

Association of Monogenic and Polygenic Risk With the Prevalence of Open-Angle Glaucoma

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 Supplemental content

IMPORTANCE Early diagnosis of open-angle glaucoma can lead to vision-saving treatment, and genetic variation is an increasingly powerful indicator in disease risk stratification.

OBJECTIVE To compare polygenic and monogenic variants in risk of glaucoma.

DESIGN, SETTING, AND PARTICIPANTS Clinical and genetic data were obtained for 2507 individuals from the Australian and New Zealand Registry of Advanced Glaucoma (ANZRAG) and 411 337 individuals in cross-sectional cohort studies including individuals of European ancestry in the UK Biobank. Recruitment to the UK Biobank occurred between 2006 and 2010, and data analysis occurred between September 2019 and August 2020.

MAIN OUTCOMES AND MEASURES Association of monogenic and polygenic variants with glaucoma risk.

RESULTS Individuals at high polygenic risk, defined as those in the top 5% of an unselected population, had a glaucoma risk (odds ratio [OR], 2.77; 95% CI, 2.58-2.98) comparable with the risk among individuals heterozygous for the *MYOC* p.Gln368Ter variant (OR 4.19; 95% CI, 3.25-5.31), which is the most common single-gene variant known to cause primary open-angle glaucoma. High polygenic risk was more than 6 times more common than *MYOC* p.Gln368Ter heterozygosity in ANZRAG (15.7% vs 2.6%) and more than 15 times more common in the general population (5.0% vs 0.32%). Within ANZRAG, high polygenic risk was associated with a mean (SD) age at glaucoma diagnosis that did not differ from the age at glaucoma diagnosis among individuals heterozygous for *MYOC* p.Gln368Ter (57.2 [14.2] vs 54.8 [13.6] years; $P > .99$).

CONCLUSIONS AND RELEVANCE Monogenic and high polygenic risk were each associated with a more than 2.5-fold increased odds of developing glaucoma and an equivalent mean age at glaucoma diagnosis, with high polygenic risk more than 15 times more common in the general population.

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Although open-angle glaucoma (OAG) is highly treatable, asymptomatic and irreversible vision loss can occur prior to diagnosis, and approximately half of all individuals with glaucoma are thought to be undiagnosed.¹ As such, there is a clinical need to improve stratification of OAG risk in the general population.

OAG and OAG-associated endophenotypes are highly heritable, with genetic variants of both large and small effect sizes contributing to heritability.² Heterozygous variants in *MYOC* represent the most common known single-gene cause of primary OAG, accounting for 2% to 4% of all cases,³ with the most common variant (p.Gln368Ter) being carried by approximately 1 of every 300 European individuals and 1 of every 60 probands with primary OAG.³ Glaucoma penetrance in individuals hetero-

zygous for *MYOC* p.Gln368Ter has been estimated at 15.5% in European individuals 65 years and older, corresponding to an odds ratio (OR) of 4.4,⁴ which is comparable with the risk of premature coronary artery disease in individuals carrying familial hypercholesterolemia variants (OR, 3.7).⁵

Polygenic risk scores (PRS) can improve risk stratification in common complex diseases, including glaucoma.^{6,7} While single-gene testing in individuals with glaucoma is performed in a limited number of academic centers and can lead to earlier identification of at-risk relatives,⁸ the clinical utility of PRS testing is yet to be demonstrated. This study benchmarked and compared the influence of monogenic and polygenic factors in glaucoma risk in 2 independent cohorts.

Methods

A total of 2507 individuals aged 9 to 100 years at recruitment diagnosed with advanced or nonadvanced primary OAG or juvenile OAG were referred by their treating ophthalmologist to the Australian and New Zealand Registry of Advanced Glaucoma (ANZRAG). Participants were considered to have glaucoma if they had glaucomatous visual field defects on standard automated perimetry and neuroretinal rim thinning (vertical cup-to-disc ratio [VCDR] greater than or equal to 0.7 or VCDR asymmetry greater than or equal to 0.2). Advanced glaucoma was defined as glaucomatous visual field loss in at least 1 eye, with at least 2 of 4 central visual field locations having a pattern standard deviation less than 0.5% on a 24-2 field using the Humphrey Field Analyzer (ZEISS), or a mean deviation of worse than -15 dB (or in the absence of field testing, loss of central visual acuity related to glaucoma), along with evidence of glaucomatous optic disc changes (even if mild) in the other eye. Diagnostic criteria for juvenile OAG were the same, with an age at diagnosis between 3 and 40 years. Cases of primary congenital glaucoma, anterior segment dysgenesis, pseudoexfoliative glaucoma, pigmentary glaucoma, steroid-induced glaucoma, angle-closure glaucoma, oculodentodigital dysplasia, aniridia, nanophthalmos, Stickler syndrome, Nail-patella syndrome, or other forms of syndromic glaucoma were excluded. The highest recorded intraocular pressure (IOP) was defined as the IOP at diagnosis or the highest IOP prior to or during treatment. Unless otherwise specified, we included individuals with either advanced or nonadvanced glaucoma. Given that the PRS applied in this study were derived using data from individuals of European ancestry, we only included individuals with White British ancestry on genetic principal components or self-reported White ancestry for those without genotype data. For population controls, we used 17 642 genotyped individuals from the population-based QSkin cohort: a prospective cohort of men and women aged 40 to 69 years randomly sampled from the population of Queensland, Australia, in 2011.⁹ Of the 2507 individuals with glaucoma, 1366 underwent genome-wide genotyping and were assigned a PRS. An additional 259 individuals who were unaffected family members of individuals with glaucoma were included in the analyses (eFigure 1 in the Supplement). The frequency of individuals heterozygous for *MYOC* p.Gln368Ter among 64 562 non-Finnish European individuals was obtained from the Genome Aggregation Database version 2.1.1 (gnomAD). This study was approved by the QIMR Berghofer Medical Research Institute and the Southern Adelaide Clinical Human Research Ethics Committee in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants, with no compensation or other incentives offered.

Exome and Capillary Sequencing

High-penetrance single-gene variants in the ANZRAG cohort were identified either by gene-based capillary sequencing or multiplex ligation-dependent probe amplification in a National Association Of Testing Authorities, Australia

Key Points

Question What is the association of monogenic and polygenic variants with glaucoma risk?

Findings In this cross-sectional study of 2507 individuals with open-angle glaucoma, high polygenic risk was associated with risk of developing glaucoma comparable with the risk associated with the most common single-gene pathogenic variant, but was more than 15 times more prevalent in the general population than this single-gene variant.

Meaning In this study, polygenic variants were associated with a comparable risk of developing glaucoma as some monogenic risk variants and were more prevalent in the general population.

(NATA)-accredited laboratory (SA Pathology, Flinders Medical Centre, Adelaide, Australia) or were identified first by exome sequencing and subsequently validated by capillary sequencing in the same NATA-accredited laboratory.⁴ Of the 2507 individuals with glaucoma in ANZRAG, 2300 had *MYOC* sequencing, 1015 were tested for *TBKI* copy number variants by multiplex ligation-dependent probe amplification, 995 were tested for the *OPTN* p.Glu50Lys variant; 141 had *CYP11B1* sequencing, and 795 underwent whole-exome sequencing, with some individuals tested in more than one assay.

Genotyping and Imputation

All ANZRAG samples were genotyped on Omni 1M (Illumina), OmniExpress (Illumina), or HumanCoreExome (Illumina) arrays. Genotype imputation was performed using Minimac version 3¹⁰ through the Michigan Imputation Server, with the Haplotype Reference Consortium release 1.1¹¹ as the reference panel. UK Biobank sample genotyping and imputation has been described in detail elsewhere.¹²

PRS

Derivation of the multitrait analysis of genome-wide association studies (MTAG) glaucoma PRS is described in detail elsewhere,⁷ including validation in OAG cohorts, and identification of an optimum *P* value threshold for maximum discriminatory power. Briefly, summary statistics from 5 separate genome-wide association studies were integrated into a single weighted score of 2673 uncorrelated variants (not including variants in *MYOC*) after linkage disequilibrium clumping at $r^2 = 0.1$ and a *P* value threshold of $\leq .001$: glaucoma in the UK Biobank (7947 individuals with glaucoma and 119 318 control individuals), a meta-analysis of IOP in the UK Biobank (103 914 individuals) and International Glaucoma Genetics Consortium (29 578 individuals), 7 individuals with vertical disc diameter-adjusted VCDR in the UK Biobank (67 040 individuals); and nonadjusted VCDR in the International Glaucoma Genetics Consortium (23 899 individuals). For ease of interpretation, raw glaucoma PRS values were transformed to *z* scores using mean and standard deviation of raw PRS values from the QSkin population cohort.

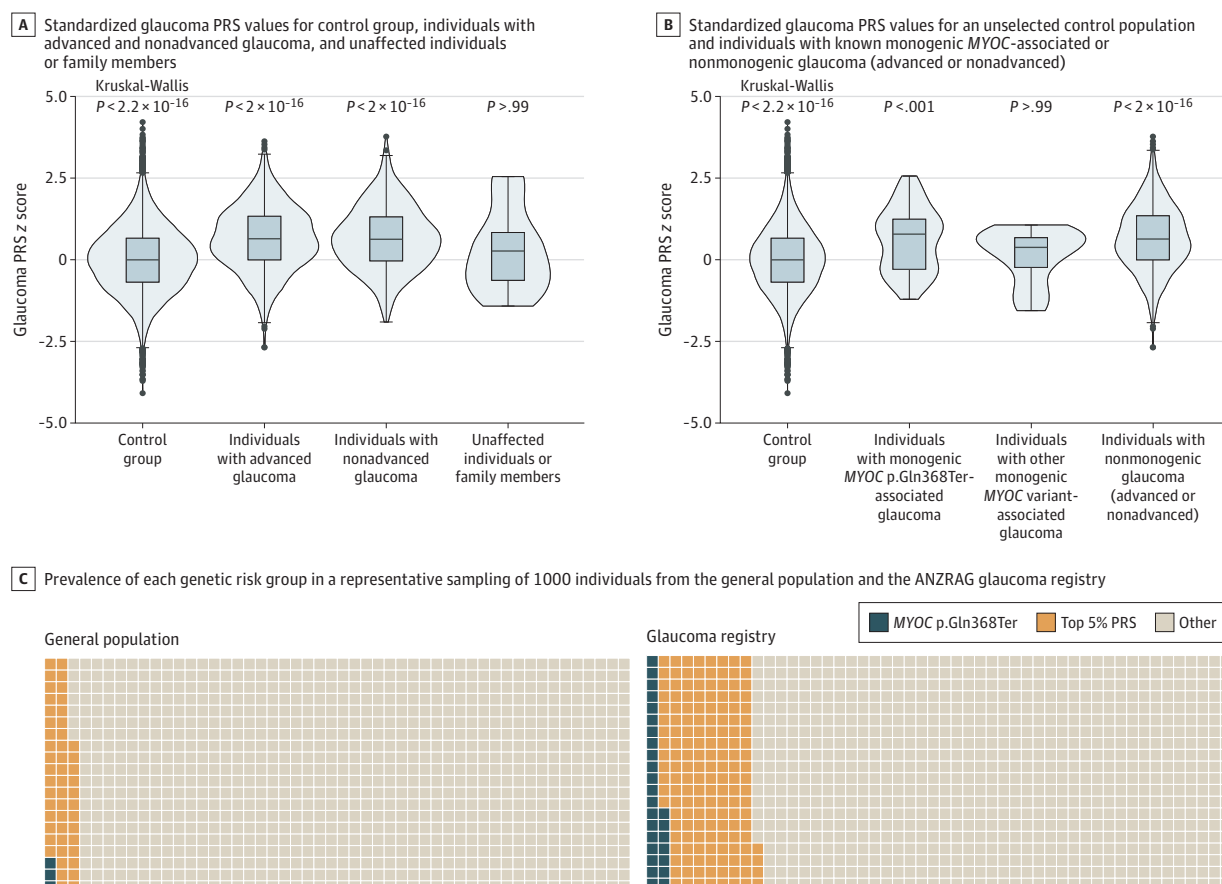
To benchmark the relative predictive performance of the glaucoma PRS and *MYOC* p.Gln368Ter, we derived a series of glaucoma ORs on 411 337 individuals from the UK Biobank (aged between 40 and 69 years at recruitment). To avoid sample overlap between the MTAG PRS and the UK Biobank target population, we rederived the MTAG PRS after excluding the UK Biobank case and control samples from the glaucoma genome-wide association study component (ie, 3071 ANZRAG individuals with glaucoma and 6750 control individuals were used in their place).⁷ Individuals with glaucoma were excluded from the UK Biobank VCDR and IOP genome-wide association studies to avoid inflation of glaucoma status prediction. Within the UK Biobank, individuals with glaucoma were identified by: (1) *International Classification of Diseases, Ninth Revision (ICD-9)* and *ICD-10* diagnoses of primary OAG, other glaucoma, or unspecified glaucoma; (2) reported glaucoma in a survey item inquiring about eye problems or disorders (UK Biobank data field 6148); or (3) reported glaucoma in a survey item on self-reported noncancer illness (UK Biobank data field 20002). ORs were calculated by comparing the higher PRS group with the remainder of the population in a logistic regression

model adjusted for the effects of sex and the first 4 principal components of ancestry.

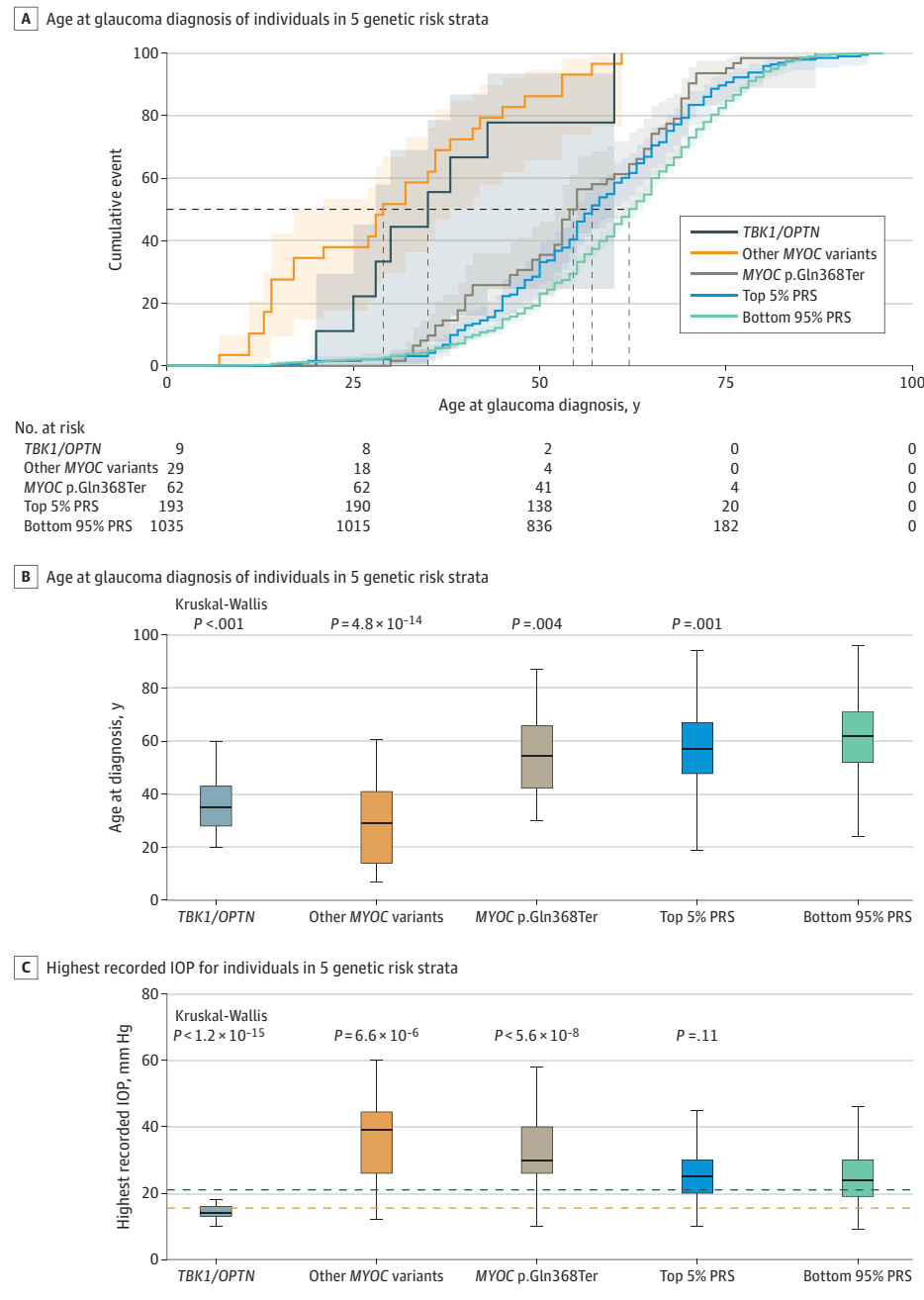
Statistical Analysis

Statistics are presented as means (with SDs) for continuous variables or as numbers (with percentages) for categorical variables. Normal continuous variables were compared by 2-tailed *t* test, with nonnormal continuous variables compared between groups by Kruskal-Wallis rank sum test, followed by pairwise comparisons using Wilcoxon rank sum test with Bonferroni correction of *P* values. Categorical variables were compared by χ^2 test. Significance level (α) was set at .05. Age-at-diagnosis survival curves stratified by genetic risk group were compared initially using log-rank test using 1 eye per individual (earlier progressing). Expected carrier frequencies (REF/ALT or ALT/ALT) were calculated under a Hardy-Weinberg equilibrium model using allele frequencies (AF), where REF/REF = $(1 - AF)^2$, REF/ALT = $2 \times AF(1 - AF)$, and ALT/ALT = AF^2 . All statistical analyses were performed using R version 4.0.2 (The R Foundation). Sequencing, genotyping, and derivation of the glaucoma PRS have been described in detail elsewhere.^{7,13}

Figure 1. Polygenic and Monogenic Glaucoma Risk in the Australian and New Zealand Registry of Advanced Glaucoma



A and B, Numbers above each group indicate Bonferroni-corrected *P* values for pairwise comparisons with the control group by Wilcoxon rank sum test. C, Each square represents one individual. ANZRAG indicates Australian and New Zealand Registry of Advanced Glaucoma; PRS, polygenic risk score.

Figure 2. Comparison of Polygenic and Monogenic Glaucoma Risk in Age at Glaucoma Diagnosis and Differential Effects on Maximum IOP

Results

We first defined the contribution of known monogenic variants to 2507 cases of advanced or nonadvanced OAG (eTable 1 and eFigure 1 in the [Supplement](#)). Individuals with a pathogenic or likely pathogenic variant in a mendelian glaucoma gene (*MYOC*, *CYP11B1*, *OPTN*, or *TBK1*) were identified as individuals with monogenic variants, while those without were identified as individuals with nonmonogenic variants, with the caveat that the latter may still harbor unidentified monogenic variants.

Overall, 109 of 2507 individuals with glaucoma (4.4%) were identified as monogenic. Of these, 94 of 109 (86.2%) had a pathogenic or likely pathogenic heterozygous variant in *MYOC*, with p.Gln368Ter accounting for 64 of 94 (68.1%) of all *MYOC* variants and 64 of 2507 (2.6%) of all glaucoma cases (eTable 1 in the [Supplement](#)). Individuals with monogenic variants had a younger mean (SD) age at diagnosis (44.8 [18.6] vs 60.4 [14.3] years; *P* < .001), and higher mean (SD) maximum IOP (31.78 [11.66] vs 25.75 [9.08] mm Hg; *P* < .001) compared with nonmonogenic cases (eFigure 1 and eTable 2 in the [Supplement](#)), with the notable exception of individuals with high-

Table. Characteristics of Individuals With Advanced or Nonadvanced Open-Angle Glaucoma Stratified by Genetic Risk

Characteristic	<i>TBK1/OPTN</i>	Other <i>MYOC</i> variants	<i>MYOC</i> p.Gln368Ter	Top 5% PRS	Bottom 95% PRS	P value ^a	
						Gln368Ter vs top 5% PRS	Top 5% PRS vs bottom 95%
No.	9	29	64	203	1075	NA	NA
Male, No. (%) ^b	5 (55.6)	12 (41.4)	34 (53.1)	87 (42.9)	506 (47.1)	>.99	>.99
Age at diagnosis, mean (SD), y	37.7 (14.4)	30.1 (15.5)	54.8 (13.7)	57.2 (14.2)	60.7 (14.4)	>.99	.003
Family history of glaucoma, No. (%)	9 (100.0)	28 (96.6)	59 (92.2)	147 (72.4)	661 (61.5)	.01	.03
Highest recorded IOP, mean (SD), mm Hg	14.1 (2.5)	35.9 (11.9)	32.1 (10.1)	26.6 (8.9)	25.3 (8.5)	<.001	.28
Trabeculectomy, No./total No. (%)	3/9 (33.3)	22/29 (75.9)	32/62 (51.6)	76/197 (38.6)	349/1027 (34.0)	.69	>.99

Abbreviations: IOP, intraocular pressure; NA, not applicable; PRS, polygenic risk score.

^a P values represent Bonferroni-corrected posthoc pairwise comparisons between *MYOC* p.Gln368Ter and top 5% PRS groups, to compare characteristics between groups with comparable glaucoma risk. P values from

the same posthoc comparisons are included for comparisons of the top 5% and bottom 95% of the population PRS distribution. Numbers in each group may differ from eTable 1 in the [Supplement](#) due to missing data.

^b Refers to self-reported sex.

penetrance variants in the normal-tension glaucoma genes *TBK1* and *OPTN*.

To compare the effect of monogenic risk and polygenic risk in OAG, we used the most common single-gene cause of primary OAG (*MYOC* p.Gln368Ter) and a multitrait glaucoma PRS.⁷ Compared with an ancestrally matched control population (**Figure 1A**), individuals with either advanced or nonadvanced glaucoma had an increased glaucoma PRS z score (a transformation representing standard deviations from the control cohort PRS mean; $P < 2 \times 10^{-6}$ for both pairwise comparisons), which was not statistically different between advanced and nonadvanced groups (mean [SD], 0.65 [0.99] and 0.66 [0.98], respectively; $P > .99$). Unaffected relatives of individuals with glaucoma had a higher mean (SD) glaucoma PRS z score (0.25 [1.26]) than an unselected control population (0 [1.00]), although there was no statistical difference between the 2 groups ($P > .99$) (**Figure 1A**). Compared with an unselected control population, individuals with nonmonogenic glaucoma had a higher mean (SD) glaucoma PRS z score (0.66 [0.99]; $P < 2 \times 10^{-6}$), which was not significantly different compared with individuals heterozygous for *MYOC* p.Gln368Ter (0.60 [0.97]; $P > .99$), nor individuals heterozygous for other pathogenic *MYOC* variants (0.12 [0.83]; $P = .25$) (**Figure 1B**).

To better define the effect of polygenic risk, we set a threshold for high polygenic risk as the top 5% of an unselected and ancestrally matched population. This corresponded to a glaucoma OR of 2.77 (95% CI, 2.58-2.98, compared with the bottom 95%) in the UK Biobank, which was comparable with individuals heterozygous for *MYOC* p.Gln368Ter in the same population cohort (glaucoma OR, 4.19; 95% CI, 3.25-5.31) (eTable 3 in the [Supplement](#)). Applying the same top 5% threshold to our glaucoma registry captured 15.7% of individuals with glaucoma (eFigure 2 in the [Supplement](#)), compared with 2.6% explained by the most common monogenic glaucoma risk variant, *MYOC* p.Gln368Ter (**Figure 1C**¹⁶; eTable 1 in the [Supplement](#)). By definition, in the population at large, individuals with a glaucoma PRS in the top 5% of the population distribution were more than 15 times more prevalent than individuals heterozygous for *MYOC* p.Gln368Ter (based on 0.32% of non-

Finnish European individuals being heterozygous for the variant in gnomAD version 2.1.1).¹⁴

PRS can also inform the age at which at-risk individuals are most likely to develop disease,^{7,15} providing important guidance for risk-stratified screening. Using ANZRAG, we compared the age at glaucoma diagnosis across 5 key genetic risk groups. Those with heterozygous pathogenic variants in *TBK1* or *OPTN* developed early-onset disease, with a mean (SD) age at diagnosis of 37.7 (14.4) years (**Figure 2A**). For individuals carrying heterozygous *MYOC* variants other than p.Gln368Ter, mean (SD) age at glaucoma diagnosis was 30.1 (15.5) years: 24.7 years younger than individuals heterozygous for *MYOC* p.Gln368Ter. For individuals in the top 5% of the polygenic risk distribution, mean (SD) age at glaucoma diagnosis (57.2 [14.2] years vs 54.8 [13.6] years) was 3.5 years younger than the remaining 95% (60.7 [14.4] years) and did not differ statistically from individuals heterozygous for *MYOC* p.Gln368Ter (54.8 [13.7]; $P > .99$) (**Figure 2A and 2B**; **Table**).

Discussion

In this cross-sectional study, a glaucoma PRS in the top 5% of the population distribution was associated with a risk comparable with the risk associated with a single monogenic glaucoma variant (*MYOC* p.Gln368Ter), but at a 6-fold higher prevalence among individuals with glaucoma and a more than 15-fold higher prevalence in the general population (eFigure 3 in the [Supplement](#)). An analogous comparison has been reported in early-onset myocardial infarction, where familial hypercholesterolemia variants conferred a comparable risk to the top 5% of the control distribution for a myocardial infarction PRS.^{6,17}

Current glaucoma screening guidelines target high-risk groups, including first-degree relatives or individuals of a certain age or ancestry.¹⁸ The use of genetic risk stratification may be a valuable screening adjunct, allowing higher-risk individuals to be monitored earlier and more frequently, and lower-risk individuals later and less frequently. Importantly, a glaucoma PRS can provide additional predictive ability on top of

traditional risk factors, including age, sex, and self-reported family history.⁷

Limitations

Limitations of this study include the case definition used by the UK Biobank (self-report and ICD codes), which will not capture all individuals with glaucoma, or with sufficient phenotypic resolution; as such, glaucoma PRS instruments derived from it are likely to underestimate true polygenic risk. Related to this, these PRS instruments were derived from populations predominantly of British European ancestry, and therefore they may not be as predictive in other populations.⁷ Finally, a limitation of using a disease registry

such as ANZRAG is ascertainment bias, whereby inclusion of affected relatives may lead to an overestimation of the true prevalence of both monogenic and polygenic risk variants.

Conclusions

Single-gene testing in glaucoma and other conditions has established clinical utility and is embedded in clinical practice. Given the similarity of monogenic and polygenic risk demonstrated in this study, we propose that both may be used with established risk factors in glaucoma risk stratification.

ARTICLE INFORMATION

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Concept and design: Siggs, Souzeau, Mackey, Hewitt, MacGregor.

Acquisition, analysis, or interpretation of data:

Siggs, Han, Qassim, Souzeau, Kuruville, Marshall, Mullany, Gharahkhani, MacGregor, Craig.

Drafting of the manuscript: Siggs, Qassim, Marshall, Mullany.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Siggs, Han, Qassim, Mullany, Gharahkhani, MacGregor.

Obtained funding: Siggs, Mackey, Hewitt, MacGregor, Craig.

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Supervision: Siggs, Souzeau, Mackey, Hewitt.

Conflict of Interest Disclosures: Drs Siggs, Hewitt, MacGregor, and Craig report holding equity in StratifEye Pty Ltd. Drs MacGregor, Hewitt, and Craig are coinventors on a patent application for the use of genetic risk scores in predicting glaucoma risk. No other disclosures were reported.

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