 2000); IOP is an objective parameter that is less influenced by between-study variability in definitions. Third, there may be greater statistical power for identifying associations with a continuous outcome parameter compared to a binary outcome.

SNP: single-nucleotide polymorphism

GWAS: genome-wide association study

FAMILY AGGREGATION AND HERITABILITY STUDIES FOR INTRAOCULAR PRESSURE

Several studies have demonstrated the heritable nature of IOP. The lifetime risk of raised IOP (OHT) was almost seven times higher (42.5% versus 6.7%) in individuals with a family history of POAG compared to general population controls in the Rotterdam studies (Wolfs et al. 1998). Additionally, IOP measurements have been shown to be strongly correlated among family members; IOP is most strongly correlated between first-degree family pairs ($r = 0.13–0.18$), but the correlations progressively wane in avuncular relationships and in more distant cousin pairs (Duggal et al. 2005, Klein et al. 2004). The increased IOP correlation observed with closer degrees of relationship suggests that a mixture of heritable and nongenetic, or environmental, factors is the most likely explanation for IOP variability in the population (Duggal et al. 2005).

A more accurate assessment of the relative importance of genetic versus environmental determinants of IOP variation in the population is often achieved using methods estimating heritability. Generally, all of these methods compare the degree of correlation of IOP measurements between any pairs of individuals and the degree of shared genetic ancestry between members of the same pair. At their simplest, these methods compare the correlation observed in monozygotic twins, who are virtually identical in terms of their DNA and broadly share the same living environment in the early years of life, with correlations observed among pairs of dizygotic twins, who share only half of the DNA that they inherited from their parents and have similarly shared environmental exposures compared to monozygotic twin pairs. Since any difference between the two correlation coefficients can safely be attributed to the extra 50% genetic allele sharing in monozygotic twins, one can assume that, the greater is the difference, the greater is the contribution of genes to the trait being examined (Falconer 1981). This principle can be further extended, using more sophisticated methods, into more variable degrees of relatedness in a family, and researchers can even take advantage of the small proportion of shared genetic identity that any two individuals in the general population derive from the founders of their ancestral populations (Yang et al. 2017).

Several twin and family studies have estimated the heritability of IOP (**Table 1**; **Figure 1**). Most studies converge in their estimates of heritability in the range of 0.4–0.7 (Asefa et al. 2019, Sanfilippo et al. 2010). The variation in heritability estimates between studies may in part be due to varying levels of environmental exposures between populations. Studies also varied in their IOP measurement methods. **Table 1** also presents single-nucleotide polymorphism (SNP)-based IOP heritability estimates from genome-wide association studies (GWASs); these estimates only

Table 1 A list of published heritability studies for intraocular pressure

Authors	Year of publication	h^2	Ethnicity	Study design	*N*
Levene et al. (1970)	1970	0.41	European	Family	91
		0.49	European	Family	68
		0.48	European	Family	67
		0.54	European	Family	60
		0.71	European	Family	35
Kalenak & Paydar (1995)	1995	0.65	Mixed	Twins	186
Klein et al. (2004)	2004	0.36	European	Family	514
Chang et al. (2005)	2005	0.29	Mixed	Family	726
		0.35	European	Family	531
		0.14	African	Family	195
Duggal et al. (2005)	2005	0.18	European	Family	3,292
		0.30	European	Family	2,250
		0.04	European	Family	1,430
		0.26	European	Family	1,020
Parssinen et al. (2007)	2007	0.64	European	Twins	380
van Koolwijk et al. (2007)	2007	0.35	European	Family	2,457
Carbonaro et al. (2008)	2008	0.62	European	Twins	844
		0.71	European	Twins	343
		0.74	European	Twins	343
		0.69	European	Twins	688
Carbonaro et al. (2009)	2009	0.33	European	Twins	688
		0.64	European	Twins	688
		0.69	European	Twins	688
Zheng et al. (2008)	2008	0.67	East Asian	Twins	946
Charlesworth et al. (2010)	2010	0.42	European	Family	630
Lee et al. (2010)	2010	0.48	East Asian	Family	860
Lee et al. (2012)	2012	0.48	East Asian	Family	1,431
		0.47	East Asian	Family	859
		0.51	East Asian	Family	806
Freeman et al. (2013)	2013	0.79	European	Family	94
		0.94	European	Family	94
		0.53	European	Family	94
Kim et al. (2014)	2014	0.36	East Asian	Family	9,700
Ge et al. (2017)	2017	0.20	Mixed	GWAS	21,953
		0.27	Mixed	GWAS	21,949
		0.25	Mixed	GWAS	11,461
		0.33	Mixed	GWAS	11,398
		0.18	Mixed	GWAS	10,555
		0.25	Mixed	GWAS	10,551
Springelkamp et al. (2017)	2017	0.13	European	GWAS	29,240

Data from previously published reviews and meta-analyses (Asefa et al. 2019, Sanfilippo et al. 2010). Abbreviation: GWAS, genome-wide association study.

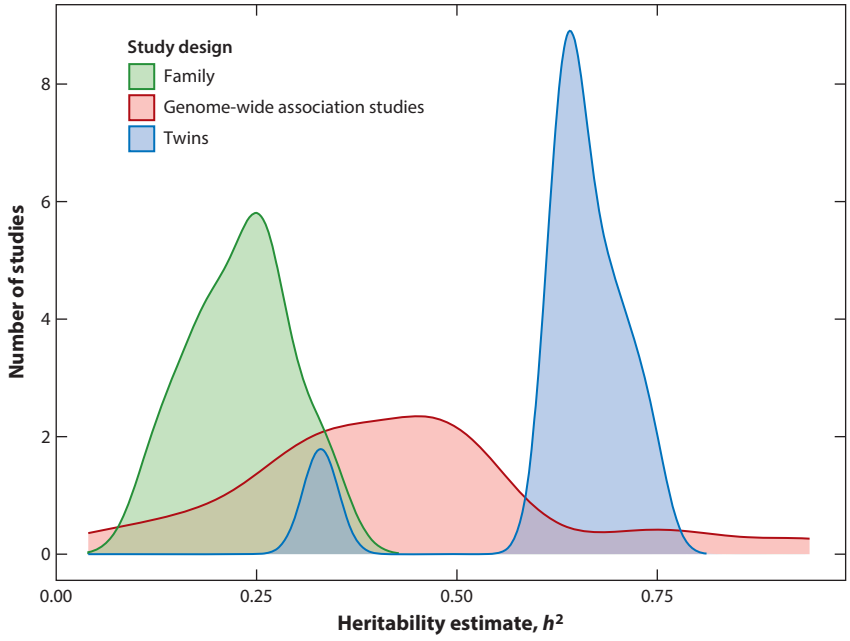

Figure 1

Distribution of heritability estimates from published studies, according to the study design used. Data used were taken from Asefa et al. (2019).

include that proportion of variance that can be explained by SNPs that are included in the genotyping platform used or directly inferred through imputation. For this reason, SNP-based heritability estimates are always lower than the true heritability by virtue of the genotyping information that is always missing in any platform (Visscher et al. 2008). Notably, the IOP heritability estimates derived from twin samples are consistently higher than estimates calculated in extended families (**Figure 1**). These differences are explained by the fact that twin siblings share a significantly higher proportion of environmental factors compared to nonsiblings. Genetic heritability is therefore not an intrinsic constant property of any phenotype, but instead can vary widely according to the environmental context in which the genes operate. Interestingly, the results of the interplay between genes and environments become more pronounced with age, as heritability is inversely correlated with age (Asefa et al. 2019).

IDENTIFYING INTRAOCULAR PRESSURE GENES THROUGH FAMILY STUDIES

Genome-Wide Linkage Scans for High-Tension Glaucoma

Measures of heritability of a trait estimate the amount of the trait's variance that is due to genetic variants that are shared among family members but do not provide information regarding the identity of the specific genes involved in a disease, which can be located anywhere in the human genome. Linkage analyses are among the earliest-developed methods used to help identify regions of the genome where variation strongly associates with a particular trait. The basis of the linkage analysis is the cosegregation of a trait and an entire or a portion of a parental chromosome. Each parent passes on half of their chromosomes to an offspring; nonidentical siblings

share half of their own genetic material with each other, but on average, a quarter of their shared DNA has been received from each parent. This proportion gets progressively smaller with further relatedness distance in an extended family. If a small part of one of the parental chromosomes is consistently passed on to individuals who also express a particular value for the trait of interest, for example, OHT, then it is possible to calculate the risk that is likely to arise from that that fragment of the genome (rather than being due to chance). The power and accuracy of this method tend to improve with the number of generations and offspring within a family and when several, often unrelated, families are examined concurrently; with a larger number of generations, there is increased opportunity for unrelated traits and genes to decouple during random shuffling of the chromosomes or during the meiotic processes that cause their recombination.

PCG: primary congenital glaucoma

Several linkage scans for POAG have been published over the years, and they have often implicitly targeted high-tension glaucoma (i.e., POAG with IOP > 21 mm Hg) because high IOP was often used as a defining criterion for POAG. Therefore, it can be inferred that the genetic loci identified harbor genes that are involved in IOP pathophysiology. Studies have identified 14 loci as being associated with glaucoma with high IOP; these include loci associated with adult-onset and earlier-onset POAG, as well as with primary congenital glaucoma (PCG), and one locus associated with glaucoma secondary to pigment dispersion syndrome (**Table 2**). In addition, genome-wide

Table 2 List of loci identified by linkage studies for glaucoma with raised intraocular pressure

Genomic locus	Location	Reference(s)	Type of glaucoma	Gene harboring mutations
GLC1A	1q24.3-q25.2	Johnson et al. (1993), Sheffield et al. (1993)	Juvenile POAG	*MYOC* (Stone et al. 1997)
GLC1C	3q21-q24	Wirtz et al. (1997)	POAG	Not known
GLC1F	7q35-q36	Wirtz et al. (1999)	POAG	Not known
GLC1H	2p15-p16	Suriyapperuma et al. (2007)	POAG	Not known
GLC1I	15q11-q13	Allingham et al. (2005)	Early-onset POAG	Not known
GLC1J	9q22	Wiggs et al. (2004)	Early-onset POAG	Not known
GLC1K	20p12	Wiggs et al. (2004)	Early-onset POAG	Not known
GLC1M	5q22.1-q32	Pang et al. (2006)	Juvenile POAG	Not known
GLC1N	15q22-q24	Wang et al. (2006)	Juvenile POAG	Not known
GLC3A	2p22-p21	Bejjani et al. (1998), Sarfarazi et al. (1995)	PCG	*CYP1B1* (Bejjani et al. 1998)
GLC3C	14q24.3	Chen et al. (2011), Sharafieh et al. (2013)	PCG	Not known
GLC3D	14q24	Firasat et al. (2008)	PCG	*LTBP2* (Ali et al. 2009)
GLC3E	9p21.2	Souma et al. (2016)	PCG	*TEK* (Souma et al. 2016)
GPDS1	7q35-q36	Andersen et al. (1997)	Secondary—pigment dispersion	Not known
Axenfeld-Rieger syndrome	6p25	Gould et al. (1997)	Secondary—syndromic	*FOXC1* (Mirzayans et al. 2000)
Axenfeld-Rieger syndrome	13q14	Phillips et al. (1996)	Secondary—syndromic	Not known
Nail-Patella syndrome	9q34.1	Campeau et al. (1995)	Secondary—syndromic	*LMX1B* (Chen et al. 1998)

Abbreviations: PCG, primary congenital glaucoma; POAG, primary open-angle glaucoma.

linkage scans have also been performed for familial syndromes in which very early-onset high IOP and secondary glaucoma–associated anterior eye chamber anatomical defects are prominent features, such as Axenfeld-Rieger and Nail-Patella syndromes (**Table 2**).

The GLC1A locus was initially described in a family with autosomal-dominant juvenile glaucoma; 30 of the ascertained 59 family members were affected (Johnson et al. 1993). The affected individuals' glaucoma presented at around age 18, when they showed extreme elevations of IOP (mean IOP = 45 mm Hg), with most cases eventually requiring filtering surgery. A genome linkage scan conducted in this family found that markers on the long arm of chromosome 1 (1q24.3-q25.2) cosegregated with the disease. Shortly after, linkage analyses were independently conducted in other families expressing a similar phenotype (early-onset, very high IOP, absence of anatomical anomalies) by other groups (Morissette et al. 1995, Wiggs et al. 1994). Subsequently, a detailed sequencing analysis performed on affected family members identified three mutations (GLY364VAL, GLN368STOP, and TYR437HIS) within the *MYOC* gene as the origin of the linkage signal in this locus (Stone et al. 1997). A larger sequencing screen of *MYOC* mutations identified several additional changes in the protein-coding regions of the gene that were highly represented among unselected patients with POAG. In ethnically diverse populations, mutations within the *MYOC* gene are responsible for 2.6–4.3% of all POAG cases (Fingert et al. 1999). Carriers of *MYOC* mutations tend to have earlier-onset, higher IOP and more aggressive glaucoma than other POAG patients who do not carry mutations in this gene (Hewitt et al. 2007). The *MYOC* gene is expressed in many eye tissues but especially in the TM, and its levels of expression are associated with IOP levels in experimental animals (Gould et al. 2004).

Quantitative Trait Linkage Analyses for Intraocular Pressure

Linkage studies have also been carried out to identify loci associated with higher IOP as a quantitative trait. The first linkage analysis dedicated to IOP was conducted in extended pedigrees ascertained through the population-based Beaver Dam Eye Study. In this study, which used a subset of 218 sibling pairs, a region located on the long arm of chromosome 6 (6q16.3) and another on the long arm of chromosome 13 (13q22.1) were found to cosegregate with IOP (Duggal et al. 2005). The same group of investigators later used a larger sample and identified additional regions of interest, notably one on chromosome 19p13.2 (Duggal et al. 2007). Charlesworth et al. (2005) found two more linkage loci (1p32 and 10q22) in their collection of European families. Later, linkages at the 5q22 and 14q22 regions for IOP were reported in a study of African families (Rotimi et al. 2006); these loci were partially replicated in a panel of families from East Asia (Lee et al. 2010). To date, no responsible mutations have been identified by follow-up sequencing work in any of the IOP-linked regions discovered so far.

GENOME-WIDE ASSOCIATION STUDIES FOR INTRAOCULAR PRESSURE

Linkage analyses rely on chromosome recombination in cohorts consisting of family members. Their power and genomic mapping accuracy depend directly on the number of meioses observable in the cohort. Due to practical constraints in ascertaining family cohorts at a large scale, these analyses often link the phenotypes with vast chromosomal regions containing several genes; these links are notoriously difficult to replicate independently in other cohorts.

Association analyses represent an alternative way to use meioses for gene mapping. Association analyses assume that modern individuals are the descendants of a finite number of population founders. Successive generations gain new variations in the ancestral haplotypes, but also, meiotic recombination gradually shortens the lengths of the conserved haplotypes as the originally strong

pairwise correlation between markers (also called linkage disequilibrium) decays. Association analyses take advantage of the conserved haplotype lengths to tag, via selected SNP markers, chunks of the genome that are relatively short due to accumulation of meioses over millennia of population history. Genome-wide association analyses target most of the genome through genotyping of a representative set of SNP markers that can inform on the entire genotypic variability.

IGGC: International Glaucoma Genetics Consortium

GERA: Genetic Epidemiology Research on Aging

There have been several successful GWASs on POAG over the years (described elsewhere; see Choquet et al. 2020); this review focuses specifically on published analyses for IOP, even though genetic discoveries from IOP and POAG GWASs often intersect, and particular genes may have been first identified through either type of GWAS.

The first successful, large-scale GWAS for IOP was that of the Rotterdam studies in 2012. Initially using a discovery cohort of 12,000 participants, the authors found that rs7555523 and rs11656696, two intronic SNP variants within the sequences of the *TMCO1* and *GAS7* genes, were associated with IOP (van Koolwijk et al. 2012); the first of these variants had been identified in association with POAG in an earlier study (Burdon et al. 2011). The Rotterdam group also found an association with POAG for the *GAS7* locus, which increases the likelihood of having POAG by approximately 13% per risk allele.

The power to detect genetic association is larger if the genetic exposure is highly prevalent (i.e., high minor allele frequencies) and with increasing sample sizes. The International Glaucoma Genetics Consortium (IGGC) assembled data from over 27,000 subjects of European origin and almost 8,000 subjects of Asian ancestry from multiple population-based studies. Predictably, the greater power translated into the identification of more genome-wide significant ($P < 5 \times 10^{-8}$) associations with IOP, in addition to replicating the results for the previously described *TMCO1* and *GAS7* loci. Newly reported associations included variants near or within the *ABO* blood group genes; *ABCA1*; *FNDC3B*; an unusually large stretch on chromosome 11; and at the *CAV1/CAV2* locus, which had been separately identified as associated with POAG in multiple populations (Thorleifsson et al. 2010, Wiggs et al. 2011). A follow-up study by the IGGC, using an improved version of the imputation human reference haplotypes, identified a further locus associated with IOP in another region of chromosome 11, around the *ARHGEF12* gene.

The big-data science stage in the field of IOP and glaucoma genetics started in earnest with the introduction and availability of large-scale data originating from either retrospective clinical data derived from electronic medical records or ad hoc preplanned cross-sectional population-based recruitment. A large multi-ethnic collection of patient data from Genetic Epidemiology Research on Aging (GERA) was used to identify over 40 new genes that were associated with IOP (Choquet et al. 2017). Shortly after, using data from the UK Biobank (Bycroft et al. 2018), several studies examined the relationship between population-level genetic variability and IOP distribution (Gao et al. 2018, Khawaja et al. 2018, MacGregor et al. 2018, Simcoe et al. 2020b). The discovery of over 100 genetic loci that underlie IOP variation and that, in turn, confer risk for glaucoma (**Figure 2**) has improved our understanding of both IOP and glaucoma and generated new hypotheses for disease pathogenesis, helping to guide future research directions. Biological processes that have been implicated in IOP regulation by GWAS loci have included cell division (*GAS7*, *TMCO1*), membrane biology (*CAV1/CAV2)*, lipid metabolism *(CAV1/CAV2*, *ABCA1*, *ARHGEF12*, *DGKG*), cytokine signaling (*FNDC3B*), mitochondrial function (*TXNRD2*, *ME3*, *VPS13C*, *GCAT*, *PTCD2*), extracellular matrix processes (*AFAP1*), and ocular development (*FOXC1*, *PITX2*, *LMX1B*, *LTBP2*) (Choquet et al. 2017, 2018; Gao et al. 2018; Hysi et al. 2014; Khawaja et al. 2018; Springelkamp et al. 2015; van Koolwijk et al. 2012; Wiggs 2015). IOP-associated loci at *GLIS3*, *HGF*, *PLEKHA7*, and *FERMT2* have been associated with primary angle-closure glaucoma, suggesting that angle-closure mechanisms (rather than POAG-related

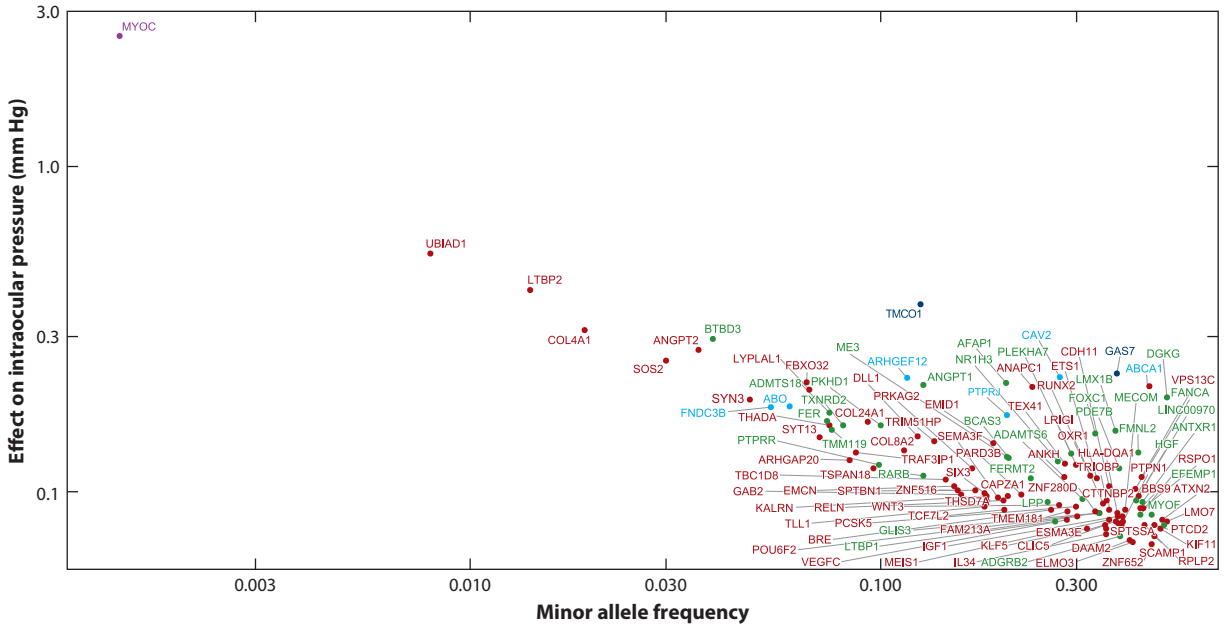

Figure 2

Genetic loci previously associated with intraocular pressure (IOP) in genome-wide association studies. For each locus, the lead variant is plotted, and its nearest gene is labeled. The per–risk allele effect size on IOP is plotted on the *y* axis, and the minor allele frequency (MAF) for the variant observed among UK Biobank participants of European ancestry is plotted on the *x* axis. Both axes are on a logarithmic scale, and the different color codes denote the different levels of sample size in the original studies that first identified them in relationship to IOP. The color codes are: deep blue = 12,000 (van Koolwijk et al. 2012), lighter blue = 35,000 (Hysi et al. 2014), green = 70,000 (Choquet et al. 2017), and red = 139,000 (Khawaja et al. 2018); purple is used for the *MYOC* GLN368STOP mutation, initially identified through positional cloning in affected families, which is shown in the upper-left corner for comparison purposes. Gene names, normally in italics, are roman in this figure for legibility.

mechanisms) contribute to IOP variation (Choquet et al. 2017, Khawaja et al. 2018, Khor et al. 2016, MacGregor et al. 2018).

RELEVANCE OF INTRAOCULAR PRESSURE–ASSOCIATED VARIANTS FOR PRIMARY OPEN-ANGLE GLAUCOMA

While the importance of IOP as a mediating factor for POAG is clear, it is important to test whether genetic variants that are associated with variation in IOP within a largely healthy population are also associated with risk of glaucoma. The NEIGHBORHOOD study, the largest POAG case-control GWAS to date (3,853 cases and 33,480 controls), examined genome-wide significant IOP-associated variants for association with POAG (Bailey et al. 2016, Khawaja et al. 2018). There was a strikingly linear relationship between the effect sizes for IOP and for POAG, supporting the role of IOP as a strong endophenotype for POAG. Furthermore, when the IOP-associated variants, together with age, sex, and three additional loci not previously associated with IOP (at *MYOC*, *SIX6*, and *CDKN2B–AS1*), were combined in a regression-based model in the NEIGHBORHOOD study, they were highly predictive of POAG (Bailey et al. 2016, Khawaja et al. 2018). The area under the receiver operating characteristic curve (AUROC) for high-tension POAG (POAG with IOP > 21 mm Hg) was 76%. Even for normal-tension POAG (with IOP ≤ 21 mm Hg), the AUROC was 71%, highlighting the importance of IOP variation even for

glaucoma that develops at lower levels of IOP. Taking a different approach, MacGregor and colleagues (2018) used a polygenic risk score (PRS) derived from IOP-associated variants to predict the risk of POAG in the Australian and New Zealand Registry of Advanced Glaucoma cohort comprising 1,734 cases of advanced POAG and 2,938 controls; participants in the top decile of the PRS were at 5.6 times the risk of POAG than those in the bottom decile. Therefore, there is clear evidence from independent studies that IOP is an important endophenotype for POAG and that genetic variants associated with IOP, when combined, can be predictive of POAG in populations.

Given the irreversible nature of glaucomatous damage, early detection is key to preventing blindness. General population screening is not currently recommended due to the lack of sufficiently predictive tests when applied to a population with low prevalence. Being able to identify subgroups of the general population that are at higher risk of POAG on the basis of genotype is important, as this may enable effective targeted population screening in the future.

EMERGING TRENDS IN GENETIC INVESTIGATION OF INTRAOCULAR PRESSURE

With the availability of a large number of genetic discoveries from well-powered clinical and population-based cohorts, the allelic structure of IOP and glaucoma risk is emerging with more clarity. Consistent with the majority of human traits and diseases, elevated IOP risk is split among a large number of variants spread throughout the genome. The distribution of effect sizes and frequency of risk alleles in the population demonstrate that, like other quantitative traits, throughout the evolutionary population history, the genetic architecture of IOP has been subjected to a form of stabilizing selection that adjusted and maintained the trait variation within a relatively narrow physiological range (Simons et al. 2018). As is the case for most other traits, variants that individually have strong effects over the phenotype are selected against (Josephs et al. 2017). Most variants associated with IOP tend to fall within a relatively narrow range of effect size versus minor allele frequency, which the currently available statistical power can detect. In other words, the majority of GWAS-identified variants for IOP are common and have a small effect, as illustrated by the majority of variants clustering in the bottom right of **Figure 2**. Although a considerable proportion of IOP heritability remains to be explained, no variants that both are common and have high effect (Manolio et al. 2009) are associated with IOP (**Figure 2**).

Availability of new data and ever-larger study cohorts will continue to increase statistical power and consequently help identify both smaller effect sizes for common variants and equivalent effect sizes for rarer variants. However, the history of IOP GWASs to the present day highlights the limitations of GWAS data with respect to low-frequency alleles. Lower-frequency alleles are too numerous to be individually targeted by the GWAS SNP array–based approach, and they are typically either evolutionarily selected against (Josephs et al. 2017) or too recent to be part of preserved and contiguous haplotypes to be studied through linkage disequilibrium–based genetic association (Risch & Merikangas 1996). Exome chip and whole-exome sequencing technologies, which have already been introduced in the field of glaucoma genetic research (Pasutto et al. 2015, Zhou et al. 2017), will be better equipped to accurately examine rarer variants and therefore identify novel variants similar to those identified in *MYOC* (i.e., rare but with strong effect). While these rare and high-risk variants will contribute relatively small population-attributable risk to IOP and glaucoma, they may be important to subgroups of patients and will be particularly predictive for the individuals in whom they are identified.

Deep sequencing techniques will continue to play an important role in further refining our understanding of the allelic structure of IOP and glaucoma by identifying additional unknown rare

variants, located inside previously identified GWAS loci, that contribute to both traits. Specifically, identifying rare variants within known GWAS loci may provide further evidence for the causal gene at the locus (which may also help prioritize future functional studies and drug development) and may also identify larger effect variants, which may be more predictive on an individual level. The experience with IOP GWASs to date demonstrates that the distinction between common and rare loci is not necessarily a hard one. GWAS analyses have identified common SNPs that confer small population-level effects for IOP and glaucoma risk in genes that harbor large-effect rare mutations that cause congenital or syndromic glaucoma (**Table 2**), such as *LTBP2* (Ali et al. 2009), *FOXC1* (Mirzayans et al. 2000), and *LMX1B* (Chen et al. 1998). Genes are functional units whose built-in functions contribute to homeostatic regulation of certain traits, and the consequences of the functional alterations brought about by genetic variations are translated to a broad spectrum of phenotypic variation.

The genetic associations discovered to date have lived up to the expectations of providing improved knowledge of the basic molecular mechanisms that contribute to IOP. Although these mechanisms are likely to be complex, and ever-larger studies will be needed to provide a more granular view, certain recurrent themes have already started to emerge as a result of the already published GWASs. Significant association with IOP has been identified for SNPs within gene loci known to be involved in lymphangiogenesis, such as *ANGPT1* (Loughna & Sato 2001), *ANGPT2* (Sato et al. 1995), and *COL4A1* (Alavi et al. 2016, Gould et al. 2006), which, alongside *LRGI1* and *FER* genes, code for protein products that interact with the product of *TEK* (Eklund et al. 2017), another gene whose rare mutations were previously linked to congenital glaucoma (Souma et al. 2016) but for which no current variants are identified in relationship to IOP in population GWAS analyses. TEK and its receptors are highly expressed in the SC (Kizhatil et al. 2014), and knockouts of *ANGPT1* and *ANGPT2* produce OHT and glaucoma in animal models (Thomson et al. 2014). These findings challenge the belief that the TM is the primary site of AH outflow obstruction in POAG and indicate that structures distal to the TM, such as the SC, may be important. If a proportion of POAG patients have primary pathology distal to the TM, then this may explain the significant nonresponse rates to TM-directed treatments (e.g., selective laser trabeculoplasty or TM-bypass microstents), and genotype-based algorithms may help predict such nonresponse in the future.

There is strong or over-representation in IOP association analyses of genes involved in corneal development and function. This may be related to either an IOP measurement artifact from corneal biomechanics or mechanisms related to anterior segment development. This corneal element is pervasive in analyses that have used Goldmann applanation tonometry (Gao et al. 2018) but is also present even in analyses of IOP that have compensated for corneal properties as far as possible. Several genes at IOP-associated loci have been previously connected to corneal phenotypes, including *FDCN2B*, *COL8A2*, and *ADAMTS18*, which are associated with central corneal thickness (Iglesias et al. 2018), and *ANAPC1*, which is associated with other corneal biomechanical properties (Khawaja et al. 2019, Simcoe et al. 2020a). In addition, many genes involved in high lipid and cardiovascular risk are also involved in IOP, suggesting that anomalies of lipid metabolism confer added risk for POAG. Among these genes are *CAV1/CAV2* (Li et al. 2005), *ABCA1* (Clee et al. 2001), and *KALRN* (Hauser et al. 2004, Krug et al. 2010), all of which are involved in lipid metabolism and confer considerable degrees of risk to cardio- and cerebrovascular diseases.

The GWAS work conducted to date highlights the invaluable benefits of broadening the scope to include ethnically and genetically diverse populations; despite challenges arising from the different population histories and linkage disequilibrium patterns, multi-ethnic analyses provide unique opportunities in terms of improving the accuracy of association and often improved power for new associations. Non-European cohorts often have more favorable minor allele frequencies, even

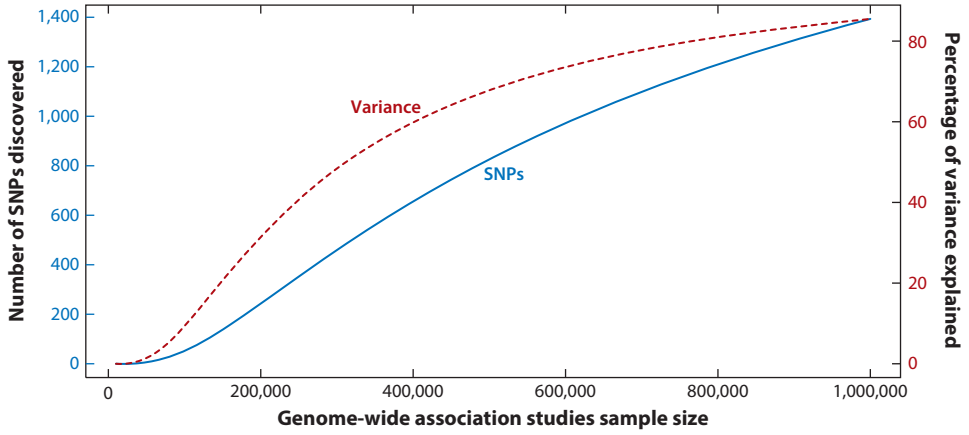

Figure 3

Projection of the number of SNPs associated with IOP and the proportion of genetic variance that they explain as a function of the sample sizes that are available for analyses in the future. The solid blue line represents the number of independent, uncorrelated SNPs (*left vertical axis*) discovered by a GWAS of the corresponding sample (*horizontal axis*), and the red dashed line represents the proportion of the genetic variance that they collectively explain (*right vertical axis*). Data are taken from Khawaja et al. (2018). Abbreviations: GWAS, genome-wide association study; IOP, intraocular pressure; SNP, single-nucleotide polymorphism.

though the genetic effect is of the same magnitude. This diversity is a likely explanation for the discovery of genetic loci that may not have been discovered if only European cohorts were examined (**Figure 2**), such as the *FDNC3B* and *ABO* loci from the IGGC study (Hysi et al. 2014) and many other loci from the GERA study (Choquet et al. 2017).

FUTURE DIRECTIONS

Current GWASs of IOP illustrate the benefits of the use of genetic studies on quantitative endophenotypes as disease proxies. As discussed above, results from IOP GWASs are already highly predictive of POAG in independent general and patient populations (Khawaja et al. 2018), and their integration with association results from endophenotypes that inform on POAG mechanisms not related to IOP promises to further improve our ability to predict POAG diagnoses (Craig et al. 2020). Future better-powered work will continue to identify more variants, explaining ever bigger proportions of IOP variation heritability (**Figure 3**), and will likely improve our understanding of POAG, as well as our ability to predict the disease in populations. Additionally, IOP-associated genes and pathways will be potential targets for new therapies, including pharmacological, gene editing, and gene therapy approaches. Glaucoma remains the leading cause of irreparable blindness globally; our rapidly increasing knowledge of the genetic determinants of IOP offers hope for new detection and treatment strategies.

SUMMARY POINTS

1. Raised IOP is a major risk factor, and the only proven modifiable risk factor, for glaucoma.

2. Genetic factors contribute substantially to variation of IOP in the population; the heritability of IOP is estimated to be 40–70%.
3. The most common form of Mendelian POAG is secondary to mutations in *MYOC*, which result in raised IOP.
4. Mutations in *CYP1B1*, *LTBP2*, and *TEK* cause Mendelian primary congenital glaucoma with high IOP, and mutations in *FOXC1* and *LMX1B* cause syndromic secondary glaucoma with high IOP.
5. Recent large GWASs have identified over 100 common variants that are associated with IOP.
6. In combination, GWAS-identified IOP loci are predictive of POAG in independent populations.
7. GWAS loci also suggest pathophysiological mechanisms underlying IOP regulation, including lymphangiogenesis and lipid metabolism.

FUTURE ISSUES

1. For the majority of IOP-associated loci, the causal gene and biology underlying the association remain uncertain, and further functional studies are required.
2. It is projected that larger GWASs in the future will continue to identify new IOP-associated variants, plateauing at approximately 1,300 variants with a sample size of 1 million participants.
3. It is also projected that a larger number of discovered IOP-associated loci will increase the proportion of IOP variance that can be explained and in turn improve prediction models for glaucoma.
4. Polygenic prediction models may inform targeted glaucoma screening strategies and stratified glaucoma management in the future, although prospective validation studies are required.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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