Genomics enabling personalised glaucoma care

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ABSTRACT

Glaucoma is a leading cause of visual impairment and a significant public health concern, but despite ongoing advances in our understanding of the disease, several important clinical challenges remain. With the number of affected people projected to increase substantially over coming decades, novel approaches to screening, risk stratification, therapy, and glaucoma research are essential to deal with this expanding burden in an efficient and cost-effective manner. Genomics may hold the key to unlocking further biological insights and enabling precision medicine, in which glaucoma care is tailored to the individual patient, based on their unique profile for disease. Here we provide an overview of how genomics may enable cost-effective targeted population screening and personalised predictions of risk, response to treatment, and effective lifestyle advice. Given rapid advances in genetic testing technology and a move toward population-level genotyping, these early results have several important implications that promise to revolutionise the way in which glaucoma is detected and managed in years to come.

CURRENT CHALLENGES IN GLAUCOMA CARE

Glaucoma is the leading cause of irreversible blindness globally and the second most common cause of certifiable visual impairment in the United Kingdom (UK).[1,2] Loss of vision threatens not only individual safety, independence, and emotional well-being, but results in an increased need for social services, responsible for an estimated annual economic burden of £28 billion in the UK alone.[3] Glaucoma affects over 80 million people worldwide,[4] or approximately 4% of all adults aged >50 years.[5] Despite substantial advances in our understanding of the disease in recent years, several important clinical questions, spanning the spectrum of glaucoma care, remain unanswered. With prevalence estimated to increase by almost 50% by 2040,[4] novel strategies to address this expanding patient load are essential.

The progressive, irreparable nature of glaucoma means that early detection and treatment are critical for the prevention of visual morbidity. However, the early stages of the disease are asymptomatic, with up to two-thirds of those affected in the UK undiagnosed, or at least unaware of their diagnosis.[5,6] Population screening would therefore necessitate mass ophthalmic examination which, in the absence of adequate tests and a sufficiently high population prevalence, is neither feasible nor recommended.[7] Is there a viable and cost-effective strategy that could potentially enable community-based glaucoma screening?

Current treatment paradigms for glaucoma patients or people at risk of glaucoma are guided by an evidence-based approach, but while landmark glaucoma trials have answered several important clinical questions, they have also generated many more. For example, the Ocular Hypertension Treatment Study (OHTS) demonstrated elevated intraocular pressure (IOP) to be a major risk factor for primary open-angle glaucoma (POAG) and established that, on average, high IOP should be treated even before manifest glaucoma is present.[8] However, only 11% of untreated participants converted to POAG during the study period, suggesting that many were treated unnecessarily. Similarly, the United Kingdom Glaucoma Treatment Study (UKGTS) showed that the use of latanoprost compared to placebo more than halved visual field progression in those with established glaucoma.[9] However, 75% of participants receiving placebo did not measurably progress, while

15% of those in the treatment group demonstrated visual field deterioration within two years of follow up. These observations beg the questions: (1) Do we need to treat everybody who meets diagnostic criteria for glaucoma; and (2) would those who progressed, despite receiving therapy, benefit from different or more intensive treatment?

Routine glaucoma monitoring is typically achieved through serial visual field assessment, but presently, baseline prediction of which patients will progress is poor. Additionally, questions remain as to which of the various treatment options available – including medication, laser, minimally-invasive and penetrating surgery – represents the best therapeutic approach. Recently, the Laser in Glaucoma and Ocular Hypertension (LiGHT) trial demonstrated that selective laser trabeculoplasty (SLT) may be preferable to topical agents as a first-line therapy, with 74% of those in the SLT arm maintaining target IOP after 3 years of follow up.[10] A large analysis of real-world SLT outcomes showed that the average IOP response following therapy was an initial decrease, followed by a slow rise over time.[11] However, a range of responses were observed, with some participants responding well, and others not at all. Is there a way to predict who will respond to particular therapies and who would benefit from alternative approaches?

The problem with evidence-based medicine is that it tells you what is best *on average*, and this one-size-fits-all approach may not benefit all patients. However, with the increasing affordability and availability of publicly available genotyping platforms, a more nuanced approach may be possible through consideration of an individual's underlying genetic profile. Genomics may hold the key for precision medicine, in which care is tailored to the individual patient, based on their unique profile for disease susceptibility, prognosis, and response to therapy. This personalised approach could ensure that treatment is provided to only those who would benefit, sparing unnecessary cost and side effects for those who would not, ensuring efficient and effective healthcare provision.

GENETICS AND PRECISION MEDICINE

Glaucoma is one of the most heritable of all complex human diseases (estimated h^2, 0.70) and may be inherited as a simple (monogenic) or complex (polygenic) trait.[12,13] In adults, certain highly

penetrant genetic variants may be sufficient to cause disease, but are estimated to account for only 4% of all POAG cases.[13] The most common form – caused by myocilin (*MYOC*) gene sequence variations, first identified in 1997 – results in abnormal protein accumulation in the trabecular meshwork (TM), impeded aqueous outflow and elevated IOP.[14,15]

Characterisation and improved understanding of the genetic and anatomical basis underlying myocilin glaucoma holds promise for the development of curative therapeutic options for these patients in the future. Disruption of mutant *MYOC* and its function using CRISPR-Cas9 gene-editing technology has been shown to lower IOP and prevent further glaucomatous damage in a mouse model of the disease.[16] Several clinical reports have also highlighted the potential benefit of gonioscopy-assisted transluminal trabeculotomy (thereby directly bypassing the obstructed TM) in patients with myocilin glaucoma and uncontrolled IOP despite maximal medical therapy.[17,18] If we knew which POAG patients harboured pathogenic *MYOC* variants, then we could personalise their treatment by targeting the TM with a precise surgical approach.

The genetics underpinning more than 95% of adult-onset POAG, however, is far more complex. In these cases, multiple genetic risk factors, each with small effect, cumulatively contribute to disease. While a single variant is generally insufficient to cause glaucoma, the combined burden across an individual's genome may confer a risk equivalent to that seen in monogenic disease.[19] However, high genetic risk is not deterministic – some patients with multiple risk factors don't develop glaucoma, while others with only a few may develop disease – and this complexity makes identifying individual risk factors difficult.

Despite this challenge, there have been considerable advances in the identification of POAG-related genetic variants over the last decade. As recently as 2016, traditional case-control genome-wide association studies (GWAS) had identified less than 10 common genetic variants significantly associated with POAG at a genome-wide level of significance ($P<5\times10^{-8}$).[20] These results explained very little underlying biology and were insufficient to enable clinically relevant risk prediction. This all changed with the advent of large-scale epidemiological studies and the realisation that many answers could be provided through genetic analysis of IOP.

It has long been known that IOP represents a key mediating factor for glaucoma.[21] The prevalence of glaucoma increases exponentially with increasing IOP,[5] and lowering IOP reduces the risk of both glaucoma onset and progression.[9] Even within a healthy population, IOP can vary twofold and still be in the normal range.[5] IOP also has strong genetic basis (estimated h^2, 0.55) and examining variation within the normal range may therefore offer insights into pathologically elevated IOP and glaucoma.[22]

The population-based UK Biobank study provided the necessary participant numbers to examine these associations in substantially greater detail than previous GWAS.[23,24] Over 100,000 participants took part in a comprehensive eye and vision study,[25] including IOP measurement with an Ocular Response Analyser (ORA).[26] The ORA is able to account for corneal biomechanical properties and provides an estimate of true IOP, relatively independent of potential corneal artefact.[27]

Combining this data with that from several smaller studies resulted in the identification of >100 genetic variants significantly associated with IOP and provided many important biological insights.[21] Nearly all risk loci identified in the 2016 POAG GWAS were shown to be associated with IOP (two were not), highlighting the importance of IOP as a risk factor for disease. Two genes related to mitochondrial function (*ATXN2* and *TXNRD2*), previously thought to influence glaucoma risk through a direct effect on the optic nerve, were shown instead to influence IOP. Four loci previously associated with primary angle-closure glaucoma (*HGF*, *GLIS3*, *PLEKHA7*, and *FERMT2*) were shown to influence IOP, suggesting that more subtle features of the angle-closure phenotype might explain a proportion of IOP variance in the normal population. Many other novel associations, including genes previously associated with childhood glaucoma (*LMX1B* and *LTBP2*), ocular development (*MEIS1*, *SIX3*, and *ADAMTS18*), axial length (*RSPO1*), and iris architecture (*TRAF3IP1*), were identified.

Notably, pathways involved in ocular development were found to be strongly enriched, suggesting that IOP may be genetically determined through anatomical development of the eye. If the aqueous outflow pathway is poorly developed, IOP may decompensate within the normal human lifespan,

increasing the risk for glaucoma in these individuals. Interestingly, the primary biological pathway implicated in these analyses was for angiogenesis, with the main genes driving this relationship (*VEGFC*, *ANGPT1*, and *ANGPT2*) known to play a role in lymphangiogenesis. While the trabecular meshwork (TM), derived from epithelium and neural crest cells, and often considered the primary site of dysfunction in glaucoma, bears no embryological or anatomical relationship to lymphatic tissue, Schlemm's canal and collector channels, derived from endothelium and mesoderm, are related to lymphatic vessels. This finding suggests that the distal aqueous outflow pathways, and not just the TM, may be important in glaucoma pathogenesis.

This hypothesis is well demonstrated in mouse models of glaucoma, with eyes from mice with induced *ANGPT1* and *ANGPT2* deletions showing no Schlemm's canal development but a normal TM.[28] Similarly, intracameral delivery of *VEGFC* resulted in sprouting, proliferation, and growth of Schlemm's canal and a sustained reduction in IOP in adult mice.[29] These results raise the question of whether we may be able to predict which patients will respond to treatments that target the TM (like SLT or trabeculotomy) or identify those that may benefit from alternative therapies. Our hypothesis is that patients with a genetic signature for raised IOP due to a Schlemm's canal and collector channel problem will not respond as well to TM-targeted treatments.

PREDICTION AND RISK STRATIFICATION

Aside from biological insights, an important question is whether these genetic factors can be used to predict IOP and whether this may be clinically relevant to glaucoma. Applied to an independent study, these genome-wide significant genetic factors explained 17% of variance in IOP, and when examined in a second independent US cohort of 3,853 POAG cases and 33,480 controls, there was a strong correlation between the genetic variants' association with IOP and their association with glaucoma.[21] This dose-response relationship suggests that, genetically, any variant that influences IOP has a corresponding magnitude of effect on glaucoma risk.

Receiver operator characteristic (ROC) curves were then used to examine whether these IOP genetic factors, combined with age and sex, could predict prevalent glaucoma. These POAG predictive

models performed well for both high tension glaucoma (HTG) and normal tension glaucoma (NTG), with areas under the ROC curve of 0.76 and 0.71, respectively.[21] While this level of predictive ability is not diagnostic, and we would never expect a genetic test to be diagnostic, this level of performance is sufficient to enable identification of a high-risk subset of the population (see below). The relatively strong performance of IOP genetic factors in predicting NTG confirms that IOP is an important risk factor even in low-tension glaucoma subtypes.

Another approach to glaucoma risk stratification and prediction is the use of polygenic risk scores (PRS). The total number of risk variants present, often weighted by their magnitude of effect, are combined into a single probabilistic value (the PRS) that represents a quantitative summary of an individual's genetic susceptibility to a specific trait or disease.[30] In a clinical context, a PRS can then be used to stratify a population based on underlying levels of genetic susceptibility to disease. A recent POAG PRS demonstrated considerable risk stratification in an independent Australian cohort, with those in the top 10% of the PRS distribution having a >15-fold risk for glaucoma compared to those in the bottom 10%, and a >4-fold risk compared to the bottom 90%.[31]

The ability to identify those at high genetic risk for glaucoma has important implication for future screening strategies. Although early detection and timely intervention are essential to prevent glaucoma-related visual morbidity, population-based screening for the disease is not currently recommended.[7,32] Even with good diagnostic tests, screening for relatively low prevalence conditions such as undetected glaucoma, results in many false positive referrals and has the potential to overburden healthcare services. However, in the future, should population-level genetic data be available, those at the highest risk for glaucoma (in the top 10% of the PRS distribution, for example) could be identified. Applying the same diagnostic test to this selected population (with a much higher glaucoma prevalence) would result in far fewer false positives and may potentially prove to be a cost-effective screening strategy.[7]

With ongoing population ageing and increased access to eyecare services, the global burden of glaucoma (which is projected to increase to 112 million by 2040) threatens to overwhelm already stretched healthcare services.[4,33] In the OHTS trial, almost 90% of participants with ocular

hypertension did not develop glaucoma after more than 6 years of follow up.[8] Risk stratification of these patients will therefore become essential to delivering cost-effective and efficient care. In the future, genomics may facilitate this by enabling prediction of which patients will progress, allowing for targeted and appropriate allocation of limited resources.

A risk stratification calculator based on the results of the OHTS trial has already been developed and incorporates several clinical parameters, including IOP, central corneal thickness, vertical cup-disc ratio (vCDR), visual field pattern standard deviation, and age.[34] However, addition of a single well-known genetic risk factor for IOP and glaucoma – a variant in the *TMCO1* gene (rs4656461) – to the calculator, demonstrated a hazard ratio of 1.73 per additional risk allele (equivalent to a 3-fold greater risk in homozygotes), a magnitude of effect equivalent to a participant being 33 years older, having a baseline vCDR 0.43 larger, or having a baseline IOP 12mmHg higher.[35] Although this study needs replication, it provides a good indication of how genomics may further enhance current clinical risk stratification strategies.

LIFESTYLE ADVICE

While genomics has the potential to revolutionise decision making for the treating clinician, in future it may also help to inform lifestyle advice for individuals with glaucoma. Despite patients often asking what additional measures they can take to complement their treatment plan, for many years there has been limited evidence to support lifestyle and dietary recommendations in glaucoma.[30] If genetics is able to identify those at substantially higher risk for glaucoma, but before the overt onset of disease, these individuals need to be empowered with advice on behaviours that may reduce their risk for progression. However, these environmental and dietary factors are often difficult to quantify precisely, and previous studies have often been limited by small sample sizes and a lack of genetic data. This line of research has been greatly advanced by the advent of large-scale epidemiological studies, such as the UK Biobank, with detailed participant phenotyping, as well as ocular and genetic data.[23–25]

Within the UK Biobank, investigators were able to quantify the total dietary caffeine intake (not just that from common dietary sources, such as tea and coffee) of more than 100,000 participants, using the Oxford WebQ, an online dietary questionnaire.[36] Combining this with data from a comprehensive eye and vision sub-study,[25] they were able to conduct the largest study of the relationship between caffeine and glaucoma to date. Overall, total caffeine intake was associated with slightly lower IOP and had no association with glaucoma.[37] However, after stratifying participants according to their underlying genetic risk, based on a PRS for IOP,[21] an interesting finding emerged. For those in the top quartile of the PRS distribution, caffeine was significantly associated with higher IOP and greater odds of glaucoma, suggesting that caffeine may represent an important risk factor, but only in those who are genetically predisposed. The assessment of these gene-environment interactions (in which a certain factor has a differential effect depending on genetic risk) requires very large sample sizes and may explain why the lifestyle glaucoma literature has been hampered in the past.[30] Caffeine is an adenosine receptor antagonist and may affect aqueous humour homeostasis through effects on ciliary body and TM receptors.[38,39] The authors hypothesised that in individuals at low genetic risk with a well-developed outflow system, caffeine-induced IOP fluctuations could be tolerated without consequence, but that in individuals at high genetic risk with limited outflow reserve, these could lead to higher IOP and glaucoma risk.

A similar dietary analysis for alcohol consumption has also been performed in the UK Biobank.[40] Although prior studies had suggested that alcohol may be detrimental for glaucoma, the quality of evidence supporting this relationship was poor.[41] In UK Biobank participants, alcohol intake was found to be adversely associated with IOP, glaucoma, and two structural biomarkers of glaucoma – OCT-derived macular retinal nerve fibre layer (mRNFL) thickness and ganglion cell-inner plexiform later (GCIPL) thickness – regardless of their genetic makeup. However, when participants were further stratified according to their genetic risk, based on a comprehensive glaucoma PRS,[31] a similar finding to the caffeine analysis emerged. While no association between alcohol intake and IOP was evident in those at the lowest genetic risk, progressively stronger adverse associations were

demonstrated in those at higher risk, again suggesting that genetic susceptibility to disease may determine whether certain factors influence glaucoma risk.[40]

Research into environmental risks for glaucoma continues to produce new discoveries and better characterisation of the potential role of lifestyle and dietary factors. For example, similar results have recently been demonstrated for salt intake but not for physical activity.[42,43] These discoveries may eventually lead to personalised lifestyle and dietary recommendations for glaucoma patients in the future.

FUTURE DIRECTIONS

Recent studies and novel analytical approaches, including POAG GWAS meta-analysis,[44] GWAS for optic nerve head morphology,[45] and multitrait GWAS, combining glaucoma, IOP and vCDR data,[31,46] have further enabled genetic discovery and advanced our understanding of glaucoma pathogenesis. Modelling suggests that even larger studies will lead to substantial increases in the number of genetic variants identified and variance explained.[47] Ultimately, this will lead to improved glaucoma risk scores, especially with new methods of PRS construction,[48] further enabling risk stratification and the potential for precision glaucoma management.

Unfortunately, the majority of genetic data currently available is derived from European populations, with limited generalisability and poorer PRS performance in other ancestries.[49] There is an urgent need for more and improved glaucoma genetic data from non-European participants. The first GWAS for POAG in Africans identified only one genetic risk locus,[50] but much larger ongoing projects, such as the H3 Eyes of Africa project,[51] promise to improve this genetic discovery.

While the only way to target those at high risk in the general population is if everyone has genetic data available, there are several indications that population-level genotyping may soon become a distinct reality. Direct-to-consumer genotyping platforms, such as 23andMe (www.23andme.com), already offer a glaucoma PRS and clinicians may soon start encountering patients with knowledge of their genetic risk for glaucoma.

Ambitious projects, such as the Our Future Health study (www.ourfuturehealth.org.uk), which aims to genotype 5 million UK adults (approximately 10% of the adult population) by 2025, are already underway and promise to revolutionise genomics health research. For as little as £20 per participant, the study will provide not only genetic data relevant to glaucoma, but for a range of disease outcomes and health states. This may pave the way for all healthcare users eventually being genotyped and the information being held centrally, which clinicians and researchers may be able to utilise.

CONCLUSION

Genomics promises to change the way we detect glaucoma in the general population, enabling early detection and the prevention of glaucoma-related visual impairment and blindness. It will assist with risk stratification so that we can focus appropriate interventions on those at high risk, but also save limited resources by avoiding unnecessary treatment on individuals who will not benefit. It has the potential to lead to personalised glaucoma treatment, allowing clinicians to provide the most appropriate therapy to the individual patient from the outset, rather than following the trial-and-error approach of traditional treatment algorithms. It may also inform lifestyle and dietary advice for glaucoma patients in the future. Although much research is still needed, every indication suggests that genomics holds the key to unlocking further biological insights and to delivering personalised, cost-effective, and efficient glaucoma care in years to come.

REFERENCES

1 GBD 2019 Blindness and Vision Impairment Collaborators, Vision Loss Expert Group of the Global Burden of Disease Study. 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 Heal*. 2021;9:e144–60.

2 Quartilho A, Simkiss P, Zekite A, *et al.* Leading causes of certifiable visual loss in England and Wales during the year ending 31 March 2013. *Eye*. 2016;30:602–7.

3 Pezzullo L, Streatfeild J, Simkiss P, *et al.* The economic impact of sight loss and blindness in the UK adult population. *BMC Health Serv Res*. 2018;18:63.

4 Tham Y-C, Li X, Wong TY, *et al.* Global Prevalence of Glaucoma and Projections of Glaucoma Burden through 2040. *Ophthalmology*. 2014;121:2081–90.

5 Chan MPY, Broadway DC, Khawaja AP, *et al.* Glaucoma and intraocular pressure in EPIC-Norfolk Eye Study: cross sectional study. *BMJ*. 2017;358:j3889.

6 McCann P, Hogg R, Wright DM, *et al.* Glaucoma in the Northern Ireland Cohort for the Longitudinal Study of Ageing (NICOLA): cohort profile, prevalence, awareness and associations. *Br J Ophthalmol*. 2020;104:1492–9.

7 Hamid S, Desai P, Hysi P, *et al.* Population screening for glaucoma in UK: current recommendations and future directions. *Eye*. 2022;36:504–9.

8 Kass MA, Heuer DK, Higginbotham EJ, *et al.* The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. *Arch Ophthalmol*. 2002;120:701–13.

9 Garway-Heath DF, Crabb DP, Bunce C, *et al.* Latanoprost for open-angle glaucoma (UKGTS): a randomised, multicentre, placebo-controlled trial. *Lancet*. 2015;385:1295–304.

10 Gazzard G, Konstantakopoulou E, Garway-Heath D, *et al.* Selective laser trabeculoplasty versus eye drops for first-line treatment of ocular hypertension and glaucoma (LiGHT): a multicentre randomised controlled trial. *Lancet*. 2019;393:1505–16.

11 Khawaja AP, Campbell JH, Kirby N, *et al.* Real-World Outcomes of Selective Laser Trabeculoplasty in the United Kingdom. *Ophthalmology*. 2020;127:748–57.

12 Wang K, Gaitsch H, Poon H, *et al.* Classification of common human diseases derived from shared genetic and environmental determinants. *Nat Genet*. 2017;49:1319–25.

13 Stein JD, Khawaja AP, Weizer JS. Glaucoma in Adults—Screening, Diagnosis, and Management. *JAMA*. 2021;325:164.

14 Stone EM, Fingert JH, Alward WL, *et al.* Identification of a gene that causes primary open angle glaucoma. *Science*. 1997;275:668–70.

15 van der Heide CJ, Alward WLM, Flamme-Wiese M, *et al.* Histochemical Analysis of Glaucoma Caused by a Myocilin Mutation in a Human Donor Eye. *Ophthalmol Glaucoma*. 2018;1:132–8.

16 Jain A, Zode G, Kasetti RB, *et al.* CRISPR-Cas9-based treatment of myocilin-associated glaucoma. *Proc Natl Acad Sci U S A*. 2017;114:11199–204.

17 Boese EA, Alward WLM, Fingert JH. Gonioscopy-Assisted Transluminal Trabeculotomy for Myocilin Juvenile Glaucoma. *Ophthalmol Glaucoma*. 2022;5:369–70.

18 Dhillon S, Deol S, Tatham AJ. Genotype guided glaucoma surgery. *Eye*. 2023;doi:10.1038/s41433-023-02484-1.

19 Khera A V, Chaffin M, Aragam KG, *et al.* Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. *Nat Genet*. 2018;50:1219–24.

20 Bailey JNC, Loomis SJ, Kang JH, *et al.* Genome-wide association analysis identifies TXNRD2, ATXN2 and FOXC1 as susceptibility loci for primary open-angle glaucoma. *Nat Genet*. 2016;48:189–94.

21 Khawaja AP, Cooke Bailey JN, Wareham NJ, *et al.* Genome-wide analyses identify 68 new loci associated with intraocular pressure and improve risk prediction for primary open-angle glaucoma. *Nat Genet*. 2018;50:778–82.

22 Sanfilippo PG, Hewitt AW, Hammond CJ, *et al.* The heritability of ocular traits. *Surv Ophthalmol*. 2010;55:561–83.

23 Sudlow C, Gallacher J, Allen N, *et al.* UK Biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med*. 2015;12:e1001779.

24 Bycroft C, Freeman C, Petkova D, *et al.* The UK Biobank resource with deep phenotyping and genomic data. *Nature*. 2018;562:203–9.

25 Chua SYL, Thomas D, Allen N, *et al.* Cohort profile: design and methods in the eye and vision consortium of UK Biobank. *BMJ Open*. 2019;9:e025077.

26 Kaushik S, Pandav SS. Ocular Response Analyzer. *J Curr Glaucoma Pract*. 2012;6:17–9.

27 Luce DA. Determining in vivo biomechanical properties of the cornea with an ocular response analyzer. *J Cataract Refract Surg*. 2005;31:156–62.

28 Thomson BR, Heinen S, Jeansson M, *et al.* A lymphatic defect causes ocular hypertension and glaucoma in mice. *J Clin Invest*. 2014;124:4320–4.

29 Aspelund A, Tammela T, Antila S, *et al.* The Schlemm's canal is a VEGF-C/VEGFR-3-responsive lymphatic-like vessel. *J Clin Invest*. 2014;124:3975–86.

30 Stuart KV, Pasquale LR, Kang JH, *et al.* Towards modifying the genetic predisposition for glaucoma: An overview of the contribution and interaction of genetic and environmental factors. *Mol Aspects Med*. 2023;93:101203.

31 Craig JE, Han X, Qassim A, *et al.* Multitrait analysis of glaucoma identifies new risk loci and enables polygenic prediction of disease susceptibility and progression. *Nat Genet*. 2020;52:160–6.

32 Chou R, Selph S, Blazina I, *et al.* Screening for Glaucoma in Adults: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA*. 2022;327:1998–2012.

33 Fu DJ, Ademisoye E, Shih V, *et al.* Burden of Glaucoma in the United Kingdom: A Multicenter Analysis of United Kingdom Glaucoma Services. *Ophthalmol Glaucoma*. 2023;6:106–15.

34 Gordon MO, Beiser JA, Brandt JD, *et al.* The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma. *Arch Ophthalmol*. 2002;120:714–20.

35 Scheetz TE, Faga B, Ortega L, *et al.* Glaucoma Risk Alleles in the Ocular Hypertension Treatment Study. *Ophthalmology*. 2016;123:2527–36.

36 Liu B, Young H, Crowe FL, *et al.* Development and evaluation of the Oxford WebQ, a low-cost, web-based method for assessment of previous 24 h dietary intakes in large-scale prospective studies. *Public Health Nutr*. 2011;14:1998–2005.

37 Kim J, Aschard H, Kang JH, *et al.* Intraocular Pressure, Glaucoma, and Dietary Caffeine Consumption: A Gene-Diet Interaction Study from the UK Biobank. *Ophthalmology*. 2021;128:866–76.

38 Ribeiro JA, Sebastião AM. Caffeine and adenosine. *J Alzheimers Dis*. 2010;20:S3-15.

39 Spinozzi E, Baldassarri C, Acquaticci L, *et al.* Adenosine receptors as promising targets for the management of ocular diseases. *Med Chem Res*. 2021;30:353–70.

40 Stuart KV, Luben RN, Warwick AN, *et al.* The Association of Alcohol Consumption with Glaucoma and Related Traits: Findings from the UK Biobank. *Ophthalmol Glaucoma*. 2023;6:366–79.

41 Stuart KV, Madjedi K, Luben RN, *et al.* Alcohol, Intraocular Pressure, and Open-Angle Glaucoma: A Systematic Review and Meta-analysis. *Ophthalmology*. 2022;129:637–52.

42 Stuart KV, Biradar M, Luben R, *et al.* Association of urinary sodium excretion with glaucoma and related traits. *Investig Ophthalmol Vis Sci*. 2023;64:2908.

43 Madjedi KM, Stuart KV, Chua SY, *et al.* The Association of Physical Activity with Glaucoma and Related Traits in the UK Biobank. *Ophthalmology*. 2023;130:1024–36.

44 Gharahkhani P, Jorgenson E, Hysi P, *et al.* Genome-wide meta-analysis identifies 127 open-angle glaucoma loci with consistent effect across ancestries. *Nat Commun*. 2021;12:1258.

45 Alipanahi B, Hormozdiari F, Behsaz B, *et al.* Large-scale machine-learning-based phenotyping significantly improves genomic discovery for optic nerve head morphology. *Am J Hum Genet*. 2021;108:1217–30.

46 Han X, Gharahkhani P, Hamel AR, *et al.* Large-scale multitrait genome-wide association analyses identify hundreds of glaucoma risk loci. *Nat Genet*. 2023;55:1116–25.

47 Xu Z, Hysi P, Khawaja AP. Genetic Determinants of Intraocular Pressure. *Annu Rev Vis Sci*. 2021;7:727–46.

48 Choi SW, Mak TS-H, O'Reilly PF. Tutorial: a guide to performing polygenic risk score analyses. *Nat Protoc*. 2020;15:2759–72.

49 Cooke Bailey JN, Funk KL, Cruz LA, *et al.* Diversity in Polygenic Risk of Primary Open-Angle Glaucoma. *Genes*. 2022;14:111.

50 Genetics of Glaucoma in People of African Descent (GGLAD) Consortium, Hauser MA, Allingham RR, *et al.* Association of Genetic Variants With Primary Open-Angle Glaucoma Among Individuals With African Ancestry. *JAMA*. 2019;322:1682–91.

51 Olawoye O, Chuka-Okosa C, Akpa O, *et al.* Eyes of Africa: The Genetics of Blindness: Study Design and Methodology. *BMC Ophthalmol*. 2021;21:272.