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Heritability of glaucoma and glaucoma-related endophenotypes: systematic review and meta-analysis protocol

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ABSTRACT

Introduction Glaucoma is the second leading cause of age-related vision loss worldwide; it is an umbrella term that is used to describe a set of complex ocular disorders with a multifactorial aetiology. Both genetic and lifestyle risk factors for glaucoma are well established. Thus far, however, systematic reviews on the heritability of glaucoma have focused on the heritability of primary open-angle glaucoma only. No systematic review has comprehensively reviewed or meta-analysed the heritability of other types of glaucoma, including glaucoma-related endophenotypes. The aim of this study will be to identify relevant scientific literature regarding the heritability of both glaucoma and related endophenotypes and summarise the evidence by performing a systematic review and meta-analysis.

Methods and analysis This systematic review will follow the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols 2015 checklist, which provides a standardised approach for carrying out systematic reviews. To capture as much literature as possible, a comprehensive step-by-step systematic search will be undertaken in MEDLINE (PubMed), EMBASE, Web of Science and ScienceDirect, and studies published until 31 December 2017 will be included. Two reviewers will independently search the articles for eligibility according to predefined selection criteria. A database will be used for screening of eligible articles. The quality of the included studies will be rated independently by two reviewers, using the National Health Institute Quality Assessment tool for Observational Cohort and Cross-Sectional Studies. A random-effects model will be used for the meta-analysis. This systematic review is registered with the International Prospective Register of Systematic Reviews with a registration number: CRD42017064504.

Ethics and dissemination We will use secondary data from peer-reviewed published articles, and hence there is no requirement for ethics approval. The results of this systematic review will be disseminated through publication in a peer-reviewed scientific journal.

Strengths and limitations of this study

- The inclusion of endophenotypes, in addition to that of the heritability of glaucoma itself, is a novel approach of our meta-analysis and systematic review providing important information for genetic research of glaucoma.
- Possible heterogeneity in heritability estimates will be explored through conducting subgroup/sensitivity analyses.
- Heritability estimates derived from different data analysis methods may not be directly comparable.
- A straightforward interpretation of pooled heritability estimates in this meta-analyses may be complicated by the variation of heritability estimates between different environments and populations.

INTRODUCTION

The eye is one of the most important sense organs, and vision loss may generate various degrees of psychological suffering that can be greater than the distress resulting from other forms of sensory impairment.[1]

According to a 2010 WHO estimate, there are 285 million people visually impaired, of which 39 million are blind.[2] The prevalence of infection-related blindness is decreasing globally; however, age-related blindness is increasing throughout the world; this could be due to an increasingly aged population or technological advancements in screening for blindness.[3]

Some ocular diseases are more likely to occur in old age. Cataract, glaucoma, diabetic retinopathy and macular degeneration are the most common age-related eye diseases.[4–7] The prevalence of these disorders varies with different ethnicities and socioeconomic backgrounds.[6–8] Ocular functions such as visual acuity, visual field, and night vision deteriorate as these eye disorders progress. But age is not the only risk factor; many of these disorders have a genetic component as well.[9–12]

Among the age-related ocular disorders, glaucoma is the leading cause of irreversible blindness worldwide,[13] and disparities exist in its classification.[14] The International Society for Geographical and Epidemiological Ophthalmology has developed a robust definition of glaucoma for epidemiological purposes by including several empirical

factors, such as optic nerve head findings and visual field defects.[15] Thus, glaucoma is an umbrella term that is used to describe a set of complex ocular disorders with multifactorial aetiology.[14 15] It can be defined as a progressive loss of retinal ganglion cells associated with characteristic structural changes to the optic nerve and visual function.[16] It is asymptomatic until it is severe, thus many patients have a delay in diagnosis or are examined only after the advanced visual field loss has occurred.[14 17] Glaucoma is classified into primary and secondary categories. Important risk factors for primary glaucoma are intraocular pressure, age and family history; however, the biomolecular mechanisms are still poorly defined.[18–22] Secondary glaucoma is a heterogeneous group of diseases resulting from other eye diseases, trauma, use of corticosteroids or conditions such as pigment dispersion or pseudoexfoliation.[23 24]

Primary glaucoma may be subdivided into primary open-angle glaucoma (POAG) and primary angle closure glaucoma (PACG). Although POAG is the most common type of glaucoma, PACG tends to be more prevalent in certain ethnic groups.[13 22] In a 2014 systematic review, the global prevalence of POAG and PACG combined was estimated to be approximately 4% in a population aged 40–80 years.[13] The prevalence of visual impairment due to glaucoma appears to be age-related as well, and in a randomly selected sample of 5147 Australians, the prevalence was found to be low (~1%) in those aged 60 years compared with those older than 90 years (4%).[4] A systematic review of 50 population-based studies reported that the prevalence of POAG is relatively high in African populations aged ≥40, with an estimated prevalence of 2%–4%.[13 25] Moreover, the prevalence of PACG is found to be relatively higher (~1%) in adult Asian populations.[13 22]

Studies have demonstrated a strong association between the development of POAG and a positive family history.[10 25–29] In a longitudinal study of 224 siblings of 156 clinically confirmed POAG cases, there was a significantly increasing trend in both prevalence and incidence of the disease with age and a lifetime risk estimated of approximately 20% by age 70.[27] Other studies also suggested that the risk of POAG is higher in siblings of glaucoma cases than in their parents or children.[26 28 29] In a population-based study in Nottingham, UK, the risk of glaucoma among siblings of POAG cases was about 10% (with an OR of 3.69), which is greater than in parents (~6%; OR 2.17) and in children (~1%; OR 1.12).[27] Studies from the Netherlands and India reported similar findings, with a higher prevalence of POAG in siblings (~10% to 15%) than in parent–offspring family connections (~1% to 4%), respectively.[26 29]

Historically, the effect of specific genes in the development of glaucoma has been largely unknown. In the 1960s, Becker *et al* studied patients with POAG as well as their relatives, and proposed that POAG was a genetically determined disease, where the recessive homozygous 'gg' genotype represents glaucoma, and the alternative homozygous 'nn' and the heterozygous 'ng' genotypes represent non-glaucoma.[30]

More recently, however, researchers have elucidated both causative and associative genes for glaucoma risk.[20 31–33] Family studies have indicated that glaucoma can be inherited as a Mendelian autosomal-dominant or recessive trait, but only 3%–5% of adult-onset POAG cases are attributed to single-gene or Mendelian forms of glaucoma.[34 35] The vast majority of cases have a multifactorial basis and are caused by the combined effects of many genetic and environmental factors.[35]

The source of phenotypic variation among individuals in a population originates from both environmental and genetic factors, as well as various interactions between them.[31 36] Heritability (h^2) can be defined as 'the proportion of variance in a particular trait due to variation in genetic factors among individuals in that population'.[37–39] The total variation (variance) in a phenotype (V_P) can then be broken down into two parts: the genotypic variance (V_G) and the remaining variance (V_E), due to the environment.[38]

Within the last 30 years, classical twin studies have been conducted to establish the relative importance of genes and environment in glaucoma risk. Twin studies are an excellent source of information to disentangle and quantify the relative contributions of genes, the shared environment and the unique environment with respect to complex traits.[39 40]

Population-based genetic studies continue to confirm that many ocular traits have a genetic component.[9] These traits show substantial variation in human populations and many are highly heritable.[9 25 30 31 41–44] Glaucoma-related endophenotypes, sometimes called intermediate phenotypes, are powerful tools in the identification of genes contributing to glaucoma as they are more likely to be directly influenced by the genes than the resulting disease itself.[45–47] An endophenotype is defined as a heritable trait that is associated with a disease and that can be objectively measured, but is not a direct symptom of the disease.[47 48] Traits such as central corneal thickness, optic cup area, optic disc area, vertical cup-to-disc ratio and intraocular pressure are some well established endophenotypes for glaucoma.[45]

Heritability estimates for glaucoma endophenotypes differ between studies. For example, for intraocular pressure, estimates range from h^2=0.35, in a total of 2620 subjects from extended pedigrees from The Netherlands,[41] to h^2=0.50 in 133 subjects from nuclear family groups in the USA.[42] Similarly, heritability estimates for optic disc parameters range from 0.66 to 0.77 for optic cup area, 0.52 to 0.83 for disc area and 0.48 to 0.66 for vertical cup-to-disk ratio.[9]

So far, systematic reviews on the heritability of glaucoma have only focused on the heritability of POAG.[9 25] Indeed, no systematic review has comprehensively reviewed nor meta-analysed the heritability of other types of glaucoma, including PACG and congenital glaucoma, or glaucoma-related endophenotypes. Accurate estimates

of genetic risk (ie, heritability) are imperative when studying diseases with differing prevalences in different ethnicities. It will be an important factor in the near future when patients' genotypes may be used for personalised estimates of disease risk, and it is also a prerequisite for further gene finding studies. Heritability estimates are to be specific to the disease being studied (eg, POAG vs PACG), the populations studied (eg, Caucasians vs Asians) and the particular circumstances from which they were derived.[9 43] A systematic review and meta-analysis of the genetic contribution to glaucoma and glaucoma-related endophenotypes will thus provide important insights and assist researchers in designing gene finding studies in the future.

The objective of this systematic review will be to identify relevant studies regarding the heritability of glaucoma and related endophenotypes and summarise the evidence through meta-analysis. Heritability estimation, commonly reported in per cent, is the outcome measurement that we will synthesise and report from several studies.

The current study will address the following research questions: (1) How much of the variance in glaucoma and glaucoma-related endophenotypes is due to genetic factors? (2) What is the proportion of variance accounted for by additive genetic influences (A), common environment (C) and unique environment (E)? (3) Do heritability estimates vary between different populations and study designs?

METHODS AND ANALYSIS

This systematic review was initiated in March 2017 and is registered with the International Prospective Register of Systematic Reviews with a registration number CRD42017064504, available at http://www.crd.york.ac.uk/PROSPERO/. This systematic review will follow the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) 2015 checklist, which consists of a list of 17 items that provide a standardised guide for carrying out systematic reviews, including construction of a protocol, testing for bias and heterogeneity, and other aspects of the review process.[49] Similarly, the quality of the individual studies included in the systematic review will be rated independently by two reviewers using the National Health Institute Quality Assessment tool for Observational Cohort and Cross-Sectional Studies.[50]

Inclusion criteria

Articles describing heritability results based on (1) family, (2) twin, (3) adoption and (4) Genome Wide Association study designs or that could be estimated from intraclass correlations or linear regression coefficients will be included. Heritability estimates for any type of glaucoma or endophenotypes related to pressure (intraocular pressure), angle (anterior chamber depth, anterior chamber volume, angle opening distance, angle recess area, trabecular iris space area or Bruch's membrane opening), disc morphology (cup area, cup diameter, disc area, disc diameter, rim area, vertical or horizontal cup-to-disc ratio), ganglion cell complex, retinal nerve fibre layer, or central corneal thickness will be considered. The search will be restricted to articles describing studies in human subjects written in the English language. However, papers written in other languages with at least an English abstract will also be considered. All heritability studies from peer-reviewed journals, published until 31 December 2017, will be included.

Exclusion criteria

Papers that did not estimate heritability, did not specify ethnicity or estimated explained genetic variance from only significant Single-Nucleotide Polymorphisms (SNPs) or genetic loci will be excluded.

Search strategy

To capture as much literature as possible, an initial limited search of MEDLINE (PubMed) will be performed using an initial set of search terms. This will be followed by the identification of additional search terms from the titles and abstracts, and from the Medical Subject Heading (MeSH) index terms used to describe the initial identified articles (table 1). Second, using all identified keywords and index terms, a comprehensive and systematic search will be undertaken in MEDLINE, EMBASE, Web of Science, and ScienceDirect. In addition, Google Scholar will be used as a supplementary search database. Third, relevant papers from the reference lists of those articles captured in step 2 will be manually searched for additional input. References will be exported to RefWorks citation management software and duplicates will be removed. Full text, as well as relevant data, of all selected papers will be retrieved, and authors of the original articles will be contacted by email if additional information is required.

Two reviewers (NGA and AN), will independently evaluate the abstracts for eligibility, according to predefined selection criteria. A database will be used for screening of eligible articles. Any disagreements will be resolved through discussion between the two evaluators, but if consensus cannot be reached, a third person will be consulted. Finally, selected publications will be approved by a senior investigator.

Quality control and data extraction

For assessing the quality of individual articles in a systematic review, there are a variety of standard tools currently in use. However, most of these tools failed to include critical assessment elements relevant to heritability and genetic studies.[51]

We found that the National Health Institute Quality Assessment tool for Observational Cohort and Cross-Sectional Studies[50] is most suitable to assess the quality of selected articles in this current study. Quality assessment evaluation includes whether the research question/objective is clearly stated; if the study population, sample size,

Table 1 Search terms and number of articles found from a preliminary PubMed search

Step	Searching terms	Articles found (n)*
#1	"Quantitative Trait, Heritable" [MeSH] OR "Endophenotypes"[MeSH] OR Heritab*[tiab]	36 287
#2	Glaucoma[MeSH] OR Glaucoma*[tiab]	62 936
#3	Normal tension glaucoma[MeSH] OR Low tension glaucoma[MeSH] OR Exfoliation Glaucoma[MeSH] OR pseudoexfoliation glaucoma[MeSH] OR Exfoliation Syndrome[MeSH] OR Pigment dispersion syndrome[MeSH] OR Pigment dispersion syndrome[tiab] OR pds[tiab] OR Congenital glaucoma [MeSH] OR Buphthalmos[tiab] OR Buphthalmus[tiab] OR "Juvenile glaucoma"[tiab]	19 552
#4	"Intraocular pressure"[tiab] OR '"Ocular pressure"[tiab] OR iop[tiab] OR "Ocular hypertension"[tiab] OR "ocular biometric"[tiab] OR "Central corneal thickness"[tiab] OR "Corneal shape"[tiab] OR "Axial length"[tiab] OR Linear cup-disc ratio OR lcdr OR "Vertical cup to disc ratio"[tiab] OR Vertical cup-to-disc ratio[tiab] OR vcdr[tiab] OR vertical cup:disc ratio[tiab] OR vertical cup-disc ratio[tiab] OR "Corneal hysteresis"[tiab] OR "Anterior chamber depth"[tiab] OR "Anterior chamber angle" OR "Narrow anterior chamber" OR "Optic disc diameter"[tiab] OR "Cup area"[tiab] OR "Disc area"[tiab] OR "Rim area"[tiab] OR "Retinal nerve fibre layer"[tiab] OR "Cilioretinal arteries"[tiab] OR "Retinal ganglion cell layer" OR Horizontal cup:disc ratio[tiab] OR "Disc diameter"[tiab] OR "Cup disc ratio"[tiab] OR "Ganglion cell complex thickness"[tiab] OR "Shallow anterior chamber"[tiab] OR "Iris thickness"[tiab] OR "Iris area"[tiab] OR "Plateau iris" OR "Pupil diameter"[tiab] OR "Pupil size"[tiab] OR "Iridotrabecular angle width"[tiab] OR "Bruch's membrane opening" OR "Neuroretinal rim" OR Excavation[tiab] OR Cupping[tiab] OR "Inner plexiform layer thickness"[tiab] OR "angle opening" distance"[tiab] OR aod[tiab] OR "trabecular iris space area" OR tisa[tiab] OR "angle recess area"[tiab] OR ara [tiab]	62 213
#5	#2 OR #3 OR #4	106 800
#6	#1 AND #5	194

*Preliminary search conducted on 14 December 2017 at 07:20:51.
MeSH, Medical Subject Heading; tiab, title abstract text.

randomness of participation and inclusion/exclusion criteria are clearly specified and defined; whether quality of measurement is ensured in the clinical examination of quantitative (endo)phenotypes; if the method of data analysis and outcome measure was clearly; defined and if confounding variables were controlled for their impact on the dependent variable. The heterogeneity of heritability estimation between articles will also be reported using Cochrane's Q test and I^2 statistic. These tests assess whether there are genuine differences underlying the results of the studies, or whether the variation in results is through chance alone. The presence of any potential publication bias will be visualised with funnel plots, and any asymmetry of the funnel plots will be statistically tested with an Egger's test.

The quality of this study will be reported according to the PRISMA-P 2015 checklist, which guides the reviewer in planning and carrying out systematic reviews[49] (online supplementary file 1). The full text of the potentially eligible articles will be retrieved and stored in an online citation manager (RefWorks) for accessibility and data synthesis.

The data extraction for eligible articles will be archived in a database, and in order to ensure all relevant data are collected per study, a standardised form will be used (online supplementary file 2). To minimise the risk of transcription errors, data extraction will be conducted independently by two reviewers. The number of articles reviewed, the number of full-text studies retrieved and the number of studies excluded will be reported using the PRISMA flow chart (online supplementary file 3).

Data synthesis and statistical analysis

The endophenotypes will be clustered into groups: pressure, angle, cornea, retinal nerve fibre layer and disc morphology. The different types of glaucoma will also be clustered into primary and secondary: open-angle glaucoma, angle-closure glaucoma or exfoliation, as well as congenital glaucoma. Presuming that heritability estimates are different between populations, we will use a random-effects model for meta-analyses. Separate meta-analyses will be performed for each cluster. Pooled heritability estimates including 95% confidence intervals, and summary statistics for quantitative data will be described and presented in tables and figures. Quantitative assessment of heterogeneity in findings between studies and publication bias will be performed and reported. Heritability estimates from different study designs and statistical methods, as well as the possible factors that might explain the variation in heritability, will be discussed in detail.

Subgroup analysis

For assessing the possible factors that might explain the variation in heritability, we will use a number of approaches. The factors we will explore include ethnicity, study design, data analysis method, number of variables controlled for confounding, mean age and methodological quality score. Ethnicity will be classified according

to reference [52], which meta-analysed the global prevalence of POAG in different ethnicities. Additionally, for intraocular pressure, h^2 estimates will be subgrouped based on the device reported in the literature. The potential effect of mean age, sex, ethnicity, study design, data analysis method and the number of variables controlled for confounding will also be statistically tested with meta-regression analyses.

Sensitivity analysis

Possible sources of heterogeneity will be determined with the Baujat plot.[53] Following the discovery of outliers, sensitivity analysis will be carried out by excluding the three most heterogeneous articles per cluster. To explore the sensitivity of h^2 estimates to mean age and ethnicity, analyses will be conducted on a series of combinations of these variables.

Ethical consideration and result dissemination

This systematic review will use secondary data from peer-reviewed published articles, hence there is no requirement for ethics approval. The results of this systematic review will be disseminated through publication in a relevant, peer-reviewed journal and presented at pertinent conferences.

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Contributors NGA and HS conceived and designed the study. NGA, AN and NMJ developed the search strategy. NGA and AN wrote the protocol. HS and NMJ evaluated and revised the protocol. All the authors read the protocol and have given the final approval for publication.

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