1. Introduction:

Glaucoma is a diverse group of ocular disorders that eventually results in the progressive degeneration of retinal ganglion cells (RGC), clinically manifesting as thinning of the retinal nerve fibre layer and cupping of the optic disc. If untreated, the condition leads to visual impairment and eventually, blindness (Jonas et al., 2017, 2018; Stein et al., 2021; Weinreb et al., 2014). The lack of symptoms in the early stages of the disease precludes an early diagnosis, contributing to its status as the leading cause of irreversible blindness worldwide, afflicting about 3-5% of people above 40 years of age (Blindness et al., 2021; Weinreb et al., 2014). As the world's population ages, the prevalence of glaucoma is expected to double by 2040 (Tham et al., 2014). Vision loss from glaucoma not only impacts quality of life, but exerts a significant socio-economic burden (~US$ 2.9 billion in direct costs of glaucoma treatment for the United States in 2011, or an average of ~US$ 1450 in direct costs of glaucoma treatment per patient, excluding indirect costs such as loss of productivity), which increases markedly as the disease progresses (Varma et al., 2011).

The main risk factors for late-onset glaucoma are age, ancestry, family history, and increased intraocular pressure (IOP) (Jonas et al., 2017, 2018; Stein et al., 2021; Weinreb et al., 2014). Under normal conditions, IOP is balanced between aqueous humour production by the ciliary body, and aqueous drainage, mainly through the trabecular meshwork and Schlemm's canal which comprises the conventional pathway, and alternatively through the non-conventional uveoscleral outflow pathways. In glaucoma, resistance to outflow or blockage of aqueous outflow results in increased IOP. The type of primary glaucoma can be differentiated by the configuration of the iridio-trabecular meshwork angle (**Figure 1**). In primary angle-closure glaucoma (PACG), there is iris-angle apposition, blocking aqueous drainage and resulting in increased IOP (Sun et al., 2017). Conversely for primary open-angle glaucoma (POAG) (Wiggs and Pasquale, 2017), the iridio-trabecular meshwork angle remains open, but outflow resistance is increased, mainly due to pathological alterations along the trabecular outflow or elsewhere along the drainage pathway. Although the majority of patients with POAG present with elevated IOP, up to a third of cases present with IOP within the normal population range (Sommer et al., 1991). Such patients are classified as having 'normal tension glaucoma' (Wiggs and Pasquale, 2017), which could be a misnomer as some patients may have IOP spikes that are missed due to classification based on single IOP measurements. Yet another common form of glaucoma (accounting for up to a quarter of glaucoma cases worldwide) is exfoliation glaucoma (Ritch and Schlotzer-Schrehardt, 2001), a secondary glaucoma. In this condition, aqueous outflow may be blocked by abnormal deposition of white extracellular debris in the trabecular outflow and other structures of the anterior chamber.

Family history and ancestry-specific susceptibilities to different forms of glaucoma suggest an underlying genetic basis (Jonas et al., 2017, 2018; Weinreb et al., 2014). Segregation studies have been fairly successful at identifying gene mutations in pedigrees with early onset and family-linked glaucoma. These are typically rare mutations in genes with very large effect sizes (odds ratio > 5 to 10) and are thought to be directly causative of disease. Such examples include dominant negative mutations in the *MYOC* gene that are found in a sizeable proportion (~10%)

of juvenile onset glaucoma patients, and at least 4-5 percent of familial glaucoma patients (Allen et al., 2015; Alward et al., 1998; Han et al., 2019; Stone et al., 1997; Wiggs et al., 1998). In contrast, the genetic basis of late onset (above age of 40 years) glaucoma is complex, and is influenced by many factors including age, lifestyle, genetics and environment (Wiggs and Pasquale, 2017).

Currently there are two general experimental approaches in use in glaucoma genetic studies (**Figure 2**). The first, uses single nucleotide polymorphisms (SNPs) as units for risk association within the context of a genome-wide association study (GWAS) (Uffelmann et al., 2021). SNPs are a common source of human genetic variation and are dispersed throughout a person's genome, occurring on average about once in every 1,000 nucleotides. These are most commonly found in intergenic or intronic regions in the genome. Researchers study the statistical association between SNP allele frequencies in persons with glaucoma compared to individuals without disease. Strongly associated SNPs define a region of the human genome that is associated with the glaucoma risk. Because SNPs are mostly located in the non-coding regions of the human genome, they are not usually under evolutionary selective pressure. SNPs residing in conserved, non-coding regions are likely regulatory in nature and confer risk by quantitatively altering gene expression. These could exert more subtle effects compared to coding sequence mutations that directly alter encoded proteins qualitatively. In addition, it is often difficult to identify the causal gene linked with a SNP, as there could be multiple genes in the tagged region; casual genes associated with SNPs have also been found in distant locations (Smemo et al., 2014). Thus, the effect sizes of these SNPs with relation to glaucoma risk, tend to be modest (usually with Odds Ratios between 1.1 to 1.3). Nevertheless, a catalogue of SNPs that are strongly associated with glaucoma risk have potential clinical utility as they can be incorporated into polygenic risk scores to predict glaucoma susceptibility (Knoppers et al., 2021).

The second approach focuses on the coding regions of the gene (Ross et al., 2020; Yamazaki et al., 2019) termed the exome, and uses each gene as the unit of association with disease risk. Although the exome makes up about 1% of the whole genome, it has disproportionate weight in terms of importance as it specifies protein function. Thus, genetic variants that impair protein function have a significant chance to alter cellular physiology and consequently drive disease phenotypes. As opposed to SNP-based approaches, whole exome sequencing (WES)-based approaches screen protein coding sequences to find rare (often with <1% frequency) deleterious mutations that are under purifying selection. Although each variant might be rare individually, their occurrence in aggregate might be sufficient for the detection of gene-based burden signals (Povysil et al., 2019). A shortcoming of exome-based approaches is the reliance on bioinformatics algorithms that qualitatively predict deleterious changes to protein function (Genetics of Exfoliation Syndrome et al., 2021). For example, a lack of functional characterization of coding WDR36 alleles found in glaucoma case control cohorts has contributed to the confusion regarding WDR36 as a causal POAG risk gene (Fingert et al., 2007; Hauser et al., 2006; Hewitt et al., 2006; Pasutto et al., 2008). Therefore, experimental validation to determine the type of functional change, i.e., gain or loss-of-function, and quantify the extent of alteration is required for disease manifestation is imperative for coding variant data to be truly useful for follow-up investigation in disease mechanisms.

This review will cover recent advances in genetic studies of primary open-angle glaucoma, primary angle-closure glaucoma, and exfoliation glaucoma, which collectively account for the majority of all glaucoma subtypes in the world today. We

will also review the utility of these risk loci as therapeutic targets for glaucoma treatment and discuss how their discoveries could illuminate disease processes and improve clinical outcomes.

2. Primary Open-Angle Glaucoma (POAG)

2.1 Frequency of POAG

Glaucoma is classified as POAG when the iridio-trabecular meshwork drainage angle is open and there are no signs of secondary causes of raised IOP such as exfoliation syndrome (see Section 4), pigment dispersion, uveitis or exogenous steroid medication use (Stein et al., 2021).

There have been many population-based studies reporting on the prevalence of POAG, spanning across a broad range of ethnicities and geographical locations (Leske, 2007; Tham et al., 2014). The majority of these studies report prevalence in people aged 40 years and older. The prevalence of POAG in published studies is similar in Europe (1 - 3%) (Anton et al., 2004; Jonasson et al., 2003; Topouzis et al., 2007), Australia (2 – 3%) (Mitchell et al., 1996; Weih et al., 2001) and Asia (1 – 4%) (Bourne et al., 2003; Casson et al., 2007; He et al., 2006; Iwase et al., 2004; Palimkar et al., 2008; Rahman et al., 2004; Ramakrishnan et al., 2003; Raychaudhuri et al., 2005; Sah et al., 2007; Shen et al., 2008; Sia et al., 2010; Vijaya et al., 2008; Wang et al., 2010) but is higher and more variable in Africa, ranging from 1% in Nigeria (Murdoch et al., 2001) to over 8% in Ghana (Ntim-Amponsah et al., 2004). Reported prevalence is also higher in other African-Caribbean populations (7 – 9%) (Leske et al., 1994; Mason et al., 1989). Prevalence appears to be related to country of origin rather than country of residence, as evidenced by the variable rates within different ethnicities in the United States (Tielsch et al., 1991). European derived populations in the United States have a reported POAG prevalence of 1 – 2% (Klein et al., 1992; Tielsch et al., 1991) compared with 2 – 5% in Hispanic-Americans (Quigley et al., 2001; Varma et al., 2004) and 4% in African-Americans (Tielsch et al., 1991). The lowest reported prevalence of POAG is 0.06% in Eskimos residing in Alaska (Arkell et al., 1987). However, a major limitation of comparing reported prevalence figures between studies is the different definitions of glaucoma that were adopted. For example, when diagnostic criteria from different large epidemiological studies were applied to one analytical dataset, prevalence estimates varied by up to 10-fold (Wolfs et al., 2000). To address this issue, the International Society for Geographical and Epidemiological Ophthalmology (ISGEO) published a consensus definition of POAG for epidemiological studies (Foster et al., 2002), and a growing number of studies now report according to this classification (Casson et al., 2007; He et al., 2006; Iwase et al., 2004; Jonasson et al., 2003; Rahman et al., 2004; Raychaudhuri et al., 2005; Shen et al., 2008; Sia et al., 2010; Vijaya et al., 2008; Vijaya et al., 2005; Wang et al., 2010). However, even comparisons between ISEGO-compliant studies are not straight-forward due to lack of standardisation of prevalence, particularly for age. Investigators have carried out meta-analyses of POAG prevalence using Bayesian techniques to account for variation in age-structure between populations (Rudnicka et al., 2006; Tham et al., 2014). The most recent meta-analysis, comprising 50 population-based studies, reported the global prevalence of POAG in 2013 to be 3.1% (95% CI 1.7-5.3) in people aged 40-80 years, with 44 (95% CI 31-61) million people affected (Tham et al., 2014). The number of people affected is forecast to increase rapidly to 80 million

in 2040, primarily due to the ageing population (Tham et al., 2014). Fewer studies have reported the incidence of POAG, with estimates ranging from 0.29% per year in Sweden to 0.5% per year in Barbados (de Voogd et al., 2005; Ekstrom, 2008; Founti et al., 2021; Leske et al., 2007; Mukesh et al., 2002). Again, however, comparing rates is not simple due to differences in case definition and population structures.

2.2 Risk factors for POAG

Older age is a very strong risk factor for POAG, regardless of ethnicity (Tham et al., 2014) or the study definition of glaucoma (Wolfs et al., 2000). Raised IOP is the cardinal modifiable risk factor for POAG (Stein et al., 2021). 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). Incidence studies have reported an increased risk of POAG of 10-18% per 1-mmHg higher baseline IOP (Jiang et al., 2012; Kim et al., 2011; Le et al., 2003; Leske et al., 2008; Sommer et al., 1991). The commonly used definition for “raised IOP” is >21 mmHg, based on the population mean IOP plus 2 standard deviations (Hollows and Graham, 1966; Leydhecker et al., 1958). The relative risk of developing POAG is much higher for a person with ocular hypertension compared with a person whose IOP is within the normal range. However, there are limitations to defining a normal range of IOP as IOP is a dynamic trait with a distinct diurnal pattern. Thus, many individuals with glaucoma could have IOP<21 at least some of the time. Previous studies have estimated the proportion of patients with POAG that were classified as normal-tension glaucoma NTG; (IOP ≤ 21 mmHg) at between 20-90% (Iwase et al., 2004). Nevertheless, lowering IOP is still an effective strategy for treating NTG (1998a; 1998b; Anderson and Normal Tension Glaucoma, 2003).

Other well-established risk factors for POAG are ancestry (Tham et al., 2014) (higher risk in people of African and Hispanic descent compared to Europeans) and a family history of glaucoma. First-degree relatives of POAG patients have a 22% lifetime risk of developing disease compared with 3% for people without a family history (Wolfs et al., 1998). This supports the heritable nature of POAG and the importance of genetic risk factors (see below).

Other factors reported to be associated with POAG have less clear evidence for a causal link. While myopic refractive error is associated with a higher prevalence of POAG in cross-sectional studies (Marcus et al., 2011), there is less clear evidence for an association with POAG incidence in longitudinal studies or glaucoma progression in large clinical trials. A thinner central corneal thickness (CCT) has also been associated with higher risk of conversion from ocular hypertension to POAG (Gordon et al., 2002) and an increased risk of incident open-angle glaucoma (Jiang et al., 2012). However, CCT is associated with IOP due to measurement artefacts (Hoffmann et al., 2013) and it remains unclear whether observed associations between CCT and glaucoma are due to biases related to this.

2.3 Pathophysiology of POAG

The very strong association between IOP and POAG, and the high-level evidence that lowering IOP can reduce the risk of POAG progression (Garway-Heath et al., 2015) both point towards IOP-related mechanisms as critical in disease pathogenesis. However, the mechanisms for higher IOP causing RGC death and optic nerve degeneration remain unclear. There are several pathophysiological theories

regarding the mechanism of damage in glaucoma, and it is likely that numerous factors are concurrently at play in this complex disease **(Figure 3**; (Stein et al., 2021).

The biomechanical theory of glaucoma suggests that higher IOP mechanically induces glaucomatous changes in the optic nerve at the level of the optic nerve head (Burgoyne, 2011; Strouthidis and Girard, 2013). Evidence supports the primary site of RGC injury in glaucoma to be at the optic nerve head, at the level of the lamina cribrosa (Anderson and Hendrickson, 1974; Quigley and Anderson, 1976; Quigley et al., 1981). 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 and Girard, 2013). Depending on these factors in an individual, a threshold may be reached where higher IOP results in damage to RGCs; this may be 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 and Girard, 2013).

The vascular theory of glaucoma proposes that insufficient blood supply to the optic nerve is a key factor in the pathogenesis of RGC loss (Caprioli et al., 2010; Cherecheanu et al., 2013; Hayreh, 1969; Hayreh et al., 1994; Yanagi et al., 2011). This reduced blood supply may be caused by systemic hypotension, vasospasm, atherosclerosis, or by compression of vasculature secondary to raised IOP. While studies have demonstrated associations between glaucoma and blood pressure, as well as statistically flawed ocular perfusion pressure parameters (Khawaja et al., 2013b), autoregulation of blood flow in the optic nerve head occurs over a large range of blood pressure and IOP, and therefore surrogate measures of end-tissue perfusion are problematic (Drance et al., 1988).

Data from the >100 gene loci that have been identified via genome-wide association studies of glaucoma (Chen et al., 2014; Choquet et al., 2018; Genetics of Glaucoma in People of African Descent et al., 2019; Gharahkhani et al., 2014; Gharahkhani et al., 2021; Taylor et al., 2019) do not provide definitive evidence for either biomechanical or vascular theories for glaucoma. Rather, they suggest the involvement of multiple distinct cellular processes, each potentially with small effects (Danford et al., 2017; Janssen et al., 2013).

Considerable evidence implicates oxidative stress in the pathophysiology of POAG (Chrysostomou et al., 2013; Kumar and Agarwal, 2007; Zanon-Moreno et al., 2008). Oxidative stress may damage the trabecular meshwork, resulting in raised IOP and, in turn, optic nerve damage. Additionally, free radicals may interact with incident light and directly damage the optic nerve. Primary mitochondrial dysfunction may increase the tendency towards oxidative stress and be a trigger for the onset of glaucoma (Chrysostomou et al., 2013).

Like other neurodegenerative disorders such as dementia, POAG is strongly age-related. The optic nerve is often considered as part of the central nervous system (CNS) because, unlike other cranial nerves, it shares the same embryonic origins as the CNS and is encased by the meninges (Bron et al., 1998). It has therefore been suggested that POAG may be, at least in part, a manifestation (Teikari, 1987) of general CNS degeneration (Gupta and Yucel, 2007). In the same way that some degree of cognitive decline with ageing is considered physiological, some degree of RGC loss is considered normal with increasing age. Dementia and glaucoma are characterized by faster, pathological rates of cognitive and RGC decline respectively, and accelerated ageing has been implicated in both diseases (Caprioli, 2013).

2.4 Heritability of POAG

Studies estimating heritability suggest a significant genetic contribution to POAG. Among the twin and family-based heritability studies, h^2 (narrow sense heritability), varied from 0.13-0.81 (Charlesworth et al., 2010; Cuellar-Partida et al., 2016; Teikari, 1987). Recent reports using electronic medical records and insurance claims data suggest higher glaucoma heritability estimates (0.70 and 0.93; (Polubriaginof et al., 2018; Wang et al., 2017)). A recent systematic meta-analysis (Asefa et al., 2019) showed that individual endophenotypes related to POAG also demonstrate significant heritability including intraocular pressure, 0.43 (0.38-0.48); cup-to-disc ratio, 0.56 (0.44-0.68); disc size, 0.61(0.37-0.81); cup size, 0.58 (0.35-0.78); corneal hysteresis, 0.40 (0.29-0.51); retinal nerve fiber layer thickness, 0.73 (0.42-0.91); cup shape, 0.62 (0.22-0.90); and peripapillary atrophy, 0.73 (0.70-0.75). Studies included in the meta-analysis were primarily from European Caucasian and Asian populations and showed significant heritability in both ethnic groups (Asefa et al., 2019). Interestingly, age is a significant factor influencing heritability of glaucoma-related endophenotypes with heritability decreasing with increasing age suggesting increasing impact of potential environmental risk factors over time.

2.5 Linkage studies for POAG

Initial POAG gene discovery efforts focused on family linkage studies designed to identify single gene (Mendelian) causes of glaucoma (Allingham et al., 2009);. This approach resulted in 13 loci (*GLC1A*-*GLC1P*) (Crooks et al., 2011; Fan et al., 2007; Monemi et al., 2005; Morissette et al., 1995; Sarfarazi et al., 1998; Sherwin et al., 2009; Stoilova et al., 1996; Suriyapperuma et al., 2007; Trifan et al., 1998; Wiggs et al., 2004; Wirtz et al., 1997; Wirtz et al., 1999; Woodroffe et al., 2006) identified with varying levels of genetic linkage. Likely causative genes have been identified for 4 of these loci including *MYOC* (*GLC1A*) (Stone et al., 1997), *OPTN* (*GLC1E*) (Rezaie et al., 2002), and *EFEMP1* (*GLC1H*) (Collantes et al., 2021; Mackay et al., 2015) and *TBK1* (GLC1P) (Fingert et al., 2011). Mutations in these genes, particularly the *MYOC* Gln368X mutation can account for up to 5% of POAG cases (Sears et al., 2019). Genes that may modify POAG risk but are not definitively pathogenic have also been identified at *GLC1F* (*ASB10*) (Pasutto et al., 2012) and *GLC1G* (*WDR36*) (Hauser et al., 2006). Two loci (*GLC1J* and *GLC1K*) were identified as part of a genome-wide sibling pair analysis for early-onset POAG (Wiggs et al., 2004). Another genome-wide linkage study offered further support for *GLC1D* and *GLC1I* (Crooks et al., 2011). *GLC1I* on chromosome 15 was originally defined by an ordered subset analysis that stratifies by age of diagnosis (Woodroffe et al., 2006). Genome-wide association studies (GWAS) have also shown significant association with SNPs located in several of these regions including *GLC1A* (1q23), *GLC1H* (2p15-16) and *GLC1J* (9q22). Although genetic linkage studies remain a useful tool towards uncovering risk loci, this approach could be supplanted by more comprehensive SNP- and sequencing- based approaches that directly interrogate all possible loci for risk association.

2.6 Genome-wide association studies for POAG

Genome-wide association studies (GWAS) have identified many genomic loci associated with POAG risk (Allingham et al., 2009; Liu and Allingham, 2017;

Youngblood et al., 2019). The genetic variants (SNPs) associated with disease are typically common in populations (minor allele frequencies 10% to 30%) and individually have small overall effects (Odds ratios of 1.1-1.4). Initial POAG GWAS used relatively small numbers of cases and controls providing sufficient statistical power for identification of only those loci with larger effects such as *CAV1/CAV2* (Thorleifsson et al., 2010) and *TMCO1*, *CDKN2BAS* (Burdon et al., 2011). Larger POAG GWAS were completed by consortia such as the NEIGHBORHOOD (Bailey et al., 2016) and the International Glaucoma Genetics Consortium (IGGC) (Hysi et al., 2014). Recently trans-ancestry meta-analyses involving datasets from the NEIGHBORHOOD, IGGC and others have discovered 127 independent POAG genomic loci (Gharahkhani et al., 2021).

While the majority of POAG GWAS studies have been carried out in European Caucasians, several studies in Asian populations revealed novel loci including *TGFBR3* (Li et al., 2015) and *PMM2* (Chen et al., 2014). Recently, a GWAS of African ancestry cases and controls (Genetics of Glaucoma in People of African Descent) identified *APPB2* (Genetics of Glaucoma in People of African Descent et al., 2019), a novel locus not identified in other populations or in the trans-ancestry meta-analyses (Gharahkhani et al., 2021). Future larger studies of cases with African and Asian ancestry will be necessary to fully define the POAG genetic architecture in these populations.

GWAS of normal tension glaucoma (NTG) cases and controls have also identified several novel loci including 8q22 in European Caucasians (Wiggs et al., 2012) and *ELOVL5* in Japanese (Writing Committee for the Normal Tension Glaucoma Genetic Study Group of Japan Glaucoma et al., 2010). Additionally, the *CDKN2B-AS* locus appears to have larger effects in the NTG subgroup compared to POAG overall (Burdon et al., 2012; Wiggs et al., 2012).

Gene-set enrichment and pathway analyses (Gharahkhani et al., 2021) implicated a diverse array of cellular processes potentially contributing to POAG pathogenesis. Additionally, several loci harboring genes involved in mitochondrial function are also associated with disease risk including *TXNRD2* and *ME3*, both influencing NADPH metabolism (Santana-Garrido et al., 2021).

Several low frequency (minor allele frequency less than 1%) variants have also been associated with POAG risk. Unlike most of the common variants associated with disease that are located in noncoding genomic regions, these low frequency variants affect coding sequences and protein structure. *ANGPTL7* coding variants have been shown to reduce glaucoma risk in European Caucasian populations (Tanigawa et al., 2020). A relatively common *MYOC* variant (p.Gln368Ter) increases POAG risk in European Caucasian and Asian populations (Gharahkhani et al., 2021; Zebardast et al., 2021). The MYOC Gln368Ter variant was initially discovered as a Mendelian cause of glaucoma with reduced penetrance (Stone et al., 1997). In some populations this variant has been noted to be as frequent as 1.5% and can account for up to 5% of POAG cases ((Alward et al., 1998; Wiggs et al., 1998). The penetrance is age-dependent (Allingham et al., 1998; Nag et al., 2017) and is also influenced by a POAG polygenic risk score suggesting that many genetic variants of smaller effects can modify the main effect of this mutation on disease. (Han et al., 2019; Siggs et al., 2021; Zebardast et al., 2021)

2.7 Functional investigation of POAG risk genes.

Most of the genetic variants (SNPs) associated with POAG are located in noncoding genomic regions and many are 'eQTLs' or expression quantitative trait loci that influence gene expression. Of note, it is customary to 'name' the genomic regions associated with disease according to the gene closest to the lead variant (i.e. the variant SNP with the best evidence for association) however in about half the GWAS loci tested by the GTEx (Genotype Tissue Expression) consortium, eQTL-gene correlations suggest that the putative causal gene(s) are not the nearest gene to the lead GWAS variant (Claussnitzer et al., 2015; Gamazon et al., 2018). Fine-mapping studies defining causal genes have not yet been completed for all POAG loci, however some functional and animal studies have provided supporting evidence for several genes implicated by GWAS associations.

The first of these is *SIX6* located on chromosome 14q. This was one of the first POAG loci to be discovered (Wiggs et al., 2012) and was also found to be associated with cup-to-disc ratio (CDR; (Ramdas et al., 2010)). *SIX6* codes for Sine Oculis Homeobox Homolog 6 a protein known to contribute to ocular development (Slavotinek, 2011). Several *SIX6* missense variants were found primarily in POAG cases and these variants were found to alter ocular metrics such as eye size and optic nerve structure in a zebrafish complementation assay (Carnes et al., 2014; Iglesias et al., 2015). Further studies have shown that human carriers of a common *SIX6* missense variant, (p. Asn141His) have a thinner nerve fiber layer compared to controls (Cheng et al., 2014a; Khawaja et al., 2018a). Together these results suggests that *SIX6* influences glaucoma susceptibility through a mechanism involving development of the neural retina.

SNPs located in the genomic region that includes *CAV1* and *CAV2* are associated with POAG and with IOP (Khawaja et al., 2018b; Loomis et al., 2014; Thorleifsson et al., 2010). *CAV1* and *CAV2* code for caveolins 1 and 2 that are necessary for the formation of caveolae, specialized membrane structures involved in a number of signaling pathways including NOS3 and cholesterol metabolism (Hu et al., 2020a). A *CAV1* mouse knockout has elevated IOP (Elliott et al., 2016) and loss of caveolae in the Schlemm's canal (SC) and trabecular meshwork. In addition, in the *CAV1* knockout mouse outflow tissues are more susceptible to plasma membrane rupture suggesting a role for caveolae in mechanoprotection, and aqueous drainage from knockout mouse eyes was more sensitive to nitric oxide (NO) synthase inhibition than controls, suggesting that excess NO partially compensates for outflow pathway dysfunction(De Ieso et al., 2020).

Finally, SNPs in an intergenic region between *EFEMP1* and *PNPT1* have been associated with IOP (Khawaja et al., 2018b) and POAG (Gharahkhani et al., 2021). Recently, rare *EFEMP1* variants have also been found in families with early-onset POAG (diagnosis before age 35) in China (Liu et al., 2020) and the Philippines (Collantes et al., 2021) as well as an adult-onset POAG family from the U.S. (Mackay et al., 2015). The discovery of rare coding variation segregating with disease in these families suggest that *EFEMP1* mutations can cause glaucoma and that the causal gene in this locus is likely to be *EFEMP1*.

Future GWAS studies using larger and more ethnically diverse populations are likely to reveal additional POAG-risk loci providing more insight into disease pathogenesis. Fine-mapping studies that define the likely causative genes residing in associated genomic loci will also help define underlying disease mechanisms.

2.8 Genetic associations with POAG endophenotypes

While the primary trait of interest is POAG status, and case-control studies remain the gold standard for identifying disease associations, analysis of heritable quantitative traits related to glaucoma (endophenotypes; (Sakurada et al., 2020)) has multiple advantages. Objective continuous measures offer greater statistical power compared to binary outcomes and are less prone to misclassification biases. Additionally, variation in the quantitative trait can be observed within the general population, meaning that data from healthy participants of population-based studies can be leveraged. Insights from quantitative trait analyses may also be more specifically interpreted according to a component part of the causal pathway for glaucoma. In contrast, it would be unclear whether a genetic association with POAG overall was related to IOP or other direct optic nerve effects.

As described above, IOP is the cardinal modifiable risk factor for POAG, and lowering of IOP is its only proven treatment. As IOP is a highly heritable trait (estimated at 40%-70%; (Asefa et al., 2019; Sanfilippo et al., 2010), understanding the genetic basis of IOP variation (Ojha et al., 2013; Xu et al., 2021) may uncover biological insights into the pathological processes underlying POAG susceptibility. Despite bringing together multiple population studies globally for the International Glaucoma Genetics Consortium (IGGC), and a sample size of 37,930 participants, only 9 genome-wide significant associations with IOP were identified in 2017 (Springelkamp et al., 2017). Shortly following this, three very large GWAS for IOP (two with considerable overlap) have provided a step-change advance in our discovery of the genetic architecture underlying IOP (Choquet et al., 2017; Khawaja et al., 2018b; MacGregor et al., 2018). A multi-ethnic GWAS for IOP was carried out in 69,756 participants of the Kaiser Permanente Genetic Epidemiology Research in Adult Health and Aging (GERA) study (Choquet et al., 2017). GERA is a clinical cohort and IOP measurements were extracted from patients' electronic medical records; only measurements taken before any IOP-lowering treatment were used. The study confirmed most of the previously reported IOP-associated genetic loci, demonstrating the validity of using clinical IOP measurements in a patient cohort rather than the traditional population-based approach. Additionally, 40 novel IOP-associated loci were identified at genome-wide significance (Choquet et al., 2017). Following the GERA study, two independent groups reported even larger GWAS of IOP (Khawaja et al., 2018b; MacGregor et al., 2018) which included analysis of data from the Eye and Vision component of the UK Biobank study (Chua et al., 2019). A meta-analysis of IOP data from UK Biobank, IGGC (Springelkamp et al., 2017) (see above) and the EPIC-Norfolk Eye Study (Khawaja et al., 2013a) resulted in a GWAS for IOP in 139,555 participants of European descent; 112 genome-wide significant loci were identified, 68 of which were novel (Khawaja et al., 2018b). These loci explained 17% of the variance of IOP in the EPIC-Norfolk Eye Study, a considerable proportion given the variance likely caused by measurement error, measurement artefact from corneal biomechanics, and the likelihood that measurements at a single point in time do not accurately reflect the overall physiological IOP level. The IOP-associated loci were subsequently examined for association with POAG in the US NIEGHBORHOOD case-control study (Khawaja et al., 2018b). Strikingly, there was a highly linear correlation between the effect estimates for IOP and POAG from the two studies for the 112 loci. This strongly supports the utility of IOP as an endophenotype for glaucoma and suggests that the genetic factors which predispose individuals to higher IOP also incrementally increase the risk of POAG. There were also loci previously associated with PACG (at *GLIS3*, *FERMT2*, *PLEKHA7* and *HGF,* see below); this suggests that a proportion of why healthy populations vary in IOP is due to mechanisms which

contribute to angle-closure disease, even in the absence of disease. The most enriched gene set in the results were for lymphangiogenesis, driven predominantly by IOP-associated loci in *ANGPT1*, *ANGPT2* and *VEGFC* (Khawaja et al., 2018b). Schlemm's canal and collector channels have a very similar phenotype to lymphatic vessels (Aspelund et al., 2014), and it is likely that these lymphangiogenic loci exert their IOP-altering effects via this part of the aqueous outflow pathway, rather than the trabecular meshwork (which is traditionally considered as the site of pathology in POAG). *ANGPT1* and *ANGPT2* both encode Receptor Tyrosine Kinase (TEK) ligands. Mutations in TEK coding regions have been shown to cause primary congenital glaucoma (Souma et al., 2016) suggesting that severe alteration of lymphangiogenesis can cause severe disease manifest at birth while more common genetic variation may less severely impact lymphangiogenesis and result in an increased risk of decompensation of IOP as an adult.

Another commonly examined quantitative trait related to POAG is the optic disc vertical cup-disc-ratio (VCDR; (Choquet et al., 2020b; Sakurada et al., 2020)). An enlarged VCDR is a key sign of glaucoma, and forms part of the ISGEO definition of glaucoma (see above). In an IGGC meta-analysis comprising 32,272 individuals, 25 VCDR-associated loci were identified (Springelkamp et al., 2017). The majority of these loci were not associated with POAG in subsequent case-control analyses, and only two were significantly associated with POAG following correction for multiple testing (Springelkamp et al., 2017). This suggests that VCDR is a less strong endophenotype for POAG than IOP, and genetic factors underlying VCDR variation may not in turn confer risk for POAG. It is hypothesized that a considerable proportion of VCDR variation is genetically determined variation in baseline anatomy that is unrelated to glaucoma. There has been a recent step-change in genetic discovery for VCDR by leveraging machine-learning to conduct large-scale grading of retinal photographs. Previously, human grading of retinal photographs was required to derive VCDR in many studies, and this was not practicable in very large studies like UK Biobank. Two independent groups have developed deep learning models to automatically derive VCDR from retinal photographs and applied the algorithm to UK Biobank (Alipanahi et al., 2021; Han et al., 2021) and the Canadian Longitudinal Study on Aging (Han et al., 2021). This enabled the largest GWAS of VCDR to date, identifying over 150 significantly associated loci (Alipanahi et al., 2021; Han et al., 2021). Again, the relevance of these loci for POAG risk is unclear, and a substantial proportion of the loci more likely underlying anatomical variation unrelated to glaucomatous processes. Interestingly, several loci involved in neuronal and synaptic biology were strongly associated with VCDR (Alipanahi et al., 2021).

Another glaucoma-related trait that aids in the diagnosis of POAG is inner retinal thickness at the macula (Stein et al., 2021). The thickness of both the retinal nerve fiber layer (mRNFL) and the ganglion cell inner plexiform layer (GCIPL) at the macula has been derived from optical coherence tomography scans in UK Biobank participants (Khawaja et al., 2020). The first adequately powered GWAS for these parameters was conducted in 31,434 European participants of UK Biobank, identifying 46 genome-wide significant loci associated with either mRNFL or GCIPL (Currant et al., 2021). Despite mRNFL and GCIPL being important diagnostic biomarkers for glaucoma, only one of the 46 loci was significantly associated with POAG. This suggests that the genetic determinants of mRNFL and GCIPL variation do not in turn affect POAG risk, and that these parameters are not useful endophenotypes for POAG. In agreement with this are Mendelian randomisation experiments looking at

the causal influence of mRNFL and GCIPL instrument variables on POAG which were non-significant (Currant et al., 2021).

As discussed above, while CCT has been associated with POAG (Dimasi et al., 2010; Swierkowska and Gajecka, 2017), it is uncertain whether this is a causal relationship, or the result of the strong artefact corneal biomechanical properties exert on IOP measurements. A cross-ancestry GWAS meta-analysis for CCT in the IGGC (n = 25,910) identified 44 genome-wide significance loci, none of which were significantly associated with POAG after considering multiple testing (Iglesias et al., 2018). Also, there was no significant correlation between the CCT and POAG effect sizes for the CCT-associated variants (r=−0.17, P=0.2), in contrast to the strong correlation of CCT and keratoconus effect sizes (r=−0.62, $P=5.3\times10^{-5}$) (Aung et al., 2017). A more recent GWAS meta-analysis for CCT including the GERA cohort identified a further 41 associated loci (Choquet et al., 2020a); only one of these loci was significantly associated with glaucoma (Choquet et al., 2020a). Furthermore, a Mendelian randomisation experiment did not find evidence for a causal effect of CCT on POAG (Choquet et al., 2020a). Overall, the genetic association studies of CCT strongly support the hypothesis that CCT is not causally related to POAG and that previous observational associations are due to IOP measurement artefact.

2.8 Polygenic prediction modelling for POAG

Given the recent large-scale discovery of genetic associations with POAG, there has been interest in whether the knowledge of a person's genotype can help predict their risk of POAG. A regression-based model combining 133 SNPs associated with IOP at genome-wide significance with age, sex and 3 SNPs known to be associated with POAG but not IOP (rs74315329 in *MYOC*, rs2157719 in *SIX6* and rs8015152 in *CDKN2B-As1*) was able to predict high-tension POAG in the NEIGHBORHOOD study with an area under the receiver operating characteristic curve (AUC) of 76% (Khawaja et al., 2018b). This was a striking finding, and the first time it had been demonstrated that genotype could predict POAG with a level of accuracy that may enable targeted population screening. Improved predictive ability was achieved in a later study which combined genetic association results for IOP, VCDR and POAG in a multitrait analysis, creating a polygenic risk score (PRS) that included all uncorrelated SNPs with a significance threshold of $P \leq 0.001$ (n = 2,673) (Craig et al., 2020). Applying this PRS to the independent ANZRAG cohort (Australian and New Zealand Registry of Advanced Glaucoma; 1,734 advanced POAG cases and 2,938 controls) demonstrated that participants in the top decile of PRS were at a 15 fold increased odds of POAG than the bottom decile, and 4.2 fold odds compared to the other 90% of the cohort (Craig et al., 2020). When the PRS was combined with age, sex and reported family history of glaucoma, it predicted POAG with an AUC of 80% in the population-based Blue Mountains Eye Study (Craig et al., 2020). While this level of predictive ability is certainly not diagnostic alone, it may enable identification of a subset of the general population with a sufficiently high prevalence of glaucoma to make screening cost-effective. Currently, in most developed settings such as the UK, population screening for POAG is not recommended (Hamid et al., 2021). This is in part due to the relatively low prevalence of undetected glaucoma in the population and the resultant poor positive predictive value of current best tests. Targeting screening to a subset of the population with a higher prevalence of glaucoma would result in an improved positive predictive value with the same test. The above-mentioned studies offer hope that genetic prediction models can identify a POAG-

enriched proportion of the general population for whom glaucoma screening will be cost-effective and beneficial (Hamid et al., 2021). A recent cross-sectional, questionnaire-based study of patients with advanced glaucoma demonstrated strong support for genetic prediction testing facilitating detection of glaucoma in the future (Hollitt et al., 2021).

3. Primary Angle-Closure glaucoma

3.1 Epidemiology

Primary angle-closure glaucoma (PACG) is one of the most common types of glaucoma, currently affecting 17.4 million individuals worldwide, of which over 70% are of Asian ancestry (Chan et al., 2016; Cheng et al., 2014b; Wang et al., 2019; Zukerman et al., 2020). This number is expected to double by 2040 (Tham et al., 2014). In this form of glaucoma, anatomical alterations in the anterior chamber result in the iris occluding the iridio-trabecular meshwork angle, interfering with aqueous outflow. The resultant increase in IOP initiates a cascade of pathological alterations that lead to glaucomatous optic neuropathy, resulting in blindness.

3.2 Clinical Features/pathophysiology of PACG

Angle closure disease can be classified by the extent of disease severity (Ahram et al., 2015; Aung et al., 2005; Foster et al., 2002; Sun et al., 2017; Wang et al., 2019; Weinreb et al., 2014). Eyes classified as primary angle-closure suspects (PACS) have an occluded angle, but do not exhibit increased IOP and present with healthy optic nerves. Primary angle-closure eyes (PAC) have raised IOP and/or peripheral anterior synechiae in the angles, but the optic nerves are not damaged, representing the intermediate stage of disease. Finally, primary angle-closure glaucoma (PACG) eyes represent the fully manifest disease, and present with glaucomatous neuropathy, accompanied by visual field loss in association with angle closure.

Regardless of stage, anatomical abnormalities that occlude the iridio-trabecular meshwork angle initiate PACG disease (Sun et al., 2017; Weinreb et al., 2014). These can be broadly classified into several main mechanisms: pupillary block, non-pupillary block, and multiple or mixed mechanism. In pupillary block, there is resistance to aqueous flow at the level of the pupil between the iris and the anterior lens surface, causing build-up of aqueous behind the iris. The resultant pressure difference causes the peripheral iris to bulge anteriorly, narrowing the angle. This mechanism is the most common trigger of acute angle closure. In non-pupillary block, abnormalities in other anterior segment structures, for example, a thicker peripheral iris, an abnormally positioned iris due to anterior rotation of the ciliary body or a large lens vault, crowd the angle and hinder aqueous drainage. In mixed mechanism angle closure, multiple anatomic alterations occur concurrently to occlude the iridio-trabecular meshwork angle and initiate disease.

3.3 Risk factors for PACG

Due to the anatomical basis of angle closure, the biometric configuration of the eye is the biggest risk factor for PACG (Nongpiur et al., 2019; Razeghinejad and Banifatemi, 2013; Sun et al., 2017). Shallow anterior chamber depth (ACD), short axial length and thick, relatively anteriorly positioned lens are major anatomical risk factors for PACG (Alsbirk, 1986; Nongpiur et al., 2011; Tarongoy et al., 2009; Weinreb et al., 2014). In particular, a shallow anterior chamber depth appears to be key in PACG susceptibility. Eyes with ACD of less than 2.8mm have a high propensity to develop angle closure (Lavanya et al., 2008) and have increased risk of developing glaucomatous optic neuropathy. (Aung et al., 2005) Other risk factors for angle closure including age, East Asian ethnicity and female sex can also be explained by biometry. Eyes of East Asians tend to have shallower anterior chambers, compared to Europeans (Wang et al., 2013). Similarly, female eyes tend to be smaller and have shallower ACD compared to males (Alsbirk, 1976). Aging increases the thickness of the lens, resulting in anterior chamber crowding (Lowe, 1969; Tomlinson and Leighton, 1973), thereby accounting for the increased risk of PACG with age.

3.4 Heritability estimates for PACG

There is a strong genetic basis for PACG. The risk of developing PACG is 3.5 times higher in first degree relatives (Kavitha et al., 2014) and up to 6 times if they are of Chinese ancestry (Sim et al., 1998; Wang, 1985). Siblings of patients diagnosed with angle closure who were of Chinese ancestry also have a drastically increased (about seven times) likelihood of developing the same condition compared to the general population. As such, the heritability of angle closure has been estimated to be nearly 60% (Amerasinghe et al., 2011). This could be in part due to genetic factors strongly influencing biometric parameters of the eye. In particular, ACD is highly heritable, with estimates of 50-88% in Caucasians (Klein et al., 2009), 56% for South Indians (Ciociola et al., 2021), and up to 90% in the Chinese population (He et al., 2008). In addition, population-based studies have found that narrow angles are frequently found in of Chinese eyes (7%) and a substantial proportion (10%) will be afflicted with angle closure disease (Ye et al., 1998).

3.5 Genetic Studies of PACG

Several genetic studies have been undertaken to find risk genes for PACG and associated biometric phenotypes. Family linkage analysis of a large family afflicted with nanophthalmos, hyperopia, and angle closure glaucoma led to the discovery of *NNO1*, a locus mapping to chromosome 11 (Othman et al., 1998). *NNO1* remains the only locus that is directly linked to an angle closure phenotype, although the causal gene(s) within this locus has not been elucidated.

Since then, two cross-ancestry GWAS on PACG have identified 8 loci that are associated with risk of developing PACG (Khor et al., 2016; Vithana et al., 2012). The first study, involving more than 20,000 cases and controls from 5 countries, identified 3 loci - *PLEKHA7* rs11024102, *COL11A1* rs3753841 and rs1015213 located between *PCMTD1* and *ST18* on Chromosome 8q that were significantly associated with PACG. The follow-up study (Khor et al., 2016) comprised over 40,000 participants from 23 countries world-wide. The results replicated the initial 3 loci and uncovered 5 new loci- *EPDR1* rs3816415, *CHAT* rs1258267, *GLIS3* rs736893, *FERMT2* rs7494379, and *DPM2* - *FAM102A*. Notably, two of the loci

(*PLEKHA7* and *FERMT2*) are also associated with risk of increased IOP (Khawaja et al., 2018b; MacGregor et al., 2018), underlining the key contribution of IOP to PACG disease as well as possible shared mechanisms with POAG.

These loci have been replicated in many follow-up studies that dissect the association of these loci to PACG disease severity (Awadalla et al., 2013; Duvesh et al., 2013; Nongpiur et al., 2018; Rong et al., 2016; Shi et al., 2013; Wan et al., 2019). The results largely support the association of these loci with PACG risk, despite heterogeneity in the clinical presentation, ethnic make-up, and sample sizes of cohorts. Most notably, *EPDR1* rs3816415 was significantly associated with severe PACG disease in the Singaporean Chinese population. A weighted polygenic risk score matrix generated from the 8 key GWAS loci was also significantly associated with higher risk of fully manifest and intermediate PACG disease (Liu et al., 2021).

3.6 Functional investigation of PACG risk genes

Studies characterizing PACG risk genes have been ongoing. Notably, there is suggestive evidence from analysis of disease tissue and functional characterization in cellular models that *PLEKHA7* rs11024102, which has been associated with both PACG risk and high IOP, could be involved in some aspects of PACG pathogenesis (Lee et al., 2014; Lee et al., 2017). PLEKHA7 was found highly expressed in the anterior chamber and associated with apical junction complexes (AJCs; (Lee et al., 2014)), which are known to regulate cell polarity, adhesion and barrier permeability. The risk associated *PLEKHA7* rs11024102 (Lee et al., 2017) was also associated with lower expression of PLEKHA7, implying that this could be a regulatory SNP that controls PLEKHA7 expression. Concordant with its association with AJCs, PLEKHA7 was found to modulate cell migration and barrier permeability. While these data is somewhat informative, it is unclear how how PLEKHA7-related alterations due to its lowered expression in disease tissue manifests in PACG.disease It is also unclear whether lowered expression of PLEKHA7 is a key driver event in PACG pathogenesis. Therefore more studies, especially in animal models are required to clarify the role of PLEHA7 in PACG disease process. Similarly, a combination of functional investigation in both cellular models and animals are required to determine the importance of other risk-associated genes in PACG pathogenesis.

3.7 Candidate Gene Approaches for PACG

Additional risk loci have also been discovered by interrogating SNPs occurring within or near genes that could potentially participate in PACG pathogenesis using hypothesis-driven approaches. The most prominent of these is *MMP9*, a collagenase that is presumed to influence extracellular matrix remodelling in the eye. Multiple SNPs within or near *MMP9* have also been associated with PACG in multiple cohorts of differing ethnicity (Awadalla et al., 2011a; Cong et al., 2009; Micheal et al., 2013; Wang et al., 2006). Additionally, multiple loci linked to other *MMP9*-related genes, including *HGF* (Awadalla et al., 2011b), *HSP70* (Ayub et al., 2010), *MFRP* and *NOS3* (Rong et al., 2016) were also found to be associated with PACG in a recent meta-analysis, although it is still unclear whether they directly participate in PACG disease.

3.8 Quantitative Trait Loci Analysis for PACG

As the anatomical configuration of the eye is a major risk factor for PACG, quantitative trait loci (QTL) studies have also been undertaken to find risk genes linked to biometric parameters. The most prominent QTL loci is *ABCC5* rs1401999, which is associated with a shallower ACD (Nongpiur et al., 2014) ($\beta = -0.045$ mm ACD, $P = 8.17 \times 10^{-9}$). This locus was discovered in large, Asian cohort of 5,308 individuals, and was also associated with PACG risk in a separate cohort. However, it failed to replicate PACG risk in a much larger multi-ancestry cohort from a subsequent PACG GWAS that uncovered the 8 key risk loci for PACG (Khor et al., 2016; Vithana et al., 2012) (see above). A possible explanation for this discrepancy could be that the association of shallower ACD with PACG risk is only limited to Asians, whereas other quantitative traits that influence other biometric parameters such as lens thickness, anterior chamber width and lens vault could be universally more important for conferring risk in other ethnicities. Future QTL studies should incorporate other relevant traits to fully examine this possibility.

3.9 Insights into disease mechanism and identification of potential therapeutic targets

Despite the discovery of many well validated risk-associated loci from GWAS experiments, the identity of driver genes, and by implication, insight into disease mechanisms from genetics remain uncertain. Fundamentally, this is because the overwhelming majority of risk loci found by GWAS are non-coding, and the current practise of nominating the gene located closest to the sentinel GWAS SNP as the 'candidate gene of prime interest' is misleading. Co-localization approaches (Nicolae et al., 2010) integrating expression Quantitative Trait Loci (eQTL) and GWAS data (Giambartolomei et al., 2014; Gusev et al., 2016; He et al., 2013; Hormozdiari et al., 2016; Huang et al., 2015; Nica et al., 2010) could be helpful in identifying the causal gene in the vicinity of the risk SNP. However, because non-coding variants could exert their regulatory effects beyond their immediate loci, the identity of the actual effector gene can remain obscure. To address the possibility that effector genes could reside in a distant location from the sentinel SNP (Smemo et al., 2014), advances in the understanding of chromatin interactions are needed before we can begin to elucidate driver genes linked to risk-associated SNPs located in non-coding regions.

3.10 Next Generation Sequencing approaches uncover potential risk genes in PACG

Due to the challenges in nominating effector genes arising from GWAS studies, the focus has gradually shifted towards using whole exome-sequencing to study the genetic basis of glaucoma. Indeed, new causal genes have been uncovered in other diseases using this platform, giving rise to both novel insights into disease and new therapeutic drug targets. Likewise, promising new gene candidates have emerged through interrogating coding variation in families afflicted with PACG (Sun et al., 2019; Suri et al., 2018; Waseem et al., 2020). In particular, recurrent coding mutations in *COL18A1* (Suri et al., 2018*)* and *SPATA3 (*Waseem et al., 2020) have recently been observed in familial pedigrees with multiple related individuals affected by PACG.

The c.550G>A mutation in *COL18A1* were first discovered from linkage analysis of a multi-generational Iranian family. The corresponding amino acid substitution E184K, was predicted to be deleterious. A longitudinal search uncovered two unrelated PACG patients who are heterozygous carriers of additional frameshift mutations at R505Vfs and L612Wfs in *COL18A1*. Interestingly, bi-allelic loss of function mutations in *COL18A1* are known to cause Knobloch syndrome, a rare autosomal recessive inherited disorder characterized by vitreoretinal degeneration leading to retinal detachment (Menzel et al., 2004; Sertie et al., 1996). Although homozygous mutations in *COL18A1* appear to cause ocular abnormalities in the posterior chamber of individuals afflicted with Knobloch syndrome, it remains unclear how heterozygous *COL18A1* mutations lead to PACG-associated phenotypes manifesting in the. Further characterization, including the type (i.e., gain or loss of function) and extent of functional alteration of all three alleles are needed to determine if there could be dose-dependent effects that modify disease phenotype.

SPATA13 codes for a guanine nucleotide exchange factor (GEF) for GTPases that regulate a multitude of cellular signalling pathways and processes (Bristow et al., 2009; Sagara et al., 2009). A 9 base-pair deletion in the *SPATA13* coding region was found in an initial pedigree of 3 members afflicted with angle closure and established to be transmitted in an autosomal dominant manner. Follow up evaluation in an independent cohort of 189 patients uncovered 8 additional mutations in the same gene. The researchers observed increased GEF activity in the deletion mutant and 3 out of the 8 protein altering SPATA13 variants. Although this suggests that *SPATA13* gain of function could be causing PACG phenotypes, the researchers noted that the precise cellular processes modulated by SPATA3 remain unknown. They also observed that only a subset of coding variants exhibited increased GEF activity (Waseem et al., 2020). Additional investigation in disease tissue and relevant cell lines to find the key GTPase modulated by SPATA13 will reveal mechanistic links to PACG.

Nevertheless, these initial forays into exome sequencing exemplify the power of studying coding variants to uncover risk genes that participate in PACG pathogenesis in a more direct manner. To this end, larger genetic consortia have begun to utilize whole exome sequencing approaches to find coding variants associated with PACG risk in population-based studies.

4. Exfoliation Syndrome and Glaucoma

4.1 Epidemiology

Exfoliation glaucoma (XFG) is a late-onset systemic disorder that afflicts over 60 million people worldwide (Ritch and Schlotzer-Schrehardt, 2001; Tham et al., 2014). This condition initially manifests as exfoliation syndrome (XFS), where abnormal extracellular debris termed exfoliative material are deposited visibly in the anterior chamber of the eye (Ritch and Schlotzer-Schrehardt, 2001; Ritch et al., 2003). XFS has also been epidemiologically linked to several systemic conditions including cerebrovascular disease and cardiovascular disease (Elhawy et al., 2012; Ritch, 2016), although it is still unclear whether these deposits play casual roles in these conditions.

4.2 Pathophysiology of Exfoliation syndrome

XFS manifests in the eye as exfoliative deposits in the anterior segment structures of the eye, including the ciliary body, lens capsule, iris, and trabecular meshwork. This deposition may impede aqueous outflow and eventually increase in IOP. As a result, about half of all XFS patients will develop XFG, making it the most common cause of open angle glaucoma in the world (Weinreb et al., 2014). Compared to POAG, XFG is a more aggressive disease. XFG patients often present with a higher IOP accompanied by more advanced visual field loss and tend to respond poorly to IOP lowering medication (Ritch and Schlotzer-Schrehardt, 2001; Ritch et al., 2003). The severity of the clinical phenotypes has been directly correlated with the extent of exfoliation deposition – and by implication the extent of outflow impedance- at the trabecular meshwork (Ritch and Schlotzer-Schrehardt, 2001; Ritch et al., 2003; Schlotzer-Schrehardt and Naumann, 1995). Although an obvious clinical management strategy is to modulate exfoliation deposition in the eye, the lack of mechanistic understanding of processes underlying exfoliative material deposition precludes this approach. Consequently, symptomatic treatment by lowering IOP using a combination drugs and surgical intervention remains the standard-of-care in XFG management (Jonas et al., 2017; Weinreb et al., 2014).

4.3 Risk Factors

XFS/XFG risk factors include age, family history and ethnicity (Ritch and Schlotzer-Schrehardt, 2001; Ritch et al., 2003). Familial segregation analyses using pedigrees and twin studies have established XFS/XFG as a disorder with a clear genetic component. However, the mode of Mendelian inheritance is not clear, implying that XFS/XFG is a complex disease with interactions involving multiple genes and environmental factors (Wiggs and Pasquale, 2017). In line with this notion, XFS/XFG prevalence varies among ethnic groups, with the highest prevalence observed in the Scandinavian population, where XFG is observed in up to two-thirds of patients afflicted with open-angle glaucoma (Zukerman et al., 2020). Although there is some epidemiologic evidence that UV exposure and caffeine intake could be associated with XFS risk (Dewundara and Pasquale, 2015; Kim et al., 2021; Pasquale et al., 2014; Stein et al., 2011), the mechanistic basis of these findings, and whether there are additional lifestyle factors contributing to this finding, remains to be dissected.

4.4 GWAS studies

To tease out the genetic component underlying XFS/XFG risk, several genome wide association studies have been performed. SNPs located within or near *LOXL1*, *CACNA1A*, *FLT1-POMP*, *TMEM136-ARHGEF12*, *AGPAT1*, *RBMS3*, and *SEMA6A* have been reported to be associated with risk of XFS at genome-wide significance (Aung et al., 2017; Aung et al., 2015). However, as in GWAS studies of other forms of glaucoma, these loci were located either in intergenic or intronic regions, suggesting that these candidate genes might not be the effector genes directly participating in XFS pathogenesis.

4.5 LOXL1 studies and allele reversal

The only XFS risk gene discovered in GWAS studies whose effect size is substantial is *LOXL1* (Thorleifsson et al., 2007*)*. Consequently, *LOXL1* remained a key focal point of all subsequent XFS/XFG experimental efforts to understand the underlying disease mechanism (Schlotzer-Schrehardt and Zenkel, 2019). *LOXL1* was first discovered as a risk gene in a genome-wide association study conducted on the Icelandic population (Thorleifsson et al., 2007). Two common SNPs in exon 1 of *LOXL1*, rs1048661: G>T (R141L), and rs3825942: G>A (G153D) conferred more than 20-fold risk of XFS. Although these associations have been largely replicated in multiple geographical populations, the phenomenon of allele reversal observed between Europeans, Japanese, and South Africans made it impossible to discern whether gain or loss of LOXL1 function was associated with increased risk of XFS (Abu-Amero et al., 2012; Guadarrama-Vallejo et al., 2013; Jaimes et al., 2012; Liu et al., 2008; Williams et al., 2010). For example, the G allele of rs1048661 has been established as risk increasing with nearly all populations studied except in Asian populations, where it was found to be protective (Gong et al., 2008; Nakano et al., 2014; Pandav et al., 2019). Similarly, the G allele of rs3825942 was found to be associated with increased risk in all populations except in Black South Africans (Williams et al., 2010). The reasons underlying these stark allele reversals remain unknown to date.

To uncover *LOXL1* variants with larger effect sizes that are not reversed, a global research partnership carried out deep resequencing studies of the *LOXL1* gene.(Aung et al., 2017) This revealed multiple rare protein-altering variants, the vast majority of which were enriched in unaffected participants compared to patients with XFS. One particular rare variant (*LOXL1* p. Y407F, with a frequency of <1% in the Japanese control population) had a singularly striking effect size, conferring 25-fold protection against XFS.

4.6 Functional investigation of LOXL1 alleles and their roles in XFG

The *LOXL1* gene encodes a lysl oxidase that cross links collagen and elastin fibrils in the extracellular matrix (ECM) (Greene et al., 2020). Cross-linking strengthens and stabilizes elastin fibres and by extension, the ECM, increasing its resistance to mechanical stress and degradation. Analysis of LOXL1 expression in disease tissue suggests that LOXL1 could be involved in XFS pathogenesis. LOXL1 is ubiquitously expressed in nearly all ocular tissues in the anterior segment and was found to be induced in the early stages of XFS (Schlotzer-Schrehardt, 2009; Schlotzer-Schrehardt and Zenkel, 2019). The trigger(s) for induction has not been found, although cellular stress such as inappropriate growth factor abundance changes, inflammation, oxidative stress, and UV light have been suggested. Importantly, LOXL1 has been found to be major component of exfoliative deposits (Sharma et al., 2009) colocalizing with ECM components such as elastin and fibrillin (Ovodenko et al., 2007), suggesting that LOXL1 could nucleate and stabilise these deposits. In later stages of XFS, LOXL1 expression was found to be reduced in anterior segment tissues (Schlotzer-Schrehardt, 2009; Schlotzer-Schrehardt and Zenkel, 2019). This could affect structural stability of the ECM in ocular tissue and may contribute to the compromise of blood ocular barrier in the ciliary body, leading to leakage of serum proteins such as ApoE, which are also present in exfoliative material, and perpetuate additional cycles of exfoliative deposition. In agreement with this observation, the blood-ocular barrier was disrupted in mice lacking both

copies of the *LOXL1* gene, although exfoliative deposition were not observed (Wiggs et al., 2014). LOXL AS1?

Despite the wealth of correlative expression and genetic data implicating *LOXL1* in the disease process, the actual role of LOXL1 in the XFS disease process remains an enigma. Crosslinking-activity of the risk variants R141L and G153D has been demonstrated to be similar to the activity of the reference protein in vitro (Kim and Kim, 2012), implying that proteolytic processing of LOXL1 (Sharma et al., 2016) and protein-protein interactions with other participatory proteins (Schlotzer-Schrehardt and Zenkel, 2019) could be key towards uncovering its mechanism of action in cells.

Accordingly, evidence from studies in other disease contexts suggest that LOXL1 could indeed modulate cellular signal transduction by modifying the ECM (Greene et al., 2020; Hu et al., 2020b; Ma et al., 2018; Vallet and Ricard-Blum, 2019). The ECM participates in a wide variety of cellular processes, and it is not surprising that mutation of LOXL1 or pathological alteration of its expression has been linked to other systemic disorders. However, the resultant phenotypes are often the result of context-specific interactions of LOXL1 with components within the local microenvironment. This context-specificity of LOXL1 interactions underlies the difficulty in elucidating LOXL1 function in ocular contexts, as it renders characterization of *LOXL1* variants *in vitro* in the absence of the appropriate context uninformative. Complementary genetic studies focusing on rare variants with larger effect sizes are needed to pinpoint other key risk gene variants and identify additional cellular processes that could play a role in XFS pathogenesis. The recent discovery of *CYP39A1* loss-of-function gene variants as XFS susceptibility factors could be a feasible starting point to begin elucidating the role of *LOXL1* variants and the ECM in XFS disease (Genetics of Exfoliation Syndrome et al., 2021).

4.6 Whole exome sequencing studies in a large multinational cohort implicates *CYP39A1* as a XFS risk gene

An exome-wide search was recently undertaken to uncover XFS risk-associated rare coding sequence variants that might have been missed by previous GWAS studies (Genetics of Exfoliation Syndrome et al., 2021). In this multicenter case-control, study involving 20 441 participants, both *LOXL1* and *CYP39A1* were found to harbour a significant differential burden of rare, protein-altering genetic variants between patients with XFS and unaffected individuals. In particular, *CYP39A1* loss of function alleles were significantly enriched in XFS cases compared to controls (3.25% vs 1.8%). *CYP39A1* encodes a hydroxylase involved in the breakdown of cholesterol, converting its substrate 24-hydroxycholesterol (24-OHC) to 24,7-dihydroxycholesterol (Li-Hawkins et al., 2000). The association of *CYP39A1* was novel and thus subjected to additional scrutiny via replication attempts in independent cohorts. Meta-analysis of all studied samples suggested that carriage of rare *CYP39A1* loss-of-function variant had a 2-fold increased risk of developing XFS compared to non-carriers.

4.7 Functional investigation of *CYP39A1* alleles

Due to limitations with current bioinformatics prediction algorithms, all discovered CYP39A1 variants were evaluated for enzymatic activity using, and most were confirmed to have lower enzymatic activities than the reference protein. Follow-

up investigation in disease tissue revealed that the expression of CYP39A1 was decreased throughout all stages of XFS including early disease. As 24-OHC regulates the cholesterol efflux by activating the Liver X Receptor transcriptional program (Beceiro et al., 2018; Traversari et al., 2014; Wang and Tontonoz, 2018), XFS tissue was examined for alterations in cholesterol homeostasis. Strikingly, esterified cholesterol, the form packaged by cells for storage and/or transport was found to be enriched and colocalized in exfoliation deposits. Most importantly, and for the first time since the discovery of *LOXL1* as an XFS risk gene, a new cellular process, cholesterol efflux had been implicated in XFS disease.

As the plasma membrane and the adjoining basement ECM is the site of cholesterol efflux, it is conceivable that LOXL1 could be involved in regulating this process. To lend further support to this possibility, WES sequencing of more cohorts should be performed to determine the co-carriage status of *LOXL1* and *CYP39A1* variants in patients or controls, to establish if there is a genetic and/or mechanistic interaction between the two genes. Experimental characterization is also needed to determine the involvement of *LOXL1* and its variants in influencing this process, and to determine if *CYP39A1* loss-of-function driven cholesterol efflux could compromise blood-aqueous barrier integrity and/or influence exfoliative deposition. A key acid test to assess the importance of CYP39A1 and LOLX1 in XFS disease would be construction of an animal model for XFS by genetic engineering of relevant CYP39A1 and/or LOXL1 alleles, since no such model presently exists presently.

4.8 Using risk alleles to predict XFS disease

Individually, the frequency of these variants in the population are rare, but collectively, carriers of *LOXL1* and *CYP39A1* variants make up a substantial proportion of the population, suggesting that functionally validated variants could have additional utility as data points for patient stratification algorithms (**Figure 4**) (Bell et al., 2021). While single gene variants had been used in risk prediction algorithms in other complex genetic diseases, incorporation of both *LOXL1* and *CYP39A1* variants into XFS risk prediction algorithms could potentially improve accuracy and precision in stratifying individual XFS risk. However, experimental work is needed to develop an appropriate assay that can appropriately reflects the contribution of variants of both genes towards disease risk.

The discovery of *CYP39A1* using WES-based approaches underscores the utility of this approach towards directly uncovering causal risk genes in complex diseases. With its increasing popularity, more WES studies performed in large cohorts will uncover more casual risk gene variants, not just in XFS/XFG, but other glaucoma subtypes. Future work done to explain the way these variants influence XFS risk will illuminate underlying disease processes. This will enable the expansion the repertoire of XFS management strategies from IOP management to actual modulation or prevention of exfoliative deposition.

5. Future directions

5.1 Coalescence of genetic discovery with functional characterization

A major weakness in glaucoma genetics has been the lack of integrative studies that translate discovery of genetic risk variation to actual functional significance in disease. This is in part due to the diversity of genetic sequence

variants associated with glaucoma risk. Thus far, all genetic discovery have been centered mostly on non-coding SNPs, which for reasons outlined above preclude experimental follow up for functional validation. With the emergence of whole exome sequencing technology, we are now well positioned to directly identify risk-associated coding variants. In contrast to SNPs, coding variants are very amenable to experimental characterisation, especially when appropriate functional assays are utilized. Therefore, instead of relying on bioinformatics algorithms, which are neither precise nor quantitative, it is increasingly likely that actual functional characterization of risk alleles will be used to confirm the direction and/or extent of genetic variation (i.e., loss or gain of function) that is associated with disease risk as part of the validation process. This would accelerate our understanding of how alterations in these gene contribute to glaucoma pathology and enable us to see disease processes in a new light. In the longer term, advances in whole genome sequencing (WGS) (Amarasinghe et al., 2020; Ng and Kirkness, 2010) accompanied by decreases in costs of sequencing will enable the application of this technology in large cohort studies, potentially implicating important non-coding alterations and copy number changes in glaucoma pathogenesis, enabling a more complete view of genomic mechanisms contributing to disease.

5.2 Complementary technologies for orthogonal functional validation

Regardless of the technological platform used for risk gene discovery, thorough functional investigation of candidates and careful interpretation of experimental results, especially in resolving inevitable discrepancies between data generated from *in vitro* and *in situ* contexts, are requisite for candidate gene validation. In particular, the appropriate use of complementary profiling technologies, including high resolution imaging modalities (Adhi and Duker, 2013) to characterize glaucoma-related anatomical alterations, and single cell transcriptomic approaches (Stuart and Satija, 2019) to investigate gene expression in disease tissue will be potentially valuable as an orthogonal means of validation. Single cell approaches could be valuable given the scarce availability of ocular disease tissue (Voigt et al., 2021). Indeed, novel insights have been obtained from scRNA studies in retina disease tissue (Menon et al., 2019; Orozco et al., 2020; Voigt et al., 2019). Indeed, recent scRNA-based studies in glaucoma (Patel et al., 2020; van Zyl et al., 2020), have begun to expand our understanding of glaucoma disease at the cellular level, bridging the knowledge gap from gene discovery to actual understanding of disease mechanisms.

5.3 Cell and animal models continue to be crucial for mechanistic validation of risk genes

Once the identity of the risk gene has been established, cellular and animal models are imperative to infer the role of these genes in disease process. Cellular models are usually the first step towards this because of its relative ease of manipulation. In particular, the deployment of CRISPR based editing techniques either to knock out genes or to introduce important risk alleles would be important towards characterizing glaucoma-related phenotypes and elucidate key downstream pathways impacted by this manipulation. Organoid models and/or other 3D-type models, are thought to recapitulate spatial aspects of disease tissue and will add an extra dimension towards the understanding of disease process. Physiologically relevant animal models can then be used to bridge the gap between in vitro

observations and their importance in actual disease tissue, These could involve crossing appropriate alleles (mouse model studies references) to existing glaucoma models in mice or rats, and/or using conditional knockouts in ocular tissue to investigate specific aspects of disease physiology and determine if they modify disease severity. These animal models can then be used as platforms to evaluate and test therapeutic modalities for glaucoma therapeutics

5.4 Validated risk genes are attractive drug targets for glaucoma therapeutics

Genetic studies based upon next generation sequencing approaches have unearth a treasure trove of validated drug targets that have been successfully translated into approved therapeutics (Abifadel et al., 2003; Cohen et al., 2005; Cohen et al., 2006; Dewey et al., 2017; Graham et al., 2017; Shapiro et al., 2018). Functional characterization of risk genes in cellular and animal models (outlined above) will also increase the number of potential drug targets for glaucoma, enabling the development of new therapeutics for glaucoma management. As these targets have strong genetic support, they are more likely to pass clinical trials and achieve regulatory approval (King et al., 2019; Nelson et al., 2015). This will eventually expand the repertoire of glaucoma treatment options and enable the use of subtype-directed treatment regimens, potentially improving prognostic outcomes.

5.5 Genetic data as a substrate for predicting glaucoma risk

A recent survey of genetic variation in the exome demonstrated that when taken in aggregate, rare protein altering genetic variants are more common than previously thought (Lek et al., 2016). It was estimated that over 90% of human genetic variation are rare (MAF<1%) and an overwhelming majority are singleton or “private” mutations that are only found once in a cohort (Lek et al., 2016). Consequently, as increasingly more patients undergo whole exome/genome diagnostic sequencing, more and more singletons will be found, representing a potentially large source of variants of uncertain significance (VUS) in risk genes. Functional readouts of individual variants will provide granularity to individual predictions of disease risk and resolve diagnostic uncertainty by clarifying the functional status of VUS (**Figure 4**; (Findlay et al., 2018). Therefore, to pre-empt this emerging problem, functional ascertainment of all possible coding variation in important risk genes should be undertaken. When the resultant data is then integrated with relevant clinical data points, for example, disease outcomes of genotyped glaucoma patients in prospective studies, or progression-relevant biometric alterations observed in genotyped eyes, the resultant data could serve as useful raw material for generating precise risk stratification databases (Majithia et al., 2014; Majithia et al., 2016). This enables patients at high risk of progression to blindness to be identified early for prioritized intervention.

5.6 Conclusions

Next generation sequencing technologies coupled with high throughput functional genomics will revitalize the field of glaucoma genetics by enabling the direct identification of causal genes for glaucoma. However, close multidisciplinary collaborations are required to transcend beyond statistical associations and obtain crucial insight into glaucoma pathogenesis. Only then will this enable timely and

positive real-life impacts on clinical practice to ameliorate the escalating problem of glaucoma-related blindness due to the rapid aging of the world's population.

6. References

(1998a). Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. Collaborative Normal-Tension Glaucoma Study Group. Am J Ophthalmol *126*, 487-497.

(1998b). The effectiveness of intraocular pressure reduction in the treatment of normal-tension glaucoma. Collaborative Normal-Tension Glaucoma Study Group. Am J Ophthalmol *126*, 498-505.

Abifadel, M., Varret, M., Rabes, J.P., Allard, D., Ouguerram, K., Devillers, M., Cruaud, C., Benjannet, S., Wickham, L., Erlich, D.*, et al.* (2003). Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. Nat Genet *34*, 154-156.

Abu-Amero, K.K., Osman, E.A., Azad, M.T., Allingham, R.R., Hauser, M.A., and Al-Obeidan, S.A. (2012). Lack of association between LOXL1 gene polymorphisms and primary open angle glaucoma in the Saudi Arabian population. Ophthalmic Genet *33*, 130-133.

Adhi, M., and Duker, J.S. (2013). Optical coherence tomography--current and future applications. Curr Opin Ophthalmol *24*, 213-221.

Ahram, D.F., Alward, W.L., and Kuehn, M.H. (2015). The genetic mechanisms of primary angle closure glaucoma. Eye (Lond) *29*, 1251-1259.

Alipanahi, B., Hormozdiari, F., Behsaz, B., Cosentino, J., McCaw, Z.R., Schorsch, E., Sculley, D., Dorfman, E.H., Foster, P.J., Peng, L.H.*, et al.* (2021). Large-scale machine-learning-based phenotyping significantly improves genomic discovery for optic nerve head morphology. Am J Hum Genet *108*, 1217-1230.

Allen, K.F., Gaier, E.D., and Wiggs, J.L. (2015). Genetics of Primary Inherited Disorders of the Optic Nerve: Clinical Applications. Cold Spring Harb Perspect Med *5*, a017277.

Allingham, R.R., Liu, Y., and Rhee, D.J. (2009). The genetics of primary open-angle glaucoma: a review. Exp Eye Res *88*, 837-844.

Allingham, R.R., Wiggs, J.L., De La Paz, M.A., Vollrath, D., Tallett, D.A., Broomer, B., Jones, K.H., Del Bono, E.A., Kern, J., Patterson, K.*, et al.* (1998). Gln368STOP myocilin mutation in families with late-onset primary open-angle glaucoma. Invest Ophthalmol Vis Sci *39*, 2288-2295.

Alsbirk, P.H. (1976). Primary angle-closure glaucoma. Oculometry, epidemiology, and genetics in a high risk population. Acta Ophthalmol Suppl, 5-31.

Alsbirk, P.H. (1986). Limbal and axial chamber depth variations. A population study in Eskimos. Acta Ophthalmol (Copenh) *64*, 593-600.

Alward, W.L., Fingert, J.H., Coote, M.A., Johnson, A.T., Lerner, S.F., Junqua, D., Durcan, F.J., McCartney, P.J., Mackey, D.A., Sheffield, V.C.*, et al.* (1998). Clinical features associated with mutations in the chromosome 1 open-angle glaucoma gene (GLC1A). N Engl J Med *338*, 1022-1027.

Amarasinghe, S.L., Su, S., Dong, X., Zappia, L., Ritchie, M.E., and Gouil, Q. (2020). Opportunities and challenges in long-read sequencing data analysis. Genome Biol *21*, 30.

Amerasinghe, N., Zhang, J., Thalamuthu, A., He, M., Vithana, E.N., Viswanathan, A., Wong, T.Y., Foster, P.J., and Aung, T. (2011). The heritability and sibling risk of angle closure in Asians. Ophthalmology *118*, 480-485.

Anderson, D.R., and Hendrickson, A. (1974). Effect of intraocular pressure on rapid axoplasmic transport in monkey optic nerve. Invest Ophthalmol *13*, 771-783.
Anderson, D.R., and Normal Tension Glaucoma, S. (2003). Collaborative normal tension glaucoma study. Curr Opin Ophthalmol *14*, 86-90.
Anton, A., Andrada, M.T., Mujica, V., Calle, M.A., Portela, J., and Mayo, A. (2004). Prevalence of primary open-angle glaucoma in a Spanish population: the Segovia study. J Glaucoma *13*, 371-376.
Arkell, S.M., Lightman, D.A., Sommer, A., Taylor, H.R., Korshin, O.M., and Tielsch, J.M. (1987). The prevalence of glaucoma among Eskimos of northwest Alaska. Arch Ophthalmol *105*, 482-485.
Asefa, N.G., Neustaeter, A., Jansonius, N.M., and Snieder, H. (2019). Heritability of glaucoma and glaucoma-related endophenotypes: Systematic review and meta-analysis. Surv Ophthalmol *64*, 835-851.
Aspelund, A., Tammela, T., Antila, S., Nurmi, H., Leppanen, V.M., Zarkada, G., Stanczuk, L., Francois, M., Makinen, T., Saharinen, P.*, et al.* (2014). The Schlemm's canal is a VEGF-C/VEGFR-3-responsive lymphatic-like vessel. J Clin Invest *124*, 3975-3986.
Aung, T., Nolan, W.P., Machin, D., Seah, S.K., Baasanhu, J., Khaw, P.T., Johnson, G.J., and Foster, P.J. (2005). Anterior chamber depth and the risk of primary angle closure in 2 East Asian populations. Arch Ophthalmol *123*, 527-532.
Aung, T., Ozaki, M., Lee, M.C., Schlotzer-Schrehardt, U., Thorleifsson, G., Mizoguchi, T., Igo, R.P., Jr., Haripriya, A., Williams, S.E., Astakhov, Y.S.*, et al.* (2017). Genetic association study of exfoliation syndrome identifies a protective rare variant at LOXL1 and five new susceptibility loci. Nat Genet *49*, 993-1004.
Aung, T., Ozaki, M., Mizoguchi, T., Allingham, R.R., Li, Z., Haripriya, A., Nakano, S., Uebe, S., Harder, J.M., Chan, A.S.*, et al.* (2015). A common variant mapping to CACNA1A is associated with susceptibility to exfoliation syndrome. Nat Genet *47*, 387-392.
Awadalla, M.S., Burdon, K.P., Kuot, A., Hewitt, A.W., and Craig, J.E. (2011a). Matrix metalloproteinase-9 genetic variation and primary angle closure glaucoma in a Caucasian population. Mol Vis *17*, 1420-1424.
Awadalla, M.S., Thapa, S.S., Burdon, K.P., Hewitt, A.W., and Craig, J.E. (2011b). The association of hepatocyte growth factor (HGF) gene with primary angle closure glaucoma in the Nepalese population. Mol Vis *17*, 2248-2254.
Awadalla, M.S., Thapa, S.S., Hewitt, A.W., Burdon, K.P., and Craig, J.E. (2013). Association of genetic variants with primary angle closure glaucoma in two different populations. PLoS One *8*, e67903.
Ayub, H., Khan, M.I., Micheal, S., Akhtar, F., Ajmal, M., Shafique, S., Ali, S.H., den Hollander, A.I., Ahmed, A., and Qamar, R. (2010). Association of eNOS and HSP70 gene polymorphisms with glaucoma in Pakistani cohorts. Mol Vis *16*, 18-25.
Bailey, J.N., Loomis, S.J., Kang, J.H., Allingham, R.R., Gharahkhani, P., Khor, C.C., Burdon, K.P., Aschard, H., Chasman, D.I., Igo, R.P., Jr.*, et al.* (2016). Genome-wide association analysis identifies TXNRD2, ATXN2 and FOXC1 as susceptibility loci for primary open-angle glaucoma. Nat Genet *48*, 189-194.
Beceiro, S., Pap, A., Czimmerer, Z., Sallam, T., Guillen, J.A., Gallardo, G., Hong, C., N, A.G., Tabraue, C., Diaz, M.*, et al.* (2018). Liver X Receptor Nuclear Receptors Are Transcriptional Regulators of Dendritic Cell Chemotaxis. Mol Cell Biol *38*.
Bell, K.C., Ozaki, M., Mori, K., Mizoguchi, T., Nakano, S., Porporato, N., Ikeda, Y., Chihara, E., Inoue, K., Manabe, S.*, et al.* (2021). Association of the CYP39A1 G204E genetic variant with increased risk of glaucoma and blindness in patients with exfoliation syndrome. Ophthalmology.

Blindness, G.B.D., Vision Impairment, C., and Vision Loss Expert Group of the Global Burden of Disease, S. (2021). Causes of blindness and vision impairment in 2020 and trends over 30 years, and prevalence of avoidable blindness in relation to VISION 2020: the Right to Sight: an analysis for the Global Burden of Disease Study. Lancet Glob Health *9*, e144-e160.
Bourne, R.R., Sukudom, P., Foster, P.J., Tantisevi, V., Jitapunkul, S., Lee, P.S., Johnson, G.J., and Rojanapongpun, P. (2003). Prevalence of glaucoma in Thailand: a population based survey in Rom Klao District, Bangkok. Br J Ophthalmol *87*, 1069-1074.
Bristow, J.M., Sellers, M.H., Majumdar, D., Anderson, B., Hu, L., and Webb, D.J. (2009). The Rho-family GEF Asef2 activates Rac to modulate adhesion and actin dynamics and thereby regulate cell migration. J Cell Sci *122*, 4535-4546.
Bron, A., Tripathi, R., and Tripathi, B. (1998). Wolff's Anatomy of the Eye and Orbit, 8Ed (Taylor & Francis).
Burdon, K.P., Crawford, A., Casson, R.J., Hewitt, A.W., Landers, J., Danoy, P., Mackey, D.A., Mitchell, P., Healey, P.R., and Craig, J.E. (2012). Glaucoma risk alleles at CDKN2B-AS1 are associated with lower intraocular pressure, normal-tension glaucoma, and advanced glaucoma. Ophthalmology *119*, 1539-1545.
Burdon, K.P., Macgregor, S., Hewitt, A.W., Sharma, S., Chidlow, G., Mills, R.A., Danoy, P., Casson, R., Viswanathan, A.C., Liu, J.Z.*, et al.* (2011). Genome-wide association study identifies susceptibility loci for open angle glaucoma at TMCO1 and CDKN2B-AS1. Nat Genet *43*, 574-578.
Burgoyne, C.F. (2011). A biomechanical paradigm for axonal insult within the optic nerve head in aging and glaucoma. Exp Eye Res *93*, 120-132.
Caprioli, J. (2013). Glaucoma: a disease of early cellular senescence. Invest Ophthalmol Vis Sci *54*, ORSF60-67.
Caprioli, J., Coleman, A.L., and Blood Flow in Glaucoma, D. (2010). Blood pressure, perfusion pressure, and glaucoma. Am J Ophthalmol *149*, 704-712.
Carnes, M.U., Liu, Y.P., Allingham, R.R., Whigham, B.T., Havens, S., Garrett, M.E., Qiao, C., Investigators, N.C., Katsanis, N., Wiggs, J.L.*, et al.* (2014). Discovery and functional annotation of SIX6 variants in primary open-angle glaucoma. PLoS Genet *10*, e1004372.
Casson, R.J., Newland, H.S., Muecke, J., McGovern, S., Abraham, L., Shein, W.K., Selva, D., and Aung, T. (2007). Prevalence of glaucoma in rural Myanmar: the Meiktila Eye Study. Br J Ophthalmol *91*, 710-714.
Chan, E.W., Li, X., Tham, Y.C., Liao, J., Wong, T.Y., Aung, T., and Cheng, C.Y. (2016). Glaucoma in Asia: regional prevalence variations and future projections. Br J Ophthalmol *100*, 78-85.
Charlesworth, J., Kramer, P.L., Dyer, T., Diego, V., Samples, J.R., Craig, J.E., Mackey, D.A., Hewitt, A.W., Blangero, J., and Wirtz, M.K. (2010). The path to open-angle glaucoma gene discovery: endophenotypic status of intraocular pressure, cup-to-disc ratio, and central corneal thickness. Invest Ophthalmol Vis Sci *51*, 3509-3514.
Chen, Y., Lin, Y., Vithana, E.N., Jia, L., Zuo, X., Wong, T.Y., Chen, L.J., Zhu, X., Tam, P.O., Gong, B.*, et al.* (2014). Common variants near ABCA1 and in PMM2 are associated with primary open-angle glaucoma. Nat Genet *46*, 1115-1119.
Cheng, C.Y., Allingham, R.R., Aung, T., Tham, Y.C., Hauser, M.A., Vithana, E.N., Khor, C.C., and Wong, T.Y. (2014a). Association of common SIX6 polymorphisms with peripapillary retinal nerve fiber layer thickness: the Singapore Chinese Eye Study. Invest Ophthalmol Vis Sci *56*, 478-483.
Cheng, J.W., Zong, Y., Zeng, Y.Y., and Wei, R.L. (2014b). The prevalence of primary angle closure glaucoma in adult Asians: a systematic review and meta-analysis. PLoS One *9*, e103222.

Cherecheanu, A.P., Garhofer, G., Schmidl, D., Werkmeister, R., and Schmetterer, L. (2013). Ocular perfusion pressure and ocular blood flow in glaucoma. Curr Opin Pharmacol *13*, 36-42.
Choquet, H., Melles, R.B., Yin, J., Hoffmann, T.J., Thai, K.K., Kvale, M.N., Banda, Y., Hardcastle, A.J., Tuft, S.J., Glymour, M.M.*, et al.* (2020a). A multiethnic genome-wide analysis of 44,039 individuals identifies 41 new loci associated with central corneal thickness. Commun Biol *3*, 301.
Choquet, H., Paylakhi, S., Kneeland, S.C., Thai, K.K., Hoffmann, T.J., Yin, J., Kvale, M.N., Banda, Y., Tolman, N.G., Williams, P.A.*, et al.* (2018). A multiethnic genome-wide association study of primary open-angle glaucoma identifies novel risk loci. Nat Commun *9*, 2278.
Choquet, H., Thai, K.K., Yin, J., Hoffmann, T.J., Kvale, M.N., Banda, Y., Schaefer, C., Risch, N., Nair, K.S., Melles, R.*, et al.* (2017). A large multi-ethnic genome-wide association study identifies novel genetic loci for intraocular pressure. Nat Commun *8*, 2108.
Choquet, H., Wiggs, J.L., and Khawaja, A.P. (2020b). Clinical implications of recent advances in primary open-angle glaucoma genetics. Eye (Lond) *34*, 29-39.
Chrysostomou, V., Rezania, F., Trounce, I.A., and Crowston, J.G. (2013). Oxidative stress and mitochondrial dysfunction in glaucoma. Curr Opin Pharmacol *13*, 12-15.
Chua, S.Y.L., Thomas, D., Allen, N., Lotery, A., Desai, P., Patel, P., Muthy, Z., Sudlow, C., Peto, T., Khaw, P.T.*, et al.* (2019). Cohort profile: design and methods in the eye and vision consortium of UK Biobank. BMJ Open *9*, e025077.
Ciociola, E.C., Kavitha, S., Sengupta, S., Wiggs, J.L., Kader, M.A., Raman, G.V., Rajendrababu, S., Ramulu, P.Y., Venkatesh, R., and Zebardast, N. (2021). The Heritability of Primary Angle Closure Anatomic Traits and Predictors of Angle Closure in South Indian Siblings. Am J Ophthalmol *230*, 188-199.
Claussnitzer, M., Dankel, S.N., Kim, K.H., Quon, G., Meuleman, W., Haugen, C., Glunk, V., Sousa, I.S., Beaudry, J.L., Puviindran, V.*, et al.* (2015). FTO Obesity Variant Circuitry and Adipocyte Browning in Humans. N Engl J Med *373*, 895-907.
Cohen, J., Pertsemlidis, A., Kotowski, I.K., Graham, R., Garcia, C.K., and Hobbs, H.H. (2005). Low LDL cholesterol in individuals of African descent resulting from frequent nonsense mutations in PCSK9. Nat Genet *37*, 161-165.
Cohen, J.C., Boerwinkle, E., Mosley, T.H., Jr., and Hobbs, H.H. (2006). Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. N Engl J Med *354*, 1264-1272.
Collantes, E.R.A., Delfin, M.S., Jr., Fan, B., Torregosa, J.M.R., Siguan-Bell, C., Florcruz, N.V.G., Martinez, J.M.D., Masna-Hidalgo, B.J., Guzman, V.P.T., Anotado-Flores, J.F.*, et al.* (2021). EFEMP1 rare variants cause familial juvenile-onset open angle glaucoma. Hum Mutat.
Cong, Y., Guo, X., Liu, X., Cao, D., Jia, X., Xiao, X., Li, S., Fang, S., and Zhang, Q. (2009). Association of the single nucleotide polymorphisms in the extracellular matrix metalloprotease-9 gene with PACG in southern China. Mol Vis *15*, 1412-1417.
Craig, J.E., Han, X., Qassim, A., Hassall, M., Cooke Bailey, J.N., Kinzy, T.G., Khawaja, A.P., An, J., Marshall, H., Gharahkhani, P.*, et al.* (2020). Multitrait analysis of glaucoma identifies new risk loci and enables polygenic prediction of disease susceptibility and progression. Nat Genet *52*, 160-166.
Crooks, K.R., Allingham, R.R., Qin, X., Liu, Y., Gibson, J.R., Santiago-Turla, C., Larocque-Abramson, K.R., Del Bono, E., Challa, P., Herndon, L.W.*, et al.* (2011). Genome-wide linkage scan for primary open angle glaucoma: influences of ancestry and age at diagnosis. PLoS One *6*, e21967.

Cuellar-Partida, G., Craig, J.E., Burdon, K.P., Wang, J.J., Vote, B.J., Souzeau, E., McAllister, I.L., Isaacs, T., Lake, S., Mackey, D.A.*, et al.* (2016). Assessment of polygenic effects links primary open-angle glaucoma and age-related macular degeneration. Sci Rep *6*, 26885.
Currant, H., Hysi, P., Fitzgerald, T.W., Gharahkhani, P., Bonnemaijer, P.W.M., Senabouth, A., Hewitt, A.W., Eye, U.K.B., Vision, C., International Glaucoma Genetics, C.*, et al.* (2021). Genetic variation affects morphological retinal phenotypes extracted from UK Biobank optical coherence tomography images. PLoS Genet *17*, e1009497.
Danford, I.D., Verkuil, L.D., Choi, D.J., Collins, D.W., Gudiseva, H.V., Uyhazi, K.E., Lau, M.K., Kanu, L.N., Grant, G.R., Chavali, V.R.M.*, et al.* (2017). Characterizing the "POAGome": A bioinformatics-driven approach to primary open-angle glaucoma. Prog Retin Eye Res *58*, 89-114.
De Ieso, M.L., Gurley, J.M., McClellan, M.E., Gu, X., Navarro, I., Li, G., Gomez-Caraballo, M., Enyong, E., Stamer, W.D., and Elliott, M.H. (2020). Physiologic Consequences of Caveolin-1 Ablation in Conventional Outflow Endothelia. Invest Ophthalmol Vis Sci *61*, 32.
de Voogd, S., Ikram, M.K., Wolfs, R.C., Jansonius, N.M., Hofman, A., and de Jong, P.T. (2005). Incidence of open-angle glaucoma in a general elderly population: the Rotterdam Study. Ophthalmology *112*, 1487-1493.
Dewey, F.E., Gusarova, V., Dunbar, R.L., O'Dushlaine, C., Schurmann, C., Gottesman, O., McCarthy, S., Van Hout, C.V., Bruse, S., Dansky, H.M.*, et al.* (2017). Genetic and Pharmacologic Inactivation of ANGPTL3 and Cardiovascular Disease. N Engl J Med *377*, 211-221.
Dewundara, S., and Pasquale, L.R. (2015). Exfoliation syndrome: a disease with an environmental component. Curr Opin Ophthalmol *26*, 78-81.
Dimasi, D.P., Burdon, K.P., and Craig, J.E. (2010). The genetics of central corneal thickness. Br J Ophthalmol *94*, 971-976.
Drance, S.M., Douglas, G.R., Wijsman, K., Schulzer, M., and Britton, R.J. (1988). Response of blood flow to warm and cold in normal and low-tension glaucoma patients. Am J Ophthalmol *105*, 35-39.
Duvesh, R., Verma, A., Venkatesh, R., Kavitha, S., Ramulu, P.Y., Wojciechowski, R., and Sundaresan, P. (2013). Association study in a South Indian population supports rs1015213 as a risk factor for primary angle closure. Invest Ophthalmol Vis Sci *54*, 5624-5628.
Ekstrom, C. (2008). Incidence of open-angle glaucoma in central Sweden. Acta Ophthalmol *86*, 747-754.
Elhawy, E., Kamthan, G., Dong, C.Q., and Danias, J. (2012). Pseudoexfoliation syndrome, a systemic disorder with ocular manifestations. Hum Genomics *6*, 22.
Elliott, M.H., Ashpole, N.E., Gu, X., Herrnberger, L., McClellan, M.E., Griffith, G.L., Reagan, A.M., Boyce, T.M., Tanito, M., Tamm, E.R.*, et al.* (2016). Caveolin-1 modulates intraocular pressure: implications for caveolae mechanoprotection in glaucoma. Sci Rep *6*, 37127.
Fan, B.J., Ko, W.C., Wang, D.Y., Canlas, O., Ritch, R., Lam, D.S., and Pang, C.P. (2007). Fine mapping of new glaucoma locus GLC1M and exclusion of neuregulin 2 as the causative gene. Mol Vis *13*, 779-784.
Findlay, G.M., Daza, R.M., Martin, B., Zhang, M.D., Leith, A.P., Gasperini, M., Janizek, J.D., Huang, X., Starita, L.M., and Shendure, J. (2018). Accurate classification of BRCA1 variants with saturation genome editing. Nature *562*, 217-222.
Fingert, J.H., Alward, W.L., Kwon, Y.H., Shankar, S.P., Andorf, J.L., Mackey, D.A., Sheffield, V.C., and Stone, E.M. (2007). No association between variations in the WDR36 gene and primary open-angle glaucoma. Arch Ophthalmol *125*, 434-436.
Foster, P.J., Buhrmann, R., Quigley, H.A., and Johnson, G.J. (2002). The definition and classification of glaucoma in prevalence surveys. Br J Ophthalmol *86*, 238-242.

Founti, P., Coleman, A.L., Wilson, M.R., Yu, F., Harris, A., Pappas, T., Anastasopoulos, E., Koskosas, A., Salonikiou, A., Keskini, C.*, et al.* (2021). Twelve-Year Incidence of Open-angle Glaucoma: The Thessaloniki Eye Study. J Glaucoma *30*, 851-858.
Gamazon, E.R., Segre, A.V., van de Bunt, M., Wen, X., Xi, H.S., Hormozdiari, F., Ongen, H., Konkashbaev, A., Derks, E.M., Aguet, F.*, et al.* (2018). Using an atlas of gene regulation across 44 human tissues to inform complex disease- and trait-associated variation. Nat Genet *50*, 956-967.
Garway-Heath, D.F., Crabb, D.P., Bunce, C., Lascaratos, G., Amalfitano, F., Anand, N., Azuara-Blanco, A., Bourne, R.R., Broadway, D.C., Cunliffe, I.A.*, et al.* (2015). Latanoprost for open-angle glaucoma (UKGTS): a randomised, multicentre, placebo-controlled trial. Lancet *385*, 1295-1304.
Genetics of Exfoliation Syndrome, P., Li, Z., Wang, Z., Lee, M.C., Zenkel, M., Peh, E., Ozaki, M., Topouzis, F., Nakano, S., Chan, A.*, et al.* (2021). Association of Rare CYP39A1 Variants With Exfoliation Syndrome Involving the Anterior Chamber of the Eye. JAMA *325*, 753-764.
Genetics of Glaucoma in People of African Descent, C., Hauser, M.A., Allingham, R.R., Aung, T., Van Der Heide, C.J., Taylor, K.D., Rotter, J.I., Wang, S.J., Bonnemaijer, P.W.M., Williams, S.E.*, et al.* (2019). Association of Genetic Variants With Primary Open-Angle Glaucoma Among Individuals With African Ancestry. JAMA *322*, 1682-1691.
Gharahkhani, P., Burdon, K.P., Fogarty, R., Sharma, S., Hewitt, A.W., Martin, S., Law, M.H., Cremin, K., Bailey, J.N.C., Loomis, S.J.*, et al.* (2014). Common variants near ABCA1, AFAP1 and GMDS confer risk of primary open-angle glaucoma. Nat Genet *46*, 1120-1125.
Gharahkhani, P., Jorgenson, E., Hysi, P., Khawaja, A.P., Pendergrass, S., Han, X., Ong, J.S., Hewitt, A.W., Segre, A.V., Rouhana, J.M.*, et al.* (2021). Genome-wide meta-analysis identifies 127 open-angle glaucoma loci with consistent effect across ancestries. Nat Commun *12*, 1258.
Giambartolomei, C., Vukcevic, D., Schadt, E.E., Franke, L., Hingorani, A.D., Wallace, C., and Plagnol, V. (2014). Bayesian test for colocalisation between pairs of genetic association studies using summary statistics. PLoS Genet *10*, e1004383.
Gong, W.F., Chiang, S.W., Chen, L.J., Tam, P.O., Jia, L.Y., Leung, D.Y., Geng, Y.Q., Tham, C.C., Lam, D.S., Ritch, R.*, et al.* (2008). Evaluation of LOXL1 polymorphisms in primary open-angle glaucoma in southern and northern Chinese. Mol Vis *14*, 2381-2389.
Gordon, M.O., Beiser, J.A., Brandt, J.D., Heuer, D.K., Higginbotham, E.J., Johnson, C.A., Keltner, J.L., Miller, J.P., Parrish, R.K., 2nd, Wilson, M.R.*, et al.* (2002). The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma. Arch Ophthalmol *120*, 714-720; discussion 829-730.
Graham, M.J., Lee, R.G., Brandt, T.A., Tai, L.J., Fu, W., Peralta, R., Yu, R., Hurh, E., Paz, E., McEvoy, B.W.*, et al.* (2017). Cardiovascular and Metabolic Effects of ANGPTL3 Antisense Oligonucleotides. N Engl J Med *377*, 222-232.
Greene, A.G., Eivers, S.B., Dervan, E.W.J., O'Brien, C.J., and Wallace, D.M. (2020). Lysyl Oxidase Like 1: Biological roles and regulation. Exp Eye Res *193*, 107975.
Guadarrama-Vallejo, D., Miranda-Duarte, A., and Zenteno, J.C. (2013). The T allele of lysyl oxidase-like 1 rs41435250 is a novel risk factor for pseudoexfoliation syndrome and pseudoexfoliation glaucoma independently and through intragenic epistatic interaction. Mol Vis *19*, 1937-1944.
Gupta, N., and Yucel, Y.H. (2007). Glaucoma as a neurodegenerative disease. Curr Opin Ophthalmol *18*, 110-114.
Gusev, A., Ko, A., Shi, H., Bhatia, G., Chung, W., Penninx, B.W., Jansen, R., de Geus, E.J., Boomsma, D.I., Wright, F.A.*, et al.* (2016). Integrative approaches for large-scale transcriptome-wide association studies. Nat Genet *48*, 245-252.

Hamid, S., Desai, P., Hysi, P., Burr, J.M., and Khawaja, A.P. (2021). Population screening for glaucoma in UK: current recommendations and future directions. Eye (Lond).
Han, X., Souzeau, E., Ong, J.S., An, J., Siggs, O.M., Burdon, K.P., Best, S., Goldberg, I., Healey, P.R., Graham, S.L.*, et al.* (2019). Myocilin Gene Gln368Ter Variant Penetrance and Association With Glaucoma in Population-Based and Registry-Based Studies. JAMA Ophthalmol *137*, 28-35.
Han, X., Steven, K., Qassim, A., Marshall, H.N., Bean, C., Tremeer, M., An, J., Siggs, O.M., Gharahkhani, P., Craig, J.E.*, et al.* (2021). Automated AI labeling of optic nerve head enables insights into cross-ancestry glaucoma risk and genetic discovery in >280,000 images from UKB and CLSA. Am J Hum Genet *108*, 1204-1216.
Hauser, M.A., Allingham, R.R., Linkroum, K., Wang, J., LaRocque-Abramson, K., Figueiredo, D., Santiago-Turla, C., del Bono, E.A., Haines, J.L., Pericak-Vance, M.A.*, et al.* (2006). Distribution of WDR36 DNA sequence variants in patients with primary open-angle glaucoma. Invest Ophthalmol Vis Sci *47*, 2542-2546.
Hayreh, S.S. (1969). Blood supply of the optic nerve head and its role in optic atrophy, glaucoma, and oedema of the optic disc. Br J Ophthalmol *53*, 721-748.
Hayreh, S.S., Zimmerman, M.B., Podhajsky, P., and Alward, W.L. (1994). Nocturnal arterial hypotension and its role in optic nerve head and ocular ischemic disorders. Am J Ophthalmol *117*, 603-624.
He, M., Foster, P.J., Ge, J., Huang, W., Zheng, Y., Friedman, D.S., Lee, P.S., and Khaw, P.T. (2006). Prevalence and clinical characteristics of glaucoma in adult Chinese: a population-based study in Liwan District, Guangzhou. Invest Ophthalmol Vis Sci *47*, 2782-2788.
He, M., Wang, D., Zheng, Y., Zhang, J., Yin, Q., Huang, W., Mackey, D.A., and Foster, P.J. (2008). Heritability of anterior chamber depth as an intermediate phenotype of angle-closure in Chinese: the Guangzhou Twin Eye Study. Invest Ophthalmol Vis Sci *49*, 81-86.
He, X., Fuller, C.K., Song, Y., Meng, Q., Zhang, B., Yang, X., and Li, H. (2013). Sherlock: detecting gene-disease associations by matching patterns of expression QTL and GWAS. Am J Hum Genet *92*, 667-680.
Hewitt, A.W., Dimasi, D.P., Mackey, D.A., and Craig, J.E. (2006). A Glaucoma Case-control Study of the WDR36 Gene D658G sequence variant. Am J Ophthalmol *142*, 324-325.
Hoffmann, E.M., Lamparter, J., Mirshahi, A., Elflein, H., Hoehn, R., Wolfram, C., Lorenz, K., Adler, M., Wild, P.S., Schulz, A.*, et al.* (2013). Distribution of central corneal thickness and its association with ocular parameters in a large central European cohort: the Gutenberg health study. PLoS One *8*, e66158.
Hollitt, G.L., Siggs, O.M., Ridge, B., Keane, M.C., Mackey, D.A., MacGregor, S., Hewitt, A.W., Craig, J.E., and Souzeau, E. (2021). Attitudes towards polygenic risk testing in individuals with glaucoma. Ophthalmol Glaucoma.
Hollows, F.C., and Graham, P.A. (1966). Intra-ocular pressure, glaucoma, and glaucoma suspects in a defined population. Br J Ophthalmol *50*, 570-586.
Hormozdiari, F., van de Bunt, M., Segre, A.V., Li, X., Joo, J.W.J., Bilow, M., Sul, J.H., Sankararaman, S., Pasaniuc, B., and Eskin, E. (2016). Colocalization of GWAS and eQTL Signals Detects Target Genes. Am J Hum Genet *99*, 1245-1260.
Hu, C., Niu, L., Li, L., Song, M., Zhang, Y., Lei, Y., Chen, Y., and Sun, X. (2020a). ABCA1 Regulates IOP by Modulating Cav1/eNOS/NO Signaling Pathway. Invest Ophthalmol Vis Sci *61*, 33.
Hu, L., Wang, J., Wang, Y., Wu, L., Wu, C., Mao, B., Maruthi Prasad, E., Wang, Y., and Chin, Y.E. (2020b). LOXL1 modulates the malignant progression of colorectal cancer by inhibiting the transcriptional activity of YAP. Cell Commun Signal *18*, 148.

Huang, Y.T., Liang, L., Moffatt, M.F., Cookson, W.O., and Lin, X. (2015). iGWAS: Integrative Genome-Wide Association Studies of Genetic and Genomic Data for Disease Susceptibility Using Mediation Analysis. Genet Epidemiol *39*, 347-356.
Hysi, P.G., Cheng, C.Y., Springelkamp, H., Macgregor, S., Bailey, J.N.C., Wojciechowski, R., Vitart, V., Nag, A., Hewitt, A.W., Hohn, R.*, et al.* (2014). Genome-wide analysis of multi-ancestry cohorts identifies new loci influencing intraocular pressure and susceptibility to glaucoma. Nat Genet *46*, 1126-1130.
Iglesias, A.I., Mishra, A., Vitart, V., Bykhovskaya, Y., Hohn, R., Springelkamp, H., Cuellar-Partida, G., Gharahkhani, P., Bailey, J.N.C., Willoughby, C.E.*, et al.* (2018). Cross-ancestry genome-wide association analysis of corneal thickness strengthens link between complex and Mendelian eye diseases. Nat Commun *9*, 1864.
Iglesias, A.I., Springelkamp, H., Ramdas, W.D., Klaver, C.C., Willemsen, R., and van Duijn, C.M. (2015). Genes, pathways, and animal models in primary open-angle glaucoma. Eye (Lond) *29*, 1285-1298.
Iwase, A., Suzuki, Y., Araie, M., Yamamoto, T., Abe, H., Shirato, S., Kuwayama, Y., Mishima, H.K., Shimizu, H., Tomita, G.*, et al.* (2004). The prevalence of primary open-angle glaucoma in Japanese: the Tajimi Study. Ophthalmology *111*, 1641-1648.
Jaimes, M., Rivera-Parra, D., Miranda-Duarte, A., Valdes, G., and Zenteno, J.C. (2012). Prevalence of high-risk alleles in the LOXL1 gene and its association with pseudoexfoliation syndrome and exfoliation glaucoma in a Latin American population. Ophthalmic Genet *33*, 12-17.
Janssen, S.F., Gorgels, T.G., Ramdas, W.D., Klaver, C.C., van Duijn, C.M., Jansonius, N.M., and Bergen, A.A. (2013). The vast complexity of primary open angle glaucoma: disease genes, risks, molecular mechanisms and pathobiology. Prog Retin Eye Res *37*, 31-67.
Jiang, X., Varma, R., Wu, S., Torres, M., Azen, S.P., Francis, B.A., Chopra, V., Nguyen, B.B., and Los Angeles Latino Eye Study, G. (2012). Baseline risk factors that predict the development of open-angle glaucoma in a population: the Los Angeles Latino Eye Study. Ophthalmology *119*, 2245-2253.
Jonas, J.B., Aung, T., Bourne, R.R., Bron, A.M., Ritch, R., and Panda-Jonas, S. (2017). Glaucoma. The Lancet *390*, 2183-2193.
Jonas, J.B., Aung, T., Bourne, R.R., Bron, A.M., Ritch, R., and Panda-Jonas, S. (2018). Glaucoma – Authors' reply. The Lancet *391*.
Jonasson, F., Damji, K.F., Arnarsson, A., Sverrisson, T., Wang, L., Sasaki, H., and Sasaki, K. (2003). Prevalence of open-angle glaucoma in Iceland: Reykjavik Eye Study. Eye (Lond) *17*, 747-753.
Kavitha, S., Zebardast, N., Palaniswamy, K., Wojciechowski, R., Chan, E.S., Friedman, D.S., Venkatesh, R., and Ramulu, P.Y. (2014). Family history is a strong risk factor for prevalent angle closure in a South Indian population. Ophthalmology *121*, 2091-2097.
Khawaja, A.P., Chan, M.P., Hayat, S., Broadway, D.C., Luben, R., Garway-Heath, D.F., Sherwin, J.C., Yip, J.L., Dalzell, N., Wareham, N.J.*, et al.* (2013a). The EPIC-Norfolk Eye Study: rationale, methods and a cross-sectional analysis of visual impairment in a population-based cohort. BMJ Open *3*.
Khawaja, A.P., Chan, M.P.Y., Yip, J.L.Y., Broadway, D.C., Garway-Heath, D.F., Viswanathan, A.C., Luben, R., Hayat, S., Hauser, M.A., Wareham, N.J.*, et al.* (2018a). A Common Glaucoma-risk Variant of SIX6 Alters Retinal Nerve Fiber Layer and Optic Disc Measures in a European Population: The EPIC-Norfolk Eye Study. J Glaucoma *27*, 743-749.
Khawaja, A.P., Chua, S., Hysi, P.G., Georgoulas, S., Currant, H., Fitzgerald, T.W., Birney, E., Ko, F., Yang, Q., Reisman, C.*, et al.* (2020). Comparison of Associations with Different Macular Inner Retinal Thickness Parameters in a Large Cohort: The UK Biobank. Ophthalmology *127*, 62-71.

Khawaja, A.P., Cooke Bailey, J.N., Wareham, N.J., Scott, R.A., Simcoe, M., Igo, R.P., Jr., Song, Y.E., Wojciechowski, R., Cheng, C.Y., Khaw, P.T.*, et al.* (2018b). Genome-wide analyses identify 68 new loci associated with intraocular pressure and improve risk prediction for primary open-angle glaucoma. Nat Genet *50*, 778-782.
Khawaja, A.P., Crabb, D.P., and Jansonius, N.M. (2013b). The role of ocular perfusion pressure in glaucoma cannot be studied with multivariable regression analysis applied to surrogates. Invest Ophthalmol Vis Sci *54*, 4619-4620.
Khor, C.C., Do, T., Jia, H., Nakano, M., George, R., Abu-Amero, K., Duvesh, R., Chen, L.J., Li, Z., Nongpiur, M.E.*, et al.* (2016). Genome-wide association study identifies five new susceptibility loci for primary angle closure glaucoma. Nat Genet *48*, 556-562.
Kim, C.S., Seong, G.J., Lee, N.H., Song, K.C., and Namil Study Group, K.G.S. (2011). Prevalence of primary open-angle glaucoma in central South Korea the Namil study. Ophthalmology *118*, 1024-1030.
Kim, J., Aschard, H., Kang, J.H., Lentjes, M.A.H., Do, R., Wiggs, J.L., Khawaja, A.P., Pasquale, L.R., and Modifiable Risk Factors for Glaucoma, C. (2021). Intraocular Pressure, Glaucoma, and Dietary Caffeine Consumption: A Gene-Diet Interaction Study from the UK Biobank. Ophthalmology *128*, 866-876.
Kim, S., and Kim, Y. (2012). Variations in LOXL1 associated with exfoliation glaucoma do not affect amine oxidase activity. Mol Vis *18*, 265-270.
King, E.A., Davis, J.W., and Degner, J.F. (2019). Are drug targets with genetic support twice as likely to be approved? Revised estimates of the impact of genetic support for drug mechanisms on the probability of drug approval. PLoS Genet *15*, e1008489.
Klein, A.P., Suktitipat, B., Duggal, P., Lee, K.E., Klein, R., Bailey-Wilson, J.E., and Klein, B.E. (2009). Heritability analysis of spherical equivalent, axial length, corneal curvature, and anterior chamber depth in the Beaver Dam Eye Study. Arch Ophthalmol *127*, 649-655.
Klein, B.E., Klein, R., Sponsel, W.E., Franke, T., Cantor, L.B., Martone, J., and Menage, M.J. (1992). Prevalence of glaucoma. The Beaver Dam Eye Study. Ophthalmology *99*, 1499-1504.
Knoppers, B.M., Bernier, A., Granados Moreno, P., and Pashayan, N. (2021). Of Screening, Stratification, and Scores. J Pers Med *11*.
Kumar, D.M., and Agarwal, N. (2007). Oxidative stress in glaucoma: a burden of evidence. J Glaucoma *16*, 334-343.
Lavanya, R., Wong, T.Y., Friedman, D.S., Aung, H.T., Alfred, T., Gao, H., Seah, S.K., Kashiwagi, K., Foster, P.J., and Aung, T. (2008). Determinants of angle closure in older Singaporeans. Arch Ophthalmol *126*, 686-691.
Le, A., Mukesh, B.N., McCarty, C.A., and Taylor, H.R. (2003). Risk factors associated with the incidence of open-angle glaucoma: the visual impairment project. Invest Ophthalmol Vis Sci *44*, 3783-3789.
Lee, M.C., Chan, A.S., Goh, S.R., Hilmy, M.H., Nongpiur, M.E., Hong, W., Aung, T., Hunziker, W., and Vithana, E.N. (2014). Expression of the primary angle closure glaucoma (PACG) susceptibility gene PLEKHA7 in endothelial and epithelial cell junctions in the eye. Invest Ophthalmol Vis Sci *55*, 3833-3841.
Lee, M.C., Shei, W., Chan, A.S., Chua, B.T., Goh, S.R., Chong, Y.F., Hilmy, M.H., Nongpiur, M.E., Baskaran, M., Khor, C.C.*, et al.* (2017). Primary angle closure glaucoma (PACG) susceptibility gene PLEKHA7 encodes a novel Rac1/Cdc42 GAP that modulates cell migration and blood-aqueous barrier function. Hum Mol Genet *26*, 4011-4027.
Lek, M., Karczewski, K.J., Minikel, E.V., Samocha, K.E., Banks, E., Fennell, T., O'Donnell-Luria, A.H., Ware, J.S., Hill, A.J., Cummings, B.B.*, et al.* (2016). Analysis of protein-coding genetic variation in 60,706 humans. Nature *536*, 285-291.

Leske, M.C. (2007). Open-angle glaucoma -- an epidemiologic overview. Ophthalmic Epidemiol *14*, 166-172.
Leske, M.C., Connell, A.M., Schachat, A.P., and Hyman, L. (1994). The Barbados Eye Study. Prevalence of open angle glaucoma. Arch Ophthalmol *112*, 821-829.
Leske, M.C., Wu, S.Y., Hennis, A., Honkanen, R., Nemesure, B., and Group, B.E.S. (2008). Risk factors for incident open-angle glaucoma: the Barbados Eye Studies. Ophthalmology *115*, 85-93.
Leske, M.C., Wu, S.Y., Honkanen, R., Nemesure, B., Schachat, A., Hyman, L., Hennis, A., and Barbados Eye Studies, G. (2007). Nine-year incidence of open-angle glaucoma in the Barbados Eye Studies. Ophthalmology *114*, 1058-1064.
Leydhecker, W., Akiyama, K., and Neumann, H.G. (1958). [Intraocular pressure in normal human eyes]. Klin Monbl Augenheilkd Augenarztl Fortbild *133*, 662-670.
Li, Z., Allingham, R.R., Nakano, M., Jia, L., Chen, Y., Ikeda, Y., Mani, B., Chen, L.J., Kee, C., Garway-Heath, D.F.*, et al.* (2015). A common variant near TGFBR3 is associated with primary open angle glaucoma. Hum Mol Genet *24*, 3880-3892.
Li-Hawkins, J., Lund, E.G., Bronson, A.D., and Russell, D.W. (2000). Expression cloning of an oxysterol 7alpha-hydroxylase selective for 24-hydroxycholesterol. J Biol Chem *275*, 16543-16549.
Liu, C., Nongpiur, M.E., Cheng, C.Y., Khor, C.C., Yu, M., Husain, R., Ho, C.L., Wong, T.T., Boey, P.Y., Perera, S.*, et al.* (2021). Evaluation of Primary Angle-Closure Glaucoma Susceptibility Loci for Estimating Angle Closure Disease Severity. Ophthalmology *128*, 403-409.
Liu, T., Tang, C., and Shi, X. (2020). Analysis of variants in Chinese individuals with primary open-angle glaucoma using molecular inversion probe (MIP)-based panel sequencing. Mol Vis *26*, 378-391.
Liu, Y., and Allingham, R.R. (2017). Major review: Molecular genetics of primary open-angle glaucoma. Exp Eye Res *160*, 62-84.
Liu, Y., Schmidt, S., Qin, X., Gibson, J., Hutchins, K., Santiago-Turla, C., Wiggs, J.L., Budenz, D.L., Akafo, S., Challa, P.*, et al.* (2008). Lack of association between LOXL1 variants and primary open-angle glaucoma in three different populations. Invest Ophthalmol Vis Sci *49*, 3465-3468.
Loomis, S.J., Kang, J.H., Weinreb, R.N., Yaspan, B.L., Cooke Bailey, J.N., Gaasterland, D., Gaasterland, T., Lee, R.K., Lichter, P.R., Budenz, D.L.*, et al.* (2014). Association of CAV1/CAV2 genomic variants with primary open-angle glaucoma overall and by gender and pattern of visual field loss. Ophthalmology *121*, 508-516.
Lowe, R.F. (1969). Causes of shallow anterior chamber in primary angle-closure glaucoma. Ultrasonic biometry of normal and angle-closure glaucoma eyes. Am J Ophthalmol *67*, 87-93.
Ma, L., Zeng, Y., Wei, J., Yang, D., Ding, G., Liu, J., Shang, J., Kang, Y., and Ji, X. (2018). Knockdown of LOXL1 inhibits TGF-beta1-induced proliferation and fibrogenesis of hepatic stellate cells by inhibition of Smad2/3 phosphorylation. Biomed Pharmacother *107*, 1728-1735.
MacGregor, S., Ong, J.S., An, J., Han, X., Zhou, T., Siggs, O.M., Law, M.H., Souzeau, E., Sharma, S., Lynn, D.J.*, et al.* (2018). Genome-wide association study of intraocular pressure uncovers new pathways to glaucoma. Nat Genet *50*, 1067-1071.
Mackay, D.S., Bennett, T.M., and Shiels, A. (2015). Exome Sequencing Identifies a Missense Variant in EFEMP1 Co-Segregating in a Family with Autosomal Dominant Primary Open-Angle Glaucoma. PLoS One *10*, e0132529.
Majithia, A.R., Flannick, J., Shahinian, P., Guo, M., Bray, M.A., Fontanillas, P., Gabriel, S.B., Go, T.D.C., Project, N.J.F.A.S., Consortium, S.T.D.*, et al.* (2014). Rare variants in

PPARG with decreased activity in adipocyte differentiation are associated with increased risk of type 2 diabetes. Proc Natl Acad Sci U S A *111*, 13127-13132.
Majithia, A.R., Tsuda, B., Agostini, M., Gnanapradeepan, K., Rice, R., Peloso, G., Patel, K.A., Zhang, X., Broekema, M.F., Patterson, N.*, et al.* (2016). Prospective functional classification of all possible missense variants in PPARG. Nat Genet *48*, 1570-1575.
Marcus, M.W., de Vries, M.M., Junoy Montolio, F.G., and Jansonius, N.M. (2011). Myopia as a risk factor for open-angle glaucoma: a systematic review and meta-analysis. Ophthalmology *118*, 1989-1994 e1982.
Mason, R.P., Kosoko, O., Wilson, M.R., Martone, J.F., Cowan, C.L., Jr., Gear, J.C., and Ross-Degnan, D. (1989). National survey of the prevalence and risk factors of glaucoma in St. Lucia, West Indies. Part I. Prevalence findings. Ophthalmology *96*, 1363-1368.
Menon, M., Mohammadi, S., Davila-Velderrain, J., Goods, B.A., Cadwell, T.D., Xing, Y., Stemmer-Rachamimov, A., Shalek, A.K., Love, J.C., Kellis, M.*, et al.* (2019). Single-cell transcriptomic atlas of the human retina identifies cell types associated with age-related macular degeneration. Nat Commun *10*, 4902.
Menzel, O., Bekkeheien, R.C., Reymond, A., Fukai, N., Boye, E., Kosztolanyi, G., Aftimos, S., Deutsch, S., Scott, H.S., Olsen, B.R.*, et al.* (2004). Knobloch syndrome: novel mutations in COL18A1, evidence for genetic heterogeneity, and a functionally impaired polymorphism in endostatin. Hum Mutat *23*, 77-84.
Micheal, S., Yousaf, S., Khan, M.I., Akhtar, F., Islam, F., Khan, W.A., den Hollander, A.I., Qamar, R., and Ahmed, A. (2013). Polymorphisms in matrix metalloproteinases MMP1 and MMP9 are associated with primary open-angle and angle closure glaucoma in a Pakistani population. Mol Vis *19*, 441-447.
Mitchell, P., Smith, W., Attebo, K., and Healey, P.R. (1996). Prevalence of open-angle glaucoma in Australia. The Blue Mountains Eye Study. Ophthalmology *103*, 1661-1669.
Monemi, S., Spaeth, G., DaSilva, A., Popinchalk, S., Ilitchev, E., Liebmann, J., Ritch, R., Heon, E., Crick, R.P., Child, A.*, et al.* (2005). Identification of a novel adult-onset primary open-angle glaucoma (POAG) gene on 5q22.1. Hum Mol Genet *14*, 725-733.
Morissette, J., Cote, G., Anctil, J.L., Plante, M., Amyot, M., Heon, E., Trope, G.E., Weissenbach, J., and Raymond, V. (1995). A common gene for juvenile and adult-onset primary open-angle glaucomas confined on chromosome 1q. Am J Hum Genet *56*, 1431-1442.
Mukesh, B.N., McCarty, C.A., Rait, J.L., and Taylor, H.R. (2002). Five-year incidence of open-angle glaucoma: the visual impairment project. Ophthalmology *109*, 1047-1051.
Murdoch, I.E., Cousens, S.N., Babalola, O.E., Yang, Y.F., Abiose, A., and Jones, B.R. (2001). Glaucoma prevalence may not be uniformly high in all 'black' populations. Afr J Med Med Sci *30*, 337-339.
Nag, A., Lu, H., Arno, M., Iglesias, A.I., Bonnemaijer, P., Broer, L., Uitterlinden, A.G., Klaver, C.C., van Duijn, C., Hysi, P.G.*, et al.* (2017). Evaluation of the Myocilin Mutation Gln368Stop Demonstrates Reduced Penetrance for Glaucoma in European Populations. Ophthalmology *124*, 547-553.
Nakano, M., Ikeda, Y., Tokuda, Y., Fuwa, M., Ueno, M., Imai, K., Sato, R., Omi, N., Adachi, H., Kageyama, M.*, et al.* (2014). Novel common variants and susceptible haplotype for exfoliation glaucoma specific to Asian population. Sci Rep *4*, 5340.
Nelson, M.R., Tipney, H., Painter, J.L., Shen, J., Nicoletti, P., Shen, Y., Floratos, A., Sham, P.C., Li, M.J., Wang, J.*, et al.* (2015). The support of human genetic evidence for approved drug indications. Nat Genet *47*, 856-860.
Ng, P.C., and Kirkness, E.F. (2010). Whole genome sequencing. Methods Mol Biol *628*, 215-226.

Nica, A.C., Montgomery, S.B., Dimas, A.S., Stranger, B.E., Beazley, C., Barroso, I., and Dermitzakis, E.T. (2010). Candidate causal regulatory effects by integration of expression QTLs with complex trait genetic associations. PLoS Genet *6*, e1000895.
Nicolae, D.L., Gamazon, E., Zhang, W., Duan, S., Dolan, M.E., and Cox, N.J. (2010). Trait-associated SNPs are more likely to be eQTLs: annotation to enhance discovery from GWAS. PLoS Genet *6*, e1000888.
Nongpiur, M.E., Cheng, C.Y., Duvesh, R., Vijayan, S., Baskaran, M., Khor, C.C., Allen, J., Kavitha, S., Venkatesh, R., Goh, D.*, et al.* (2018). Evaluation of Primary Angle-Closure Glaucoma Susceptibility Loci in Patients with Early Stages of Angle-Closure Disease. Ophthalmology *125*, 664-670.
Nongpiur, M.E., Khor, C.C., Cheng, C.Y., Husain, R., Boey, P.Y., Chew, A., Ho, C.L., Wong, T.T., Perera, S., Wong, T.Y.*, et al.* (2019). Integration of Genetic and Biometric Risk Factors for Detection of Primary Angle Closure Glaucoma. Am J Ophthalmol *208*, 160-165.
Nongpiur, M.E., Khor, C.C., Jia, H., Cornes, B.K., Chen, L.J., Qiao, C., Nair, K.S., Cheng, C.Y., Xu, L., George, R.*, et al.* (2014). ABCC5, a gene that influences the anterior chamber depth, is associated with primary angle closure glaucoma. PLoS Genet *10*, e1004089.
Nongpiur, M.E., Ku, J.Y., and Aung, T. (2011). Angle closure glaucoma: a mechanistic review. Curr Opin Ophthalmol *22*, 96-101.
Ntim-Amponsah, C.T., Amoaku, W.M., Ofosu-Amaah, S., Ewusi, R.K., Idirisuriya-Khair, R., Nyatepe-Coo, E., and Adu-Darko, M. (2004). Prevalence of glaucoma in an African population. Eye (Lond) *18*, 491-497.
Ojha, P., Wiggs, J.L., and Pasquale, L.R. (2013). The genetics of intraocular pressure. Semin Ophthalmol *28*, 301-305.
Orozco, L.D., Chen, H.H., Cox, C., Katschke, K.J., Jr., Arceo, R., Espiritu, C., Caplazi, P., Nghiem, S.S., Chen, Y.J., Modrusan, Z.*, et al.* (2020). Integration of eQTL and a Single-Cell Atlas in the Human Eye Identifies Causal Genes for Age-Related Macular Degeneration. Cell Rep *30*, 1246-1259 e1246.
Othman, M.I., Sullivan, S.A., Skuta, G.L., Cockrell, D.A., Stringham, H.M., Downs, C.A., Fornes, A., Mick, A., Boehnke, M., Vollrath, D.*, et al.* (1998). Autosomal dominant nanophthalmos (NNO1) with high hyperopia and angle-closure glaucoma maps to chromosome 11. Am J Hum Genet *63*, 1411-1418.
Ovodenko, B., Rostagno, A., Neubert, T.A., Shetty, V., Thomas, S., Yang, A., Liebmann, J., Ghiso, J., and Ritch, R. (2007). Proteomic analysis of exfoliation deposits. Invest Ophthalmol Vis Sci *48*, 1447-1457.
Palimkar, A., Khandekar, R., and Venkataraman, V. (2008). Prevalence and distribution of glaucoma in central India (Glaucoma Survey 2001). Indian J Ophthalmol *56*, 57-62.
Pandav, S.S., Chakma, P., Khera, A., Chugh, N., Gupta, P.C., Thattaruthody, F., Seth, N.G., Raj, S., Kaushik, S., Khullar, M.*, et al.* (2019). Lack of association between lysyl oxidase-like 1 polymorphism in pseudoexfoliation syndrome and pseudoexfoliation glaucoma in North Indian population. Eur J Ophthalmol *29*, 431-436.
Pasquale, L.R., Jiwani, A.Z., Zehavi-Dorin, T., Majd, A., Rhee, D.J., Chen, T., Turalba, A., Shen, L., Brauner, S., Grosskreutz, C.*, et al.* (2014). Solar exposure and residential geographic history in relation to exfoliation syndrome in the United States and Israel. JAMA Ophthalmol *132*, 1439-1445.
Pasutto, F., Keller, K.E., Weisschuh, N., Sticht, H., Samples, J.R., Yang, Y.F., Zenkel, M., Schlotzer-Schrehardt, U., Mardin, C.Y., Frezzotti, P.*, et al.* (2012). Variants in ASB10 are associated with open-angle glaucoma. Hum Mol Genet *21*, 1336-1349.
Pasutto, F., Mardin, C.Y., Michels-Rautenstrauss, K., Weber, B.H., Sticht, H., Chavarria-Soley, G., Rautenstrauss, B., Kruse, F., and Reis, A. (2008). Profiling of WDR36 missense variants in German patients with glaucoma. Invest Ophthalmol Vis Sci *49*, 270-274.

Patel, G., Fury, W., Yang, H., Gomez-Caraballo, M., Bai, Y., Yang, T., Adler, C., Wei, Y., Ni, M., Schmitt, H.*, et al.* (2020). Molecular taxonomy of human ocular outflow tissues defined by single-cell transcriptomics. Proc Natl Acad Sci U S A *117*, 12856-12867.
Polubriaginof, F.C.G., Vanguri, R., Quinnies, K., Belbin, G.M., Yahi, A., Salmasian, H., Lorberbaum, T., Nwankwo, V., Li, L., Shervey, M.M.*, et al.* (2018). Disease Heritability Inferred from Familial Relationships Reported in Medical Records. Cell *173*, 1692-1704 e1611.
Povysil, G., Petrovski, S., Hostyk, J., Aggarwal, V., Allen, A.S., and Goldstein, D.B. (2019). Rare-variant collapsing analyses for complex traits: guidelines and applications. Nat Rev Genet *20*, 747-759.
Quigley, H., and Anderson, D.R. (1976). The dynamics and location of axonal transport blockade by acute intraocular pressure elevation in primate optic nerve. Invest Ophthalmol *15*, 606-616.
Quigley, H.A., Addicks, E.M., Green, W.R., and Maumenee, A.E. (1981). Optic nerve damage in human glaucoma. II. The site of injury and susceptibility to damage. Arch Ophthalmol *99*, 635-649.
Quigley, H.A., West, S.K., Rodriguez, J., Munoz, B., Klein, R., and Snyder, R. (2001). The prevalence of glaucoma in a population-based study of Hispanic subjects: Proyecto VER. Arch Ophthalmol *119*, 1819-1826.
Rahman, M.M., Rahman, N., Foster, P.J., Haque, Z., Zaman, A.U., Dineen, B., and Johnson, G.J. (2004). The prevalence of glaucoma in Bangladesh: a population based survey in Dhaka division. Br J Ophthalmol *88*, 1493-1497.
Ramakrishnan, R., Nirmalan, P.K., Krishnadas, R., Thulasiraj, R.D., Tielsch, J.M., Katz, J., Friedman, D.S., and Robin, A.L. (2003). Glaucoma in a rural population of southern India: the Aravind comprehensive eye survey. Ophthalmology *110*, 1484-1490.
Ramdas, W.D., van Koolwijk, L.M., Ikram, M.K., Jansonius, N.M., de Jong, P.T., Bergen, A.A., Isaacs, A., Amin, N., Aulchenko, Y.S., Wolfs, R.C.*, et al.* (2010). A genome-wide association study of optic disc parameters. PLoS Genet *6*, e1000978.
Raychaudhuri, A., Lahiri, S.K., Bandyopadhyay, M., Foster, P.J., Reeves, B.C., and Johnson, G.J. (2005). A population based survey of the prevalence and types of glaucoma in rural West Bengal: the West Bengal Glaucoma Study. Br J Ophthalmol *89*, 1559-1564.
Razeghinejad, M.R., and Banifatemi, M. (2013). Ocular biometry in angle closure. J Ophthalmic Vis Res *8*, 17-24.
Rezaie, T., Child, A., Hitchings, R., Brice, G., Miller, L., Coca-Prados, M., Heon, E., Krupin, T., Ritch, R., Kreutzer, D.*, et al.* (2002). Adult-onset primary open-angle glaucoma caused by mutations in optineurin. Science *295*, 1077-1079.
Ritch, R. (2016). Systemic Associations of Exfoliation Syndrome. Asia Pac J Ophthalmol (Phila) *5*, 45-50.
Ritch, R., and Schlotzer-Schrehardt, U. (2001). Exfoliation syndrome. Surv Ophthalmol *45*, 265-315.
Ritch, R., Schlotzer-Schrehardt, U., and Konstas, A.G. (2003). Why is glaucoma associated with exfoliation syndrome? Prog Retin Eye Res *22*, 253-275.
Rong, S.S., Tang, F.Y., Chu, W.K., Ma, L., Yam, J.C., Tang, S.M., Li, J., Gu, H., Young, A.L., Tham, C.C.*, et al.* (2016). Genetic Associations of Primary Angle-Closure Disease: A Systematic Review and Meta-analysis. Ophthalmology *123*, 1211-1221.
Ross, J.P., Dion, P.A., and Rouleau, G.A. (2020). Exome sequencing in genetic disease: recent advances and considerations. F1000Res *9*.
Rudnicka, A.R., Mt-Isa, S., Owen, C.G., Cook, D.G., and Ashby, D. (2006). Variations in primary open-angle glaucoma prevalence by age, gender, and race: a Bayesian meta-analysis. Invest Ophthalmol Vis Sci *47*, 4254-4261.

Sagara, M., Kawasaki, Y., Iemura, S.I., Natsume, T., Takai, Y., and Akiyama, T. (2009). Asef2 and Neurabin2 cooperatively regulate actin cytoskeletal organization and are involved in HGF-induced cell migration. Oncogene *28*, 1357-1365.
Sah, R.P., Badhu, B.P., Pokharel, P.K., Thakur, S.K., Das, H., and Panda, A. (2007). Prevalence of glaucoma in Sunsari district of eastern Nepal. Kathmandu Univ Med J (KUMJ) *5*, 343-348.
Sakurada, Y., Mabuchi, F., and Kashiwagi, K. (2020). Genetics of primary open-angle glaucoma and its endophenotypes. Prog Brain Res *256*, 31-47.
Sanfilippo, P.G., Hewitt, A.W., Hammond, C.J., and Mackey, D.A. (2010). The heritability of ocular traits. Surv Ophthalmol *55*, 561-583.
Santana-Garrido, A., Reyes-Goya, C., Fernandez-Bobadilla, C., Blanca, A.J., Andre, H., Mate, A., and Vazquez, C.M. (2021). NADPH oxidase-induced oxidative stress in the eyes of hypertensive rats. Mol Vis *27*, 161-178.
Sarfarazi, M., Child, A., Stoilova, D., Brice, G., Desai, T., Trifan, O.C., Poinoosawmy, D., and Crick, R.P. (1998). Localization of the fourth locus (GLC1E) for adult-onset primary open-angle glaucoma to the 10p15-p14 region. Am J Hum Genet *62*, 641-652.
Schlotzer-Schrehardt, U. (2009). Molecular pathology of pseudoexfoliation syndrome/glaucoma--new insights from LOXL1 gene associations. Exp Eye Res *88*, 776-785.
Schlotzer-Schrehardt, U., and Naumann, G.O. (1995). Trabecular meshwork in pseudoexfoliation syndrome with and without open-angle glaucoma. A morphometric, ultrastructural study. Invest Ophthalmol Vis Sci *36*, 1750-1764.
Schlotzer-Schrehardt, U., and Zenkel, M. (2019). The role of lysyl oxidase-like 1 (LOXL1) in exfoliation syndrome and glaucoma. Exp Eye Res *189*, 107818.
Sertie, A.L., Quimby, M., Moreira, E.S., Murray, J., Zatz, M., Antonarakis, S.E., and Passos-Bueno, M.R. (1996). A gene which causes severe ocular alterations and occipital encephalocele (Knobloch syndrome) is mapped to 21q22.3. Hum Mol Genet *5*, 843-847.
Shapiro, M.D., Tavori, H., and Fazio, S. (2018). PCSK9: From Basic Science Discoveries to Clinical Trials. Circ Res *122*, 1420-1438.
Sharma, S., Chataway, T., Burdon, K.P., Jonavicius, L., Klebe, S., Hewitt, A.W., Mills, R.A., and Craig, J.E. (2009). Identification of LOXL1 protein and Apolipoprotein E as components of surgically isolated pseudoexfoliation material by direct mass spectrometry. Exp Eye Res *89*, 479-485.
Sharma, S., Martin, S., Sykes, M.J., Dave, A., Hewitt, A.W., Burdon, K.P., Ronci, M., Voelcker, N.H., and Craig, J.E. (2016). Biological effect of LOXL1 coding variants associated with pseudoexfoliation syndrome. Exp Eye Res *146*, 212-223.
Shen, S.Y., Wong, T.Y., Foster, P.J., Loo, J.L., Rosman, M., Loon, S.C., Wong, W.L., Saw, S.M., and Aung, T. (2008). The prevalence and types of glaucoma in malay people: the Singapore Malay eye study. Invest Ophthalmol Vis Sci *49*, 3846-3851.
Sherwin, J.C., Hewitt, A.W., Bennett, S.L., Baird, P.N., Craig, J.E., and Mackey, D.A. (2009). Primary open angle glaucoma in subjects harbouring the predicted GLC1L haplotype reveals a normotensive phenotype. Clin Exp Ophthalmol *37*, 201-207.
Shi, H., Zhu, R., Hu, N., Shi, J., Zhang, J., Jiang, L., Jiang, H., and Guan, H. (2013). An extensive replication study on three new susceptibility Loci of primary angle closure glaucoma in han chinese: jiangsu eye study. J Ophthalmol *2013*, 641596.
Sia, D.I., Edussuriya, K., Sennanayake, S., Senaratne, T., Selva, D., and Casson, R.J. (2010). Prevalence of and risk factors for primary open-angle glaucoma in central Sri Lanka: the Kandy eye study. Ophthalmic Epidemiol *17*, 211-216.
Siggs, O.M., Han, X., Qassim, A., Souzeau, E., Kuruvilla, S., Marshall, H.N., Mullany, S., Mackey, D.A., Hewitt, A.W., Gharahkhani, P.*, et al.* (2021). Association of Monogenic and

Polygenic Risk With the Prevalence of Open-Angle Glaucoma. JAMA Ophthalmol *139*, 1023-1028.
Sim, D.H., Goh, L.G., and Ho, T. (1998). Glaucoma pattern amongst the elderly Chinese in Singapore. Ann Acad Med Singap *27*, 819-823.
Slavotinek, A.M. (2011). Eye development genes and known syndromes. Mol Genet Metab *104*, 448-456.
Smemo, S., Tena, J.J., Kim, K.H., Gamazon, E.R., Sakabe, N.J., Gomez-Marin, C., Aneas, I., Credidio, F.L., Sobreira, D.R., Wasserman, N.F.*, et al.* (2014). Obesity-associated variants within FTO form long-range functional connections with IRX3. Nature *507*, 371-375.
Sommer, A., Tielsch, J.M., Katz, J., Quigley, H.A., Gottsch, J.D., Javitt, J., and Singh, K. (1991). Relationship between intraocular pressure and primary open angle glaucoma among white and black Americans. The Baltimore Eye Survey. Arch Ophthalmol *109*, 1090-1095.
Souma, T., Tompson, S.W., Thomson, B.R., Siggs, O.M., Kizhatil, K., Yamaguchi, S., Feng, L., Limviphuvadh, V., Whisenhunt, K.N., Maurer-Stroh, S.*, et al.* (2016). Angiopoietin receptor TEK mutations underlie primary congenital glaucoma with variable expressivity. J Clin Invest *126*, 2575-2587.
Springelkamp, H., Iglesias, A.I., Mishra, A., Hohn, R., Wojciechowski, R., Khawaja, A.P., Nag, A., Wang, Y.X., Wang, J.J., Cuellar-Partida, G.*, et al.* (2017). New insights into the genetics of primary open-angle glaucoma based on meta-analyses of intraocular pressure and optic disc characteristics. Hum Mol Genet *26*, 438-453.
Stein, J.D., Khawaja, A.P., and Weizer, J.S. (2021). Glaucoma in Adults-Screening, Diagnosis, and Management: A Review. JAMA *325*, 164-174.
Stein, J.D., Pasquale, L.R., Talwar, N., Kim, D.S., Reed, D.M., Nan, B., Kang, J.H., Wiggs, J.L., and Richards, J.E. (2011). Geographic and climatic factors associated with exfoliation syndrome. Arch Ophthalmol *129*, 1053-1060.
Stoilova, D., Child, A., Trifan, O.C., Crick, R.P., Coakes, R.L., and Sarfarazi, M. (1996). Localization of a locus (GLC1B) for adult-onset primary open angle glaucoma to the 2cen-q13 region. Genomics *36*, 142-150.
Stone, E.M., Fingert, J.H., Alward, W.L., Nguyen, T.D., Polansky, J.R., Sunden, S.L., Nishimura, D., Clark, A.F., Nystuen, A., Nichols, B.E.*, et al.* (1997). Identification of a gene that causes primary open angle glaucoma. Science *275*, 668-670.
Strouthidis, N.G., and Girard, M.J. (2013). Altering the way the optic nerve head responds to intraocular pressure-a potential approach to glaucoma therapy. Curr Opin Pharmacol *13*, 83-89.
Stuart, T., and Satija, R. (2019). Integrative single-cell analysis. Nat Rev Genet *20*, 257-272.
Sun, W., Xiao, X., Li, S., Ouyang, J., Li, X., Jia, X., Liu, X., and Zhang, Q. (2019). Rare variants in novel and known genes associated with primary angle closure glaucoma based on whole exome sequencing of 549 probands. J Genet Genomics *46*, 353-357.
Sun, X., Dai, Y., Chen, Y., Yu, D.Y., Cringle, S.J., Chen, J., Kong, X., Wang, X., and Jiang, C. (2017). Primary angle closure glaucoma: What we know and what we don't know. Prog Retin Eye Res *57*, 26-45.
Suri, F., Yazdani, S., Chapi, M., Safari, I., Rasooli, P., Daftarian, N., Jafarinasab, M.R., Ghasemi Firouzabadi, S., Alehabib, E., Darvish, H.*, et al.* (2018). COL18A1 is a candidate eye iridocorneal angle-closure gene in humans. Hum Mol Genet *27*, 3772-3786.
Suriyapperuma, S.P., Child, A., Desai, T., Brice, G., Kerr, A., Crick, R.P., and Sarfarazi, M. (2007). A new locus (GLC1H) for adult-onset primary open-angle glaucoma maps to the 2p15-p16 region. Arch Ophthalmol *125*, 86-92.
Swierkowska, J., and Gajecka, M. (2017). Genetic factors influencing the reduction of central corneal thickness in disorders affecting the eye. Ophthalmic Genet *38*, 501-510.

Tanigawa, Y., Wainberg, M., Karjalainen, J., Kiiskinen, T., Venkataraman, G., Lemmela, S., Turunen, J.A., Graham, R.R., Havulinna, A.S., Perola, M.*, et al.* (2020). Rare protein-altering variants in ANGPTL7 lower intraocular pressure and protect against glaucoma. PLoS Genet *16*, e1008682.
Tarongoy, P., Ho, C.L., and Walton, D.S. (2009). Angle-closure glaucoma: the role of the lens in the pathogenesis, prevention, and treatment. Surv Ophthalmol *54*, 211-225.
Taylor, K.D., Guo, X., Zangwill, L.M., Liebmann, J.M., Girkin, C.A., Feldman, R.M., Dubiner, H., Hai, Y., Samuels, B.C., Panarelli, J.F.*, et al.* (2019). Genetic Architecture of Primary Open-Angle Glaucoma in Individuals of African Descent: The African Descent and Glaucoma Evaluation Study III. Ophthalmology *126*, 38-48.
Teikari, J.M. (1987). Genetic factors in open-angle (simple and capsular) glaucoma. A population-based twin study. Acta Ophthalmol (Copenh) *65*, 715-720.
Tham, Y.C., Li, X., Wong, T.Y., Quigley, H.A., Aung, T., and Cheng, C.Y. (2014). Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. Ophthalmology *121*, 2081-2090.
Thorleifsson, G., Magnusson, K.P., Sulem, P., Walters, G.B., Gudbjartsson, D.F., Stefansson, H., Jonsson, T., Jonasdottir, A., Jonasdottir, A., Stefansdottir, G.*, et al.* (2007). Common sequence variants in the LOXL1 gene confer susceptibility to exfoliation glaucoma. Science *317*, 1397-1400.
Thorleifsson, G., Walters, G.B., Hewitt, A.W., Masson, G., Helgason, A., DeWan, A., Sigurdsson, A., Jonasdottir, A., Gudjonsson, S.A., Magnusson, K.P.*, et al.* (2010). Common variants near CAV1 and CAV2 are associated with primary open-angle glaucoma. Nat Genet *42*, 906-909.
Tielsch, J.M., Sommer, A., Katz, J., Royall, R.M., Quigley, H.A., and Javitt, J. (1991). Racial variations in the prevalence of primary open-angle glaucoma. The Baltimore Eye Survey. JAMA *266*, 369-374.
Tomlinson, A., and Leighton, D.A. (1973). Ocular dimensions in the heredity of angle-closure glaucoma. Br J Ophthalmol *57*, 475-486.
Topouzis, F., Wilson, M.R., Harris, A., Anastasopoulos, E., Yu, F., Mavroudis, L., Pappas, T., Koskosas, A., and Coleman, A.L. (2007). Prevalence of open-angle glaucoma in Greece: the Thessaloniki Eye Study. Am J Ophthalmol *144*, 511-519.
Traversari, C., Sozzani, S., Steffensen, K.R., and Russo, V. (2014). LXR-dependent and -independent effects of oxysterols on immunity and tumor growth. Eur J Immunol *44*, 1896-1903.
Trifan, O.C., Traboulsi, E.I., Stoilova, D., Alozie, I., Nguyen, R., Raja, S., and Sarfarazi, M. (1998). A third locus (GLC1D) for adult-onset primary open-angle glaucoma maps to the 8q23 region. Am J Ophthalmol *126*, 17-28.
Uffelmann, E., Huang, Q.Q., Munung, N.S., de Vries, J., Okada, Y., Martin, A.R., Martin, H.C., Lappalainen, T., and Posthuma, D. (2021). Genome-wide association studies. Nature Reviews Methods Primers *1*.
Vallet, S.D., and Ricard-Blum, S. (2019). Lysyl oxidases: from enzyme activity to extracellular matrix cross-links. Essays Biochem *63*, 349-364.
van Zyl, T., Yan, W., McAdams, A., Peng, Y.R., Shekhar, K., Regev, A., Juric, D., and Sanes, J.R. (2020). Cell atlas of aqueous humor outflow pathways in eyes of humans and four model species provides insight into glaucoma pathogenesis. Proc Natl Acad Sci U S A *117*, 10339-10349.
Varma, R., Lee, P.P., Goldberg, I., and Kotak, S. (2011). An assessment of the health and economic burdens of glaucoma. Am J Ophthalmol *152*, 515-522.
Varma, R., Ying-Lai, M., Francis, B.A., Nguyen, B.B., Deneen, J., Wilson, M.R., Azen, S.P., and Los Angeles Latino Eye Study, G. (2004). Prevalence of open-angle glaucoma and

ocular hypertension in Latinos: the Los Angeles Latino Eye Study. Ophthalmology *111*, 1439-1448.
Vijaya, L., George, R., Baskaran, M., Arvind, H., Raju, P., Ramesh, S.V., Kumaramanickavel, G., and McCarty, C. (2008). Prevalence of primary open-angle glaucoma in an urban south Indian population and comparison with a rural population. The Chennai Glaucoma Study. Ophthalmology *115*, 648-654 e641.
Vijaya, L., George, R., Paul, P.G., Baskaran, M., Arvind, H., Raju, P., Ramesh, S.V., Kumaramanickavel, G., and McCarty, C. (2005). Prevalence of open-angle glaucoma in a rural south Indian population. Invest Ophthalmol Vis Sci *46*, 4461-4467.
Vithana, E.N., Khor, C.C., Qiao, C., Nongpiur, M.E., George, R., Chen, L.J., Do, T., Abu-Amero, K., Huang, C.K., Low, S.*, et al.* (2012). Genome-wide association analyses identify three new susceptibility loci for primary angle closure glaucoma. Nat Genet *44*, 1142-1146.
Voigt, A.P., Mulfaul, K., Mullin, N.K., Flamme-Wiese, M.J., Giacalone, J.C., Stone, E.M., Tucker, B.A., Scheetz, T.E., and Mullins, R.F. (2019). Single-cell transcriptomics of the human retinal pigment epithelium and choroid in health and macular degeneration. Proc Natl Acad Sci U S A *116*, 24100-24107.
Voigt, A.P., Mullin, N.K., Stone, E.M., Tucker, B.A., Scheetz, T.E., and Mullins, R.F. (2021). Single-cell RNA sequencing in vision research: Insights into human retinal health and disease. Prog Retin Eye Res *83*, 100934.
Wan, Y., Li, S., Gao, Y., Tang, L., Cao, W., and Sun, X. (2019). COL11A1 Polymorphisms Are Associated with Primary Angle-Closure Glaucoma Severity. J Ophthalmol *2019*, 2604386.
Wang, B., and Tontonoz, P. (2018). Liver X receptors in lipid signalling and membrane homeostasis. Nat Rev Endocrinol *14*, 452-463.
Wang, I.J., Chiang, T.H., Shih, Y.F., Lu, S.C., Lin, L.L., Shieh, J.W., Wang, T.H., Samples, J.R., and Hung, P.T. (2006). The association of single nucleotide polymorphisms in the MMP-9 genes with susceptibility to acute primary angle closure glaucoma in Taiwanese patients. Mol Vis *12*, 1223-1232.
Wang, J., Yusufu, M., Khor, C.C., Aung, T., and Wang, N. (2019). The genetics of angle closure glaucoma. Exp Eye Res *189*, 107835.
Wang, K., Gaitsch, H., Poon, H., Cox, N.J., and Rzhetsky, A. (2017). Classification of common human diseases derived from shared genetic and environmental determinants. Nat Genet *49*, 1319-1325.
Wang, R.R. (1985). [Genetic principles in primary angle-closure glaucoma]. Zhonghua Yan Ke Za Zhi *21*, 95-101.
Wang, Y.E., Li, Y., Wang, D., He, M., and Lin, S. (2013). Comparison of factors associated with occludable angle between american Caucasians and ethnic Chinese. Invest Ophthalmol Vis Sci *54*, 7717-7723.
Wang, Y.X., Xu, L., Yang, H., and Jonas, J.B. (2010). Prevalence of glaucoma in North China: the Beijing Eye Study. Am J Ophthalmol *150*, 917-924.
Waseem, N.H., Low, S., Shah, A.Z., Avisetti, D., Ostergaard, P., Simpson, M., Niemiec, K.A., Martin-Martin, B., Aldehlawi, H., Usman, S.*, et al.* (2020). Mutations in SPATA13/ASEF2 cause primary angle closure glaucoma. PLoS Genet *16*, e1008721.
Weih, L.M., Nanjan, M., McCarty, C.A., and Taylor, H.R. (2001). Prevalence and predictors of open-angle glaucoma: results from the visual impairment project. Ophthalmology *108*, 1966-1972.
Weinreb, R.N., Aung, T., and Medeiros, F.A. (2014). The pathophysiology and treatment of glaucoma: a review. JAMA *311*, 1901-1911.
Wiggs, J.L., Allingham, R.R., Vollrath, D., Jones, K.H., De La Paz, M., Kern, J., Patterson, K., Babb, V.L., Del Bono, E.A., Broomer, B.W.*, et al.* (1998). Prevalence of mutations in

TIGR/Myocilin in patients with adult and juvenile primary open-angle glaucoma. Am J Hum Genet *63*, 1549-1552.
Wiggs, J.L., Lynch, S., Ynagi, G., Maselli, M., Auguste, J., Del Bono, E.A., Olson, L.M., and Haines, J.L. (2004). A genomewide scan identifies novel early-onset primary open-angle glaucoma loci on 9q22 and 20p12. Am J Hum Genet *74*, 1314-1320.
Wiggs, J.L., and Pasquale, L.R. (2017). Genetics of glaucoma. Hum Mol Genet *26*, R21-R27.
Wiggs, J.L., Pawlyk, B., Connolly, E., Adamian, M., Miller, J.W., Pasquale, L.R., Haddadin, R.I., Grosskreutz, C.L., Rhee, D.J., and Li, T. (2014). Disruption of the blood-aqueous barrier and lens abnormalities in mice lacking lysyl oxidase-like 1 (LOXL1). Invest Ophthalmol Vis Sci *55*, 856-864.
Wiggs, J.L., Yaspan, B.L., Hauser, M.A., Kang, J.H., Allingham, R.R., Olson, L.M., Abdrabou, W., Fan, B.J., Wang, D.Y., Brodeur, W.*, et al.* (2012). Common variants at 9p21 and 8q22 are associated with increased susceptibility to optic nerve degeneration in glaucoma. PLoS Genet *8*, e1002654.
Williams, S.E., Whigham, B.T., Liu, Y., Carmichael, T.R., Qin, X., Schmidt, S., Ramsay, M., Hauser, M.A., and Allingham, R.R. (2010). Major LOXL1 risk allele is reversed in exfoliation glaucoma in a black South African population. Mol Vis *16*, 705-712.
Wirtz, M.K., Samples, J.R., Kramer, P.L., Rust, K., Topinka, J.R., Yount, J., Koler, R.D., and Acott, T.S. (1997). Mapping a gene for adult-onset primary open-angle glaucoma to chromosome 3q. Am J Hum Genet *60*, 296-304.
Wirtz, M.K., Samples, J.R., Rust, K., Lie, J., Nordling, L., Schilling, K., Acott, T.S., and Kramer, P.L. (1999). GLC1F, a new primary open-angle glaucoma locus, maps to 7q35-q36. Arch Ophthalmol *117*, 237-241.
Wolfs, R.C., Borger, P.H., Ramrattan, R.S., Klaver, C.C., Hulsman, C.A., Hofman, A., Vingerling, J.R., Hitchings, R.A., and de Jong, P.T. (2000). Changing views on open-angle glaucoma: definitions and prevalences--The Rotterdam Study. Invest Ophthalmol Vis Sci *41*, 3309-3321.
Wolfs, R.C., Klaver, C.C., Ramrattan, R.S., van Duijn, C.M., Hofman, A., and de Jong, P.T. (1998). Genetic risk of primary open-angle glaucoma. Population-based familial aggregation study. Arch Ophthalmol *116*, 1640-1645.
Woodroffe, A., Krafchak, C.M., Fuse, N., Lichter, P.R., Moroi, S.E., Schertzer, R., Downs, C.A., Duren, W.L., Boehnke, M., and Richards, J.E. (2006). Ordered subset analysis supports a glaucoma locus at GLC1I on chromosome 15 in families with earlier adult age at diagnosis. Exp Eye Res *82*, 1068-1074.
Writing Committee for the Normal Tension Glaucoma Genetic Study Group of Japan Glaucoma, S., Meguro, A., Inoko, H., Ota, M., Mizuki, N., and Bahram, S. (2010). Genome-wide association study of normal tension glaucoma: common variants in SRBD1 and ELOVL5 contribute to disease susceptibility. Ophthalmology *117*, 1331-1338 e1335.
Xu, Z., Hysi, P., and Khawaja, A.P. (2021). Genetic Determinants of Intraocular Pressure. Annu Rev Vis Sci *7*, 727-746.
Yamazaki, Y., Zhao, N., Caulfield, T.R., Liu, C.C., and Bu, G. (2019). Apolipoprotein E and Alzheimer disease: pathobiology and targeting strategies. Nat Rev Neurol *15*, 501-518.
Yanagi, M., Kawasaki, R., Wang, J.J., Wong, T.Y., Crowston, J., and Kiuchi, Y. (2011). Vascular risk factors in glaucoma: a review. Clin Exp Ophthalmol *39*, 252-258.
Ye, T., Yu, Q., Peng, S., Wang, N., and Chen, X. (1998). [Six year follow-up of suspects of primary angle-closure glaucoma]. Zhonghua Yan Ke Za Zhi *34*, 167-169.
Youngblood, H., Hauser, M.A., and Liu, Y. (2019). Update on the genetics of primary open-angle glaucoma. Exp Eye Res *188*, 107795.

Zanon-Moreno, V., Marco-Ventura, P., Lleo-Perez, A., Pons-Vazquez, S., Garcia-Medina, J.J., Vinuesa-Silva, I., Moreno-Nadal, M.A., and Pinazo-Duran, M.D. (2008). Oxidative stress in primary open-angle glaucoma. J Glaucoma *17*, 263-268.
Zebardast, N., Sekimitsu, S., Wang, J., Elze, T., Gharahkhani, P., Cole, B.S., Lin, M.M., Segre, A.V., Wiggs, J.L., and International Glaucoma Genetics, C. (2021). Characteristics of p.Gln368Ter Myocilin Variant and Influence of Polygenic Risk on Glaucoma Penetrance in the UK Biobank. Ophthalmology *128*, 1300-1311.
Zukerman, R., Harris, A., Vercellin, A.V., Siesky, B., Pasquale, L.R., and Ciulla, T.A. (2020). Molecular Genetics of Glaucoma: Subtype and Ethnicity Considerations. Genes (Basel) *12*.

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8. Figure Legends

Figure 1. Subtypes of adult onset glaucoma. Primary open-angle glaucoma (**L**), can be differentiated from Primary angle-closure glaucoma (**M**) by the irido-trabecular meshwork angle. This angle is occluded in angle closure glaucoma due to anatomical alterations, interfering with aqueous drainage and induces increased intraocular pressure (IOP). In open-angle glaucoma, the anatomical angle is unoccluded but outflow resistance is increased, resulting in increased IOP. This is mainly due to pathological alterations along the trabecular meshwork tissue or elsewhere along the drainage pathway. In Exfoliation glaucoma (**R**), abnormal deposition of extracellular debris in anterior chamber structures interferes with aqueous outflow, leading to increased IOP. Increased IOP in all glaucoma subtypes invariably leads to degeneration of retinal ganglion cells (RGC), progressively leading to blindness.

Figure 2. Comparing and contrasting Single Nucleotide Polymorphism-based and Exome sequencing-based approaches to finding risk genes in genome-wide association studies of glaucoma subtypes.

Figure 3. Possible disease mechanisms in Primary open-angle glaucoma that result in the degeneration of retinal ganglion cells.

Figure 4. Functional readouts of discovered variants can potentially improve precision in diagnosing and predicting risk of disease progression in exfoliation syndrome. A functional allelic series of CYP39A1 variants discovered by whole exome sequencing is shown. Box and whisker plots of enzymatic activities of the alleles, normalised to the wild-type reference allele re indicated. Blue rectangle denotes normal range of function. Alleles are classified as common alleles not associated with disease, predicted benign and predicted deleterious alleles. Predicted deleterious alleles were used in the initial effect size calculations. As expected, predicted benign alleles had a higher median activity, while predicted deleterious alleles had a much lower median activity. **A**. Misclassified variants, i.e., whose actual functional activities were not predicted correctly by bioinformatics

algorithms are indicated. **B**. Odds ratio that was recalculated based using an arbitrary cut-off of 95% loss of function was unchanged and highly significant, indicating that the vast majority patients with XFS carried the most severe loss of function alleles. **C**. Retrospective tracking of heterozygous carriers of the G204E alleles in the Japanese population found that carriers were 6 times more likely to progress to blindness. Tracking of carriers of this allele and other severe loss of function alleles in other populations is needed to confirm whether these alleles could be clinically actionable and whether carriers should be subjected to early clinical intervention. More data is also needed to establish the extent of loss of function that is needed for XFS to manifest .