Study profile: the Genetics of Glaucoma Study

Puya Gharahkhani 1,2,3, Weiexiong He 1,2, Santiago Diaz Torres 1,2, Yeda Wu 1, Nathan Ingold 1,3, Regina Yu 1, Mathias Seviri 1,3, Jue-Sheng Ong 1, Matthew H Law 1,2,3, Jamie E Craig 4, David A Mackey 5,6, Alex W Hewitt 6,7, Stuart MacGregor 1,2

ABSTRACT

Purpose Glaucoma, a major cause of irreversible blindness, is a highly heritable human disease. Currently, the majority of the risk genes for glaucoma are unknown. We established the Genetics of Glaucoma Study (GOGS) to identify disease genes and improve genetic prediction of glaucoma risk and response to treatment.

Participants More than 5700 participants with glaucoma or a family history of glaucoma were recruited through a media campaign and the Australian Government healthcare service provider, Services Australia, making GOGS one of the largest genetic studies of glaucoma globally. The mean age of the participants was 65.30±9.36 years, and 62% were female. Participants completed a questionnaire obtaining information about their glaucoma-related medical history such as family history, glaucoma status and subtypes, surgical procedures, and prescriptions. The questionnaire also obtained information about other eye and systemic diseases. Approximately 80% of the participants provided a DNA sample and ~70% consented to data linkage to their Australian Government Medicare and Pharmaceutical Benefits Scheme schedules.

Findings to date 4336 GOGS participants reported that an optometrist or ophthalmologist had diagnosed them with glaucoma and 3639 participants reported having a family history of glaucoma. The vast majority of the participants (N=4339) had used at least one glaucoma-related medication; latanoprost was the most commonly prescribed drug (54% of the participants who had a glaucoma prescription). A subset of the participants reported a surgical treatment for glaucoma including a laser surgery in 2008 participants and a non-laser operation in 803 participants. Several comorbid eye and systemic diseases were also observed; the most common reports were ocular hypertension (53% of the participants), cataract (48%), hypertension (40%), nearsightedness (31%), astigmatism (22%), farsightedness (16%), diabetes (12%), sleep apnoea (11%) and migraines (10%).

Future plans GOGS will contribute to the global gene-mapping efforts as one of the largest genetic studies for glaucoma. We will also use GOGS to develop or validate genetic risk prediction models to stratify glaucoma risk, particularly in individuals with a family history of glaucoma, and to predict clinical outcomes (eg, which medication works better for an individual and whether glaucoma surgery is required). GOGS will also help us answer various research questions about genetic overlap and causal relationships between glaucoma and its comorbidities.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Genetics of Glaucoma Study (GOGS) is one of the largest genetic studies of glaucoma in the world, providing a valuable source for glaucoma gene discovery.
⇒ GOGS includes a rich set of phenotypes such as family history of glaucoma as well as a range of clinical traits.
⇒ Self-reported data complemented with more detailed information through linkage to the Australian Government Medicare and Pharmaceutical Benefits Scheme schedules.
⇒ Higher female participation; a well-known limitation for many research studies developed based on volunteer participation.
⇒ The vast majority of the participants are of European descent, limiting statistical power for other ancestry groups.

INTRODUCTION

Glaucoma, a major cause of irreversible blindness worldwide, is characterised by a progressive degeneration of the optic nerve.1,2 Primary open-angle glaucoma (POAG) is one of the major types of glaucoma, often accompanied by an elevated intraocular pressure (IOP).1,2 POAG is a highly heritable human disease with 70% of the variation in risk attributed to genetics.3 However, the currently known risk genes for POAG collectively explain only ~10% of the familial relative risk.4 Hence, new studies and larger international consortia are required to accelerate discovery of new glaucoma risk genes. Identifying risk genes and genetic variants for POAG helps us understand the underlying biology of the disease. Gene discovery also has clinical implications; identifying disease genes enables genetic risk prediction and assists with target identification in efforts to develop new treatments.
Genetic risk prediction provides an opportunity to identify people at high risk before the clinical onset of the disease. Currently, nearly half of the POAG cases remain undiagnosed until the optic nerve is damaged,^2^ with associated vision loss. These people may benefit from early screening and intervention with ocular hypertension treatments that have been shown to prevent or slow down disease progression.\(^6\) Early screening and intervention may also reduce healthcare costs by reducing the need for costly surgical procedures through early disease management, and through reducing screening of those at low risk. Currently, \(-10\%\) of the general population have a family history of glaucoma, which raises their risk of glaucoma ninefold, so are recommended to be screened 1–2 times yearly.\(^7\) However, the majority of those with family history do not go on to develop glaucoma and a risk stratification approach that also includes genetic risk predictors could prioritise people who require more intensive screening and intervention while people at low risk could undergo less frequent follow-up.

We previously showed that genetic risk prediction built on common glaucoma-associated single-nucleotide polymorphisms (SNPs with minor allele frequency >0.01) is predictive of glaucoma risk, progression and age at diagnosis.\(^8\) However, given the polygenic architecture of POAG with a large number of SNPs contributing to the disease risk, each with a small effect, as well as the necessity for multiple testing correction to control the type I error rate in Genome-Wide Association Studies (GWAS), large sample sizes are needed to achieve the statistical power required for gene discovery to narrow down the ‘missing heritability’ gap. We previously estimated that increasing the sample size of glaucoma GWAS studies to 400K cases and a matched number of controls will help identify additional glaucoma risk variants that would explain up to 80\% of the genetic variance in glaucoma and improve the predictive ability of the current genetic risk prediction models up to an area under curve of \(-0.8.\)\(^9\) Given that developing a single study to target this large sample size for glaucoma is logistically and financially challenging, international collaborations are required. Hence, to improve glaucoma gene discovery and risk prediction, we aimed to develop a large glaucoma genetics study in Australia, which will contribute to international collaborative efforts.

In addition to the potential for early intervention, gene mapping also opens up additional avenues for personalised medicine. Previous studies have shown association of genetic variants with differential response to glaucoma treatment between individuals.\(^10\) We have also shown that SNP-based genetic risk prediction is capable of predicting clinical outcomes and the probability of requiring surgical intervention.\(^3\) Hence, from the personalised medicine perspective, prediction of response to treatment and surgical interventions based on an individual’s genetic architecture paves the way for establishing personalised treatments where each person could have a unique ‘treatment cocktail’ based on their distinct genetic mechanisms contributing to their glaucoma risk.

The other major clinical significance of gene mapping includes developing new treatments for POAG. Identifying novel disease genes can allow repurposing of existing, approved, drugs or provide potential new targets for developing novel drugs.\(^11\) All current treatments for POAG aim at lowering IOP, which is effective in slowing down the disease progression; however, these treatments cannot restore optic nerve damage that has already occurred. Hence, development of neuroprotective treatments by targeting the risk genes that damage the optic nerve independent of IOP would be a major advance in glaucoma prevention.

To achieve the above purposes, we established the Genetics of Glaucoma Study (GOGS), a large study comprising >5700 (as of April 2022) Australian participants with glaucoma or a family history of glaucoma. We will primarily use this data to expand our understanding of genetic risk factors for glaucoma and improve genetic risk prediction. A unique facet of this study is the involvement of a large number of people with a family history of glaucoma; studying this group may help us improve risk prediction accuracy among this high-risk group and inform mitigation strategies to help them manage their risk.

**Objectives**
Combining data collected in this study with independent glaucoma datasets worldwide, GOGS aim to achieve the following collective goals:

1. Identify novel genetic risk loci for glaucoma.
2. Improve genetic risk prediction for glaucoma, with an emphasis on risk prediction among people with a family history of glaucoma, and develop genetic risk assessment tools to identify people at high risk.
3. Investigate genetic influences on response to glaucoma therapies (such as IOP-lowering medications).
4. Investigate genetic links between glaucoma and a wide range of eye diseases, as well as systemic diseases such as Alzheimer’s disease, cardiovascular diseases and diabetes.
5. Investigate causality of modifiable putative risk factors for glaucoma such as body mass index, education levels and tobacco smoking.

**COHORT DESCRIPTION**
**Study participants**
Participants were recruited via two arms: (1) a media campaign that invited individuals with glaucoma or a family history to take part and (2) direct mailouts to people who have been prescribed a glaucoma medication within the last year (see details below).

**Patient and public involvement**
Several participants provided feedback on the study questionnaire and two participants, one with glaucoma and one with a family history of glaucoma, were involved in
the study press conference to encourage participation in this study. Moreover, we consulted three ophthalmologists to codeign the study questionnaire in order to ensure that relevant clinical and surgical information is obtained from GOGS participants. We provided participants with a newsletter to inform them about the overall study progress, with further newsletters to be provided to update them on the study results and acknowledge their contributions to related publications.

Recruitment strategy

Media campaign: For this pathway, QIMR Berghofer’s External Relations Team advertised the study through the QIMR Berghofer website and Facebook. The adverts invited participants over 18 years old, who self-reported a diagnosis of glaucoma or who reported having a family history of glaucoma to volunteer.

Recruitment through medical and pharmaceutical prescription history: This recruitment pathway was conducted with assistance from Services Australia, formerly known as the Department of Human Services. Services Australia is part of the Australia Government that provides social and healthcare services to Australians. Medical and pharmaceutical services are subsidised by the Australian Government through the Medicare Benefits Schedule (MBS) and Pharmaceutical Benefits Scheme (PBS), respectively. Following regulatory and ethics approval, Services Australia is able to send invitation letters to people with certain healthcare (MBS) and pharmaceutical (PBS) records to invite them to participate in medical research studies.

On obtaining approvals from the QIMR Berghofer and Services Australia human research ethics committees, 32,000 invitation letters were sent by Services Australia on behalf of our study. People were invited to take part based on the following glaucoma-related procedure MBS item codes—10914, 11200, 42752, 42705, 42744, 42746, 42749, 42752, 42755, 42758, 42770, 42782 and 42794—who were also prescribed any glaucoma medications (please see details in the Glaucoma medication section). This was performed in two waves. In the pilot wave to estimate the participation rate and overall success of this approach, 2000 invitation letters were sent to people over 18 years old who had at least 6 months of continuous glaucoma medication supply on their PBS records. Following the successful recruitment of more than 200 people (a response rate of 10%), we sent 30,000 additional invitation letters in the second wave.

The following changes were made to the selection criteria relative to the pilot wave: (1) we enrolled participants between 18 and 70 years old (rather than over 18 years from the pilot study). This was because people over 70 years old may be less able/willing to participate due to other health issues, and a subset of them may develop glaucoma due to advanced age rather than a high genetic load (rendering them less suitable for the gene discovery and risk prediction aims of this study). (2) Participants had to have at least 2 months of glaucoma medication supply (unlike in our pilot study, supply did not have to be continuous) within the past year at the time of invitation (ie, between 25 February 2020 and 24 February 2021). We chose a year-long inclusion period to estimate the participation rate and overall success of this recruitment pathway in an environment with a high risk of lost to follow-up (ie, participants in our pilot study were not asked to maintain continuous glaucoma medication supply (unlike in our pilot study, supply did not have to be continuous) within the past year at the time of invitation (ie, between 25 February 2020 and 24 February 2021). We chose a year-long inclusion period to estimate the participation rate and overall success of this recruitment pathway in an environment with a high risk of lost to follow-up (ie, participants in our pilot study were not asked to maintain continuous glaucoma medication supply). We opted to remove the continuity of supply requirement as it greatly limited the number of potential recruits. The vast majority of these people (91%) confirmed they have glaucoma (self-report) although a small fraction had ocular hypertension, the major risk factor for glaucoma.

Managing privacy concerns: The invitation letters highlighted that Services Australia had not provided any information to the researchers about people who have received the letters. Letters contained a brief description of the study aims, participation and withdrawal policies (highlighting that the study is completely voluntary and people can withdraw from the study at any time), as well as the study webpage and contact details (study-specific email and phone).

Enrolment procedure

People invited by both routes described above were asked to enrol in the study by filling out a survey through visiting our study webpage (https://www.qimrberghofer.edu.au/genetics-of-glaucoma/) or requesting a hard copy version of the survey. Enrolment involved reading through a participant information sheet that contained information including the study aims, participation eligibility, and the study ethics and policies on participation, withdrawal, confidentiality, storage and sharing of biological samples and questionnaire data, and any use of the data in future studies. Participants then consented that they had read and understood the information sheet, were willing to provide a sample of their saliva for DNA extraction and genotyping, and that their data may be used for other medical research studying health and behaviour in the future, subject to review by the appropriate research ethics committees. Participants were then directed to fill out the study questionnaire obtaining glaucoma and other health-related information. For subsequent research work and data analysis, all participant data were deidentified.

The questionnaire information

The study questionnaire recorded participants’ demographics and medical history related to glaucoma including glaucoma status and subtypes, their age at diagnosis, surgical procedures, prescriptions, and family history. The questionnaire also captured information about other eye conditions (eg, myopia and cataract), and other systemic diseases (eg, diabetes and dementia). A summary of the questionnaire topics is shown in online supplemental table 1 and the full questionnaire is presented as online supplemental material. Questions that were compulsory for the participant to answer have been marked with a red asterisk (*).

Consent to supply DNA

As part of the study consent, we obtained participants’ consent to provide a sample of their saliva for DNA
extraction and genotyping. For a subset of the participants (N=544) with existing genotypes, we further obtained their consent for us to access their genotypes obtained from a previous genetic test performed through a direct-to-consumer genotyping company (i.e., AncestryDNA, 23andMe, MyHeritage, FamilyTreeDNA and LivingDNA) or from QIMRB QSkin study12 or QIMRB Australian Genetics of Depression Study (AGDS).13 If people were unwilling to share their existing genotypes, we sent them a saliva collection kit, similar to the participants without existing genotypes (see details below).

Participants who consented to provide their direct-to-consumer genotyping data were advised to securely upload their existing genotypes to QIMRB server. Following consent, we also obtained internal access to existing genotypes stored at QIMRB for the consented QIMRB QSkin and AGDS participants.

Saliva collection and DNA extraction
An Isohelix GeneFix Saliva Collection Kit along with an MBS/PBS consent form (please see below) was dispatched. Saliva samples were returned to QIMR Berghofer by prepaid post. A reminder email was sent after 2 months to people who had not returned their saliva kits. DNA was extracted in the Sample Processing Lab at QIMR Berghofer.

To reduce the possibility of sample mix-up due to handling and human error, the barcodes of the saliva collection kits were linked to the participant’s study ID associated with their consent forms and questionnaires. On receipt, the kits were unpacked and the barcodes were scanned to automatically link the saliva samples to the participants’ information obtained online. We have additional QC protocols in place to ensure that the participants’ genotypes match with their questionnaire information. For example, we will compare the genotype-inferred and self-reported sex; any mismatches will be excluded from further analysis.

DNA genotyping
At the time of writing, we have plated 3978 DNA samples for genotyping using Illumina Infinium Global Screening

| Table 1 | Demographic and participation characteristics in GOGS |
|---------|------------------------|------------------------|------------------------|
|         | Total                  | Media                  | Services Australia     |
| N       | 5737                   | 3453                   | 2284                   |
| Age     |                        |                        |                        |
| Age range | 19–100              | 20–100                 | 19–96                  |
| Age mean (SD) | 65.30 (9.36) | 65.41 (9.95) | 65.13 (8.43) |
| Sex     |                        |                        |                        |
| Male    | 2193 (38.2%)           | 1085 (31.4%)           | 1108 (48.51%)          |
| Female  | 3537 (61.7%)           | 2362 (68.4%)           | 1175 (51.45%)          |
| Unspecified | 7 (0.1%)   | 6 (0.2%)               | 1 (0.04%)              |
| Education |                        |                        |                        |
| Years of education—range | 0–30                | 1–30                   | 0–29                   |
| Years of education—mean (SD) | 13.65 (3.25) | 13.72 (3.26) | 13.55 (3.24) |
| Smoking |                        |                        |                        |
| Regular smoker ever | 2120 (37% of 5684 responders) | 1228 (36% of 3416 responders) | 892 (39% of 2268 responders) |
| Mean (SD) of age at smoking initiation (in 2112 responders) | 18.33 (4.64) | 18.51 (4.87) | 18.08 (4.28) |
| Ceased smoking | 1899 (90% of 2118 responders) | 1094 (89% of 1227 responders) | 805 (90% of 891 responders) |
| Mean (SD) of age at smoking cessation (in 1856 responders) | 38.42 (12.58) | 38.41 (12.41) | 38.44 (12.80) |
| Mean (SD) of N cigarettes per day—current smokers in 210 responders | 14.22 (9.88) | 14.04 (10.93) | 14.51 (8.01) |
| Mean (SD) of N cigarettes per day—previous smokers in 1858 responders | 17.33 (11.12) | 16.65 (10.93) | 18.25 (11.31) |
| IOP     |                        |                        |                        |
| Mean (SD) of IOP—left eye (2917 responders) | 15.46 (5.40) | 15.47 (5.21) | 15.45 (5.61) |
| Mean (SD) of IOP—right eye (2919 responders) | 15.72 (5.35) | 15.70 (5.31) | 15.75 (5.40) |
| Mean (SD) of highest IOP (2082 responders) | 26.38 (9.56) | 26.00 (9.65) | 26.80 (9.45) |

DHS, Department of Human Services; IOP, intraocular pressure.
Array (San Diego, California, USA). The previously existing genotypes (N=544) were obtained from the following arrays: Illumina OmniExpress (23andMe v3/v4, AncestryDNA, FamilyTreeDNA and MyHeritage) and Illumina Global Screening Array (23andMe v5, LivingDNA, FamilyTreeDNA since 2019, QSkin and AGDS). The minimum number of discrete groups with the maximal SNP overlap will be identified for separate imputation; a batch variable will be used in subsequent analysis. In total, we obtained genotype data from 4522 participants.

MBS and PBS records linkage
Self-reported glaucoma clinical information such as age at diagnosis, treatment procedures or surgeries, and medications prescribed will be supplemented by linkage to the Australian Government MBS/PBS records, access to which provide us more accurate clinical and prescription data. For example, some participants may not recall their exact type of glaucoma surgeries or medications prescribed; by linking data to their PBS and MBS records, we can retrieve such clinical information.

On approval from Services Australia External Request Evaluation Committee, we obtained participants’ consent to access to their glaucoma-related MBS/PBS records for the last 4.5 years. As opposed to the study consent, giving consent to the MBS/PBS component was not required for participation in this study; people could still participate without agreeing to provide their MBS/PBS data. The requested MBS/PBS items are presented in online supplemental table 2). As of April 2022, approximately 70% of the participants consented to their MBS/PBS records access.

FINDINGS TO DATE
Sample characteristics
In total, 5737 people consented to participate and filled out the study questionnaire. The vast majority of participants self-reported their ancestry as European (5104 of 5520; 92.5%). Other self-reported ancestries included Asian (N=205; 3.7%), Indigenous Australian or Torres Strait Islander (N=26; 0.47%), Middle Eastern (N=25; 0.45%), Latino (N=24; 0.43%), African (N=11; 0.2%), Pacific Islander (N=5; 0.09%) and mixed ancestry (N=120; 2.17%). Participants were aged between 19 and 100 at the time of recruitment, with a mean age of 65.30 (SD=9.36), and the majority were female (N=3537; 61.7%). The demographic and study participation characteristics are summarised in table 1.

Of 5737 participants, 3453 (60%) were recruited via the media campaign and 2284 (40%) via invitation letters sent through Services Australia. The participation rate from the Services Australia recruitment arm was 7% (2284 of 32000 invited). The participation characteristics were similar between the media and Services Australia arm (table 1), apart from sex where the female-to-male ratio was higher in the media arm (2.28 and 1.06 for the media and Services Australia arms, respectively).

Of 5737 participants, 4522 (~80%) provided a saliva sample (or access to genotype data from a previous study)
and ~70% consented to the study to access their Medicare and PBS data access.

**Glaucoma status and subtypes**

Of 5737 participants, 4336 self-reported glaucoma and 3639 reported a family history of glaucoma. Figure 1 shows the number of people according to glaucoma and family history status. The proportion of glaucoma cases was higher in the Services Australia arm (91% for Services Australia vs 65% for the media arm). This was expected given that Services Australia participants were invited from people who had at least 2 months of glaucoma medication supply within the last year of recruitment. By contrast, the proportion of participants with a family history of glaucoma was higher in the media arm compared with Services Australia (51% and 71% in Services Australia and media arm, respectively). Among people with glaucoma, 52% and 59% reported a family history in the Services Australia and media arm, respectively.

The majority of the people who reported glaucoma were not aware which subtype of glaucoma they have. Of the reported subtypes, POAG was the most common (791 of 1134; 69.75%), followed by ACG (185 of 1134; 16.31%), with smaller proportions reporting other glaucoma types (figure 2). Some people reported various combinations of these glaucoma subtypes. Of 4336 people with glaucoma, only 254 were aware of their glaucoma pressure subtypes: 126 reported high-tension glaucoma and 128 normal-tension glaucoma.

**Glaucoma medication**

In addition to obtaining medication data from PBS, we asked the participants whether they had used any of the 19 commonly prescribed glaucoma medications for treatment of glaucoma in Australia (table 2). Of 4393 people who answered to this question, 1878 had used only 1 of those 19 medications, 2436 had used various combinations and 79 reported other medications (table 2). Latanoprost was the most commonly prescribed drug; 54% of the participants (2369 of 4393) had used latanoprost at least once.

**Surgical procedures for glaucoma**

We also obtained data on laser or non-laser surgical treatments for glaucoma. Among the participants who provided this information, 2008 reported a laser treatment, of whom 1048 knew of their specific surgical procedure. Of these, the majority (672 of 1048) had a selective laser trabeculoplasty while 312 had a laser peripheral iridotomy and nine underwent a cyclodiode procedure, with some people reporting a combination of these procedures (figure 3). Similarly, 803 reported a non-laser glaucoma operation, 684 of whom knew of their specific surgical procedure. Of these, 238 had stent insertion (MIGS/iStent), 237 trabecetomy, 50 glaucoma drainage device, 44 tube insertion and 1 sclerectomy, with some people reporting a various combination of these surgical procedures.

**Other diseases in GOGS**

We also obtained information on whether the participants had any other eye or systemic diseases. For eye diseases, of 5459 who provided information, 4979 had at least one of the eye conditions listed in our survey (figure 4A), 350 did not report any, and 130 reported other conditions. The most commonly reported eye diseases were ocular...
hypothesis (2913 of 5459; 53.36%), cataract (2599 of 5459; 47.61%), nearsightedness (1704 of 5459; 31.21%), astigmatism (1223 of 5459; 22.40%) and farsightedness (899 of 5459; 16.47%). Similarly, of 5674 people who provided information, 3410 had at least one of the systemic diseases listed in the survey (figure 4B), 2049 did not report any and 215 had other diseases. The most commonly reported systemic diseases were hypertension (2264 of 5674; 39.9%), diabetes (706 of 5674; 12.4%) and sleep apnoea (629 of 5674; 11.1%).

**DISCUSSION**

We developed the GOGS, a large genetic study enriched with glaucoma-related clinical information. The study comprises more than 5700 participants with glaucoma or a family history of glaucoma across Australia. Of these, ~80% provided a DNA sample and ~70% consented to data linkage to their Medicare and PBS data. GOGS is one of the largest studies of its kind internationally and when combined with previous and upcoming glaucoma genetic datasets, we anticipate GOGS improving power to detect novel risk loci for glaucoma. GOGS also allows for developing or validating genetic prediction models for glaucoma risk and response to treatment, as well as clinical outcomes (eg, whether the POAG polygenic risk score is predictive of the necessity, type and success of surgery in glaucoma patients). Another strength of GOGS is the availability of data on family history of glaucoma, enabling us to develop risk prediction models specifically for people in this high-risk group.

The demographic and characteristics of the participants (eg, age, education, smoking status) were similar between the media campaign and Services Australia recruitment arms of this study; apart from a higher rate of female participation through the media arm compared with the Services Australia approach. Although the proportion of sexes was relatively equal for the Services Australia participants, we could not systematically investigate a sex-driven selection bias in the Services Australia arm as we do not know the demographic and sex of invited people due to ethical limitations (but we should note that sex was not a selection criterion for invitation). Although participation rate for the Services Australia arm was relatively low (7%), it proved to be an effective way of recruiting people who are very likely to have glaucoma, with a per-person cost comparable to that of the media approach.

A high proportion of the GOGS participants reported a family history of glaucoma; 51% in the Services Australia arm and 71% in the media arm. While the high rate in the media arm could be due to ascertainment bias (people were invited if they had either glaucoma or a family history of glaucoma), among patients with glaucoma, the rate of reported family history was 52% and 59% in the Services Australia and media arms, respectively. These rates are consistent with the previously reported rates of 40%–60% in several studies. In particular, direct examination of relatives of patients with POAG in a previous study showed that ~60% have affected relatives, suggesting that ascertainment bias may not be the main driver of a high rate of family history among patients with glaucoma in GOGS. Although we cannot rule out various biases such as recall and survival bias in reporting family history, such biases are expected to result in underestimation of family history, which does not seem to be the case among the glaucoma patients in GOGS.

**Table 2** Frequency of self-reported glaucoma medications prescribed among the GOG participants

<table>
<thead>
<tr>
<th>Drug (brand)</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latanoprost (APO-latanoprost, Lanpro, Latanoprost Actavis, Latanoprost GH, Latanoprost Sandoz, Xalaprost, Xalatan)</td>
<td>2369</td>
<td>54</td>
</tr>
<tr>
<td>Bimatoprost (Lumigan PF)</td>
<td>691</td>
<td>16</td>
</tr>
<tr>
<td>Travoprost (Travatan)</td>
<td>609</td>
<td>14</td>
</tr>
<tr>
<td>Timolol (Timoptol, Timoptol XE, Nyogel)</td>
<td>756</td>
<td>17</td>
</tr>
<tr>
<td>Timolol+dorzolamide (APO-Dorzolamide/Timolol, Cosdor, DORZOLAMIDE/TIMOLOL AN, Cosopt, Cosopt PF)</td>
<td>256</td>
<td>6</td>
</tr>
<tr>
<td>Timolol+Travoprost (Duotray)</td>
<td>611</td>
<td>14</td>
</tr>
<tr>
<td>Timolol+Latanoprost (APO-Latanoprost/Timolol, Lantin, Latanoprost/Timolol Sandoz, Latanoprost/timolol AN, Xalacom, Xalarno)</td>
<td>681</td>
<td>16</td>
</tr>
<tr>
<td>Timolol+Bimatoprost (GANfort PF, Ganfort)</td>
<td>788</td>
<td>18</td>
</tr>
<tr>
<td>Timolol+Brimonidine (Combigan)</td>
<td>233</td>
<td>5</td>
</tr>
<tr>
<td>Timolol+Brinzolamide (Azarga)</td>
<td>232</td>
<td>5</td>
</tr>
<tr>
<td>Brimonidine (Alphagan P, Alphagan, Enidin)</td>
<td>508</td>
<td>12</td>
</tr>
<tr>
<td>Apraclonidine (lupidine)</td>
<td>31</td>
<td>0.7</td>
</tr>
<tr>
<td>Dorzolamide (APO-Dorzolamide, Trusamide, Trusopt)</td>
<td>137</td>
<td>3</td>
</tr>
<tr>
<td>Brinzolamide (BrinzoQuin, Azopt)</td>
<td>609</td>
<td>14</td>
</tr>
<tr>
<td>Brinzolamide+brimonidine (Simbrinza)</td>
<td>367</td>
<td>8</td>
</tr>
<tr>
<td>Acetazolamide (Diamox)</td>
<td>178</td>
<td>4</td>
</tr>
<tr>
<td>Betaxolol (BetoQuin, Betoptic)</td>
<td>42</td>
<td>0.96</td>
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<tr>
<td>Pilocarpine (Isopto Carpine)</td>
<td>113</td>
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</tr>
<tr>
<td>Tafufrost (Saflutan)</td>
<td>149</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>79</td>
<td>2</td>
</tr>
</tbody>
</table>

This table shows the number and percentage of participants who had a prescription filled for at least one of the 19 commonly used glaucoma drugs. Note that the total count does not sum up to 4393 (the overall number of respondents) because some participants had used various combinations of these drugs.
While all the GOGS participants reported whether they have been diagnosed with glaucoma, the majority were not aware of their glaucoma subtype. We believe that the vast majority of the glaucoma cases with unknown subtype in GOGS are POAG. This is because the vast majority (92%) of GOGS participants are of European ancestry; in a previous study of European ancestry individuals with glaucoma, 87% had POAG, and we anticipate a similarly high percentage in GOGS. Among the GOGS participants who were aware of their glaucoma subtype (1134 of 4336 glaucoma patients), 791 (~70%) reported POAG. Hence, our genetic studies on self-reported glaucoma in GOGS would predominantly identify POAG risk loci. However, once we have confirmed and updated subtype status using Medicare data, we will also perform subtype-specific genetic studies to identify or validate unique loci to each subtype. GOGS also provides valuable data to identify shared genetic risk loci across various subtypes and evaluate the ability of the POAG polygenic risk scores to predict glaucoma risk for the other subtypes.

GOGS has several strengths. First, it is one of the very largest single site studies of its kind internationally, which has collected rich glaucoma-related phenotypes such as family history (including which relatives have glaucoma) and a range of clinical information on glaucoma subtypes, medication and surgical procedures. In addition, many study participants consented to recontact and follow-up. In the future, we hope to follow-up a subset of people who have both a family history of glaucoma and an unusually high polygenic risk score; given their very high risk, these people will be targeted for follow-up in a future longitudinal study. By collecting clinical and imaging data on those at very high risk, we will be able to assess the practical utility of genetic data for stratifying people into risk groups where they can receive appropriately tailored screening and care.

Second, GOGS is a valuable source for glaucoma gene discovery. We aim to perform GWAS for glaucoma or other related phenotypes available in GOGS, followed by a meta-analysis of the results with those from other glaucoma genetics data currently in hand (eg, UK Biobank, the Canadian Longitudinal Study on Aging, and the International Glaucoma Genetics Consortium) to identify additional risk variants and genes for glaucoma. Integrating the GWAS data with publicly available omics data, we further aim to identify druggable causal genes, which may provide potential drug target candidates for development of novel treatments for glaucoma. We aim to focus on drug target genes that could lead to development of novel neuroprotective treatments, as the current treatment strategies for glaucoma focus solely on lowering IOP.

Third, GOGS is not limited to only clinical information on glaucoma but also contains other glaucoma-related data such as smoking status, educational attainment, IOP levels, presence of other related eye diseases (eg, cataract and myopia) and systemic diseases (eg, diabetes, sleep apnoea and heart disease). This information is helpful to evaluate links between glaucoma and other diseases, and to investigate whether glaucoma genetics contributes to those comorbidities, and whether the comorbidities affect response to treatment for glaucoma. However, we should note that due to the sampling design, this study is not ideal for answering research questions that require a cohort study. We should also note that the statistical power would be limited for some of the phenotypes in

Figure 3  Frequency of the laser treatment surgical procedures among the GOGS participants who provided this information (N=1048). GOG, Genetics of Glaucoma Study; PI, peripheral iridotomy; SLT, selective laser trabeculoplasty.
GOGS and hence, a joint analysis with other national and international studies would be beneficial. Participants in GOGS have provided consent for their data to be used in future related studies (subject to ethics approval), providing a great opportunity for future collaborations for glaucoma gene discovery.

We did not collect controls (ie, people without a family history of glaucoma and who have not been diagnosed with glaucoma) for this study. This is because we have access to a variety of genetic data obtained from people without a glaucoma diagnosis across Australia, genotyped on the same array used in this study. For example, we have genetic data for >16K people from the QSkin Sun and Health Study (QSkin), a cohort study to investigate the development of skin cancer and melanoma, and ~15K people from the AGDS, a study to investigate genetic and environmental risk factors for depression. Both of these studies are also housed and led by researchers within the same institute (QIMR Berghofer), making

![Figure 4](http://bmjopen.bmj.com)  
Figure 4  Frequency of other diseases among the GOGS participants. (A) Self-reported non-glaucoma eye diseases in 5459 participants. (B) Self-reported systemic diseases in 5674 participants. GOGS, Genetics of Glaucoma Study. AMD, age-related macular degeneration.
these datasets accessible for use as study controls on GOGS. We will match and select controls for GOGS for any subsequent association analyses using the standard matching and QC protocols for genetics studies.

GOGS has several limitations. First, it has a selection bias towards female participants, as well as a possible bias towards recruitment of people with less severe forms of glaucoma. This is a well-known limitation for many research studies developed based on volunteer participation. Although a higher rate of female participation imposes a lower statistical power for male-specific studies, given the high genetic correlation (rg=0.99, SE=0.06) between males and females for glaucoma, sex-stratified analysis is not a primary aim of this study. To investigate whether GOGS has a selection bias based on disease severity, we will generate genetic risk scores for glaucoma patients and compare with the scores for patients with severe forms of glaucoma in our previous study of the Australian and New Zealand Registry of Advanced Glaucoma.22 Second, most of the information collected in GOGS is self-reported data. However, as mentioned earlier, we will complement the self-reported information with more accurate and detailed MBS/PBS data. Finally, although GOGS is a multiethnic study, the vast majority of the participants are of European descent, and hence the statistical power is fairly limited for studies involving other ancestry groups.

Author affiliations
1Statistical Genetics Laboratory, QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia
2Faculty of Medicine, School of Biomedical Sciences, The University of Queensland, Brisbane, Queensland, Australia
3Faculty of Health, School of Biomedical Sciences, Queensland University of Technology, Brisbane, Queensland, Australia
4Department of Ophthalmology, Flinders Medical Centre, Flinders University, Adelaide, South Australia, Australia
5Centre for Ophthalmology and Visual Science, University of Western Australia, Lions Eye Institute, Perth, Western Australia, Australia
6Menzies Institute for Medical Research, University of Tasmania, Hobart, Tasmania, Australia
7Centre for Eye Research Australia, University of Melbourne, Melbourne, Victoria, Australia

Twitter Yeda Wu @yeda_wu

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Contributors PG and SM designed the GOGS study and are responsible for the overall content as guarantors. J-SO, ML, JEC, DAM and AWH revised the online questionnaire and provided intellectual input into the content. PG analysed the data. PG and SM drafted the manuscript. WH, SDD, YW, Ni, RY, MS, J-SO, ML, JEC, DAM and AWH revised the article for intellectual content. All authors have read and approved the final version of the manuscript.

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Competing interests SM, JEC and AWH are cofounders of and hold stock in Seonox Bio.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study involves human participants and this study was approved by the ethics committees of QIMR Berghofer Medical Research Institute and Services Australia. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. One of the primary motivators for establishing GOGS was to contribute to international efforts to better understand genetic predisposition to glaucoma. Although the individual-level data will not be available due to ethical considerations, genome wide association study summary statistics will be made available upon publication following meta-analysis with studies from the International Glaucoma Genetics Consortium. Summary statistics will be deposited to a public repository. The full GOGS questionnaire is included as online supplemental material and we encourage collaborations with researchers from other studies to help advance our collective understanding of glaucoma genetics (contact Stuart MacGregor, stuart.macgregor@qimrberghofer.edu.au).

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ORCID iDs
Puya Gharghahki @http://orcid.org/0000-0002-4203-5952
Yeda Wu @http://orcid.org/0000-0002-5977-1526

REFERENCES
Survey Instruction

- Answers to the questions with asterisk (*) are required. Everything you tell us will be treated in the strictest confidence but you are free to leave blank any specific questions that you do not wish to answer.
- Some of the questions ask you for a short written answer. If you need extra space for your answers, please use the space on the last page.
- Please fill in the survey and return in the envelope provided to you along with the study consent form.

Section A: Personal details

<table>
<thead>
<tr>
<th>Title</th>
<th>Mobile Number*</th>
</tr>
</thead>
<tbody>
<tr>
<td>First name*</td>
<td>Phone Number</td>
</tr>
<tr>
<td>Middle name</td>
<td>Address*</td>
</tr>
<tr>
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</tr>
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<td>Date of Birth*</td>
<td>Postcode*</td>
</tr>
<tr>
<td>Sex*</td>
<td>State/Territory*</td>
</tr>
<tr>
<td>Email *</td>
<td>Country*</td>
</tr>
</tbody>
</table>

Postal Address: please specify if not the same as residential address.

We will be posting updates about the study progress online once a year. Would you like us to contact you by email when we post a study update?
What is your current height (centimeters)?

What is your current weight (kg)?

How many years were you in full time education (e.g. 11 years from 5-16, 13 years from 5-18, 17 years from 5-22)?

What is your ethnicity (select all that apply)?
- Caucasian
- Asian
- Indigenous Australian/Torres Strait Islander
- African
- Pacific Islander
- Middle eastern
- Latino
- I don’t know
- Other

If you chose "other", please specify your ethnicity

Section B: Medical history related to glaucoma

Have you had your eye pressure checked recently?

If yes, what was your eye pressure (mm Hg)? If you have one measurement this is fine. If you have separate measurements for each eye, enter as left then right e.g. “20 21”.

Page | 2
Has an ophthalmologist or optometrist told you that you have glaucoma? *

If yes, are you happy for us to contact your ophthalmologist or optometrist to find out more about your glaucoma?

If yes, please provide the name of your ophthalmologist or optometrist.

If known, please provide the practice name, address, and phone number in the box below.

Which of the following glaucoma types were you diagnosed with? *

- Primary open angle glaucoma
- Angle closure glaucoma
- Congenital glaucoma
- Pigmentary glaucoma
- Pseudoexfoliative glaucoma
- Secondary glaucoma (e.g. trauma or steroid induced glaucoma)
- Neovascular glaucoma
- Uveitic glaucoma
- I don’t know
- Other

If you chose "other", please specify

Do you know what your highest eye pressure (in either eye, mm Hg) was when you were diagnosed with glaucoma?
Approximately, what age (years) were you when you were diagnosed with glaucoma?
Please specify in the box below for all glaucoma types that apply.

If you chose "Primary open angle glaucoma" please specify which type? *
- High tension glaucoma
- Normal tension glaucoma
- I don’t know

Have you had Laser treatment for glaucoma? *
If yes, do you know which approach from the list below?
- Selective Laser Trabeculoplasty “SLT” (laser into the angle of the eye to lower pressure)
- Laser Peripheral Iridotomy “PI” (laser to make a small hole in the iris, to let the fluid in the eye flow better)
- Cyclodiode Laser Treatment (destroying a portion of the ciliary body)
- I don’t know

Have you had an operation for glaucoma? *
If yes – was this a
- Trabecectomoy
- Tube insertion
- Stent insertion (MIGS/ iStent) as part of cataract surgery
- Glaucoma drainage devices
- Sclerectomy with collagen implant
- I don’t know

Do you have a family history of glaucoma? *
If yes, please specify which relatives?
If yes, which of the following glaucoma types were your relatives diagnosed with? *

- Primary open angle glaucoma
- Angle closure glaucoma
- Congenital glaucoma
- Pigmentary glaucoma
- Pseudoexfoliative glaucoma
- Secondary glaucoma (e.g. trauma or steroid induced glaucoma)
- Neovascular glaucoma
- Uveitic glaucoma
- I don’t know
- Other

If you chose "other", please specify

If any of your relatives have "Primary open angle glaucoma", please specify which type? *

- High tension glaucoma
- Normal tension glaucoma
- I don’t know

Have you ever been prescribed the following glaucoma medications (brand names in bracket)? *

- Latanoprost (APO-Latanoprost, Lanpro, Latanoprost Actavis, Latanoprost GH, Latanoprost Sandoz, Xalaprost, Xalatan)
- Bimatoprost (Lumigan PF)
- Travoprost (Travatan)
- Timolol (Timoptol, Timoptol XE, Nyogel)
- Timolol + dorzolamide (APO-Dorzolamide/Timolol, Cosdor, DORZOLAMIDE/TIMOLOL AN, Cosopt, Cosopt PF)
- Timolol + Travoprost (Duotrav)
- Timolol + Latanoprost (APO-Latanoprost/Timolol, Lantim, Latanoprost/Timolol Sandoz, Latanoprost/timolol AN, Xalacom, Xalamol)
- Timolol + Bimatoprost (GANfort PF, Ganfort)
- Timolol + Brimonidine (Combigan)
- Timolol + Brinzolamide (Azarga)
- Brimonidine (Alphagan P, Alphagan, Enidin)
- Apraclonidine (Iopidine)
- Dorzolamide (APO-Dorzolamide, Trusamide, Trusopt)
- Brinzolamide (BrinzoQuin, Azopt)
Brinzolamide + brimonidine (Simbrinza)
Acetazolamide (Diamox)
Betaxolol (BetoQuin, Betoptic)
Pilocarpine (Isopto Carpine)
If you chose "other", please specify

Have you ever been prescribed long-term (over one month) use of any of the following corticosteroids?
Betamethasone
Dexamethasone
Cortisone Acetate
Hydrocortisone
Methylprednisolone
Prednisolone
Prednisone
Budesonide
Triamcinolone
Other
I can’t remember
None
If you chose "other", please specify

If you were prescribed any of the above corticosteroids, what was the reason?
If you were prescribed any of the above corticosteroids, which of the following administration routes was used?

- Eye (drops, ointments, etc.)
- Nose (drops, ointments, etc.)
- Ear (drops, ointments, etc.)
- Topical (skin and mucous membranes)
- Oral
- Systemic (injection through muscles or vessels)
- None
- I don’t know

Has an ophthalmologist or optometrist told you that you have any of the following eye conditions? If you want to enter additional free text information about any conditions you have, check the “other” option and specify in the text box below.*

- High eye pressure
- Keratoconus
- Age-related macular degeneration
- Cataract
- Diabetic retinopathy
- Nearsightedness
- Farsightedness
- Astigmatism
- Thick/Thin cornea
- Optic nerve shape changes
- Eye injuries
- Eye infection
- Other
- None
- I don’t know

If you chose "other", please specify

Approximately, what age (years) were you when you were diagnosed with any of the above eye conditions? Please specify in the box below for all the conditions that apply.
Have you ever had eye surgery (not glaucoma-related)? *

If yes, what was the reason for doing the eye surgery? Please specify in the box below.

How old (years) were you when you had the eye surgery?

Has a doctor informed you that you have any of the following conditions? *

- High blood pressure  
- Low blood pressure  
- Anemia  
- Diabetes  
- Heart disease  
- Migraines  
- Dementia  
- Sleep apnea  
- Other  
- None  
- I don’t know

If you chose "other", please specify

Approximately, what age (years) were you when you were diagnosed with any of the above conditions? Please specify in the box below for all the above conditions that apply.
If you have been diagnosed with diabetes, which type?

- [ ] Type I
- [ ] Type II
- [ ] Gestational Diabetes
- [ ] Pre-diabetes
- [ ] I don’t know

If you have been diagnosed with dementia, which type?

- [ ] Alzheimer’s disease
- [ ] Lewy Body disease
- [ ] Dementia associated with Parkinson’s disease
- [ ] Vascular dementia
- [ ] Frontotemporal dementia
- [ ] Alcohol related dementia
- [ ] Down syndrome with Alzheimer’s disease
- [ ] Other
- [ ] I don’t know

If you chose "other", please specify

Have you ever been a regular smoker? (That is, have you ever smoked tobacco daily for at least 6 months?)

If yes, how old (years) were you when you started smoking regularly?

Are you a regular smoker now?

If yes, about how many cigarettes do you smoke on average each day?

If previous smoker, how old (years) were you when you stopped smoking regularly?
If previous smoker, about how many cigarettes did you smoke on average each day?

Have you previously given a blood or saliva sample for previous genetic studies (e.g. QIMRB QSKIN study, 23andMe, ancestry.com)?

If yes, please specify which one(s)?

How did you hear about our study? *

- Department of Human Services (DHS)
- QIMR Berghofer Newsletter
- Social media
- Other

If you chose "other", please specify

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Please use this box if you need extra space to answer any of the above questions.
Supplementary Tables

The Genetics of Glaucoma Study

**Supplementary Table 1.** The summary of the information obtained from the study questionnaire in GOGS.

<table>
<thead>
<tr>
<th>Information category</th>
<th>Information details</th>
</tr>
</thead>
</table>
| Personal details     | • Participants’ names  
                      | • Participants’ contact details  
                      | • Participants’ demographics including age, sex, ethnicity, years of education, height, and weight. |
| Glaucoma status      | • The highest eye pressure (if known)  
                      | • Glaucoma status (“Has an ophthalmologist or optometrist told you that you have glaucoma?”)  
                      | • Glaucoma subtypes if known (e.g. primary open-angle glaucoma, angle-closure glaucoma, etc.)  
                      | • Glaucoma pressure subtypes if known (e.g. high tension and normal tension subtypes for primary open angle glaucoma)  
                      | • Age at diagnosis |
| Surgical procedures  | • Laser treatment for glaucoma (i.e. Selective Laser Trabeculoplasty, Laser Peripheral Iridotomy, and Cyclodiode Laser Treatment)  
                      | • Other operations for glaucoma (i.e. Trabeculectomy, Tube insertion, Stent insertion (MIGS/iStent) as part of cataract surgery, glaucoma drainage devices, and sclerectomy with collagen implant). |
| Family history       | • Whether people had a family history of glaucoma  
                      | • If yes, which relatives were affected |
| Glaucoma prescriptions| • Whether participants have been taking any of the 19 most common medications most commonly used for treating glaucoma in Australia, as well as an “other” option to provide the name of other drugs not listed. |
| Other glaucoma related information | • Corticosteroids therapy  
                                          | • Other eye conditions (e.g. myopia, cataract, keratoconus, etc.)  
                                          | • Other eye surgeries (not glaucoma-related)  
                                          | • Other glaucoma-related systemic diseases (e.g. diabetes, dementia, heart disease, etc.)  
                                          | • Tobacco Smoking status |
**Supplementary Table 2.** The MBS/PBS items to be requested for this study.

<table>
<thead>
<tr>
<th>MBS/PBS item</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MBS - Date of service</td>
<td>Date that the provider performed the service</td>
</tr>
<tr>
<td>MBS - Item number</td>
<td>Item numbers as per the Medicare Benefits Schedule</td>
</tr>
<tr>
<td>MBS - Item description</td>
<td>Describes the service as per the Medicare Benefits Schedule</td>
</tr>
<tr>
<td>MBS - Date of referral</td>
<td>Date of referral or request for service by a provider</td>
</tr>
<tr>
<td>MBS - Item Category</td>
<td>Medicare Benefits Schedule comprises a hierarchical structure of Categories, Groups, Subgroups and Items numbers, to group similar professional services together</td>
</tr>
<tr>
<td>PBS - Date of supply</td>
<td>Date the prescription was supplied by the pharmacy</td>
</tr>
<tr>
<td>PBS - Date of prescribing</td>
<td>Date that the prescription was prescribed by a provider to a patient</td>
</tr>
<tr>
<td>PBS - Item code</td>
<td>Items number reflected in the Pharmaceutical Benefits Scheme</td>
</tr>
<tr>
<td>PBS - Item description</td>
<td>The item description as noted on the Pharmaceutical Benefits Scheme</td>
</tr>
<tr>
<td>PBS - Form Category</td>
<td>Original or repeat prescription</td>
</tr>
<tr>
<td>PBS - ATC Code</td>
<td>The ATC Code is defined by the Commonwealth Department of Health</td>
</tr>
<tr>
<td>PBS - ATC Name</td>
<td>The group the drug falls under in the Anatomical Therapeutic Chemical (ATC) classification system</td>
</tr>
</tbody>
</table>