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Genetics and epidemiology of glaucoma and myopia

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CHAPTER 1

General introduction
and thesis outline

Glaucoma epidemiology

Glaucoma is a group of complex ocular diseases that is accompanied by progressive damage to the optic nerve head.¹ The optic nerve is a collection of nerve fibers that transmit a visual message from the eye to the brain so that visual signals are converted into objects that we see.² When the optic nerve is damaged after a prolonged gradual process, it's as if an electric cable carrying electric power to a light bulb is cut off. Of course, the electric cable can be fixed, but once the optic nerve is damaged, it leads to an irreversible vision loss.

Glaucoma is the leading cause of irreversible blindness among the elderly worldwide.³ There are different forms of glaucoma;⁴ primary open-angle glaucoma (POAG) is the most prevalent subtype in Africa (~ 4%) and the western world (2.5%), whereas, primary angle-closure glaucoma (PACG) is more common in Asia (2.3% POAG vs. 3.4% PACG).³ All forms of glaucoma have common features: progressive cupping of the optic nerve head, thinning of the retinal nerve fiber layer, and retinal ganglion cell death. Glaucoma can remain asymptomatic until it is severe, often individuals are unaware of having the disease until advanced visual field loss has occurred.⁴

Both genetic variants and environmental factors, as well as various interactions between them, contribute to glaucoma risk.⁵ Advanced age,³ high intraocular pressure (IOP),^{6,7} high and low blood pressure (BP),^{8,9} autonomic dysregulation,¹⁰ and positive family history^{11,12} are commonly reported risk factors for the development and progression of glaucoma. The familial aggregation nature of the disease strongly suggests the role of genetic factors in the pathogenesis of POAG. Recently, genome-wide association studies (GWASs) have improved our understanding of the genetic basis of POAG - more than 70 genetic loci associated with POAG are identified so far.¹³ However, often convincing evidence that highlights a strong contribution of glaucoma risk factors is still lacking, making it difficult to translate research findings into clinical practice. So far, all forms of glaucoma treatments (medical, surgical, and laser) are targeted at reducing IOP, the other reported risk factors do not translate into useful therapy. In this thesis, I made an effort to increase our understanding of (1) the proportion of glaucoma (and closely related traits) variance due to variation in genetic factors, (2) likely causal genes and molecular mechanisms underlying glaucoma pathogenesis, and (3) the role of autonomic dysfunction and blood pressure in glaucoma. I also built and validated a myopia (short-sightedness) proxy, another POAG risk factor,¹⁴ that can be applied in large-scale population-based studies.

Heritability of glaucoma

Glaucoma is a heritable disease; family members of glaucomatous individuals are at a higher risk of developing the disease than the rest of the population.¹⁵ For example, in the Barbados family study, which included 230 glaucoma probands, approximately one-fourth of the family members were found to be POAG cases or suspected to have POAG.¹⁶ In the Baltimore Eye Survey, the odds ratio of POAG among siblings of 161 cases was 3.69.¹² Similarly, in the Utah Population Database, the relative risk of POAG among family members of 3,391 probands ranged from 1.45 in first cousins to 6.77 among parent-children connections.¹⁷ This was also confirmed in a longitudinal study of siblings of 156 POAG cases, which showed an increased incidence of the disease with age and a ~ 20% lifetime risk by age 70.¹⁸

Phenotypic variability that exists in a population originates from both genetic variance (V_G) and environmental variance (V_E); the proportion of variance in a particular trait attributable to variation in genetic factors is called heritability (h^2).^{19,20} The h^2 estimate represents the proportion of variance in a trait that can be explained by genetic factors. Twin and family study designs are excellent approaches to disentangle the relative contributions of genes and environment in complex traits, such as glaucoma.²¹ Evidence from twin and family studies revealed a substantial h^2 in glaucoma^{22,23} and its related endophenotypes (e.g. IOP,^{24,25} central corneal thickness,²⁶ and optic disc parameters²⁷). Glaucoma endophenotypes are heritable continuous ocular traits that are associated with the disease in the population, at least in part because of shared underlying genetic influence. These traits are not direct symptoms of glaucoma, but are considerations for functional characterization and diagnosing of the underlying disease when applied in large population-based studies.²⁸ Several studies have investigated and reported the inheritance of POAG; however, there is a need for a quantitative summation of the findings as no systematic review has comprehensively reviewed nor meta-analysed the h^2 of glaucoma or glaucoma-related endophenotypes.

Twin and family studies provided foundations for further genetic studies that aim to map genomic regions where the disease predisposing genes are located. As such, *MYOC* was the first POAG-associated gene mapped to Chromosome 1 by genome-wide linkage analysis, which was performed among 37 family members.²⁹ Later, additional linkage studies enabled researchers to map the chromosomal locations of a number of further POAG genes (e.g., *CYP1B1*, *OPTN*, and *WDR36*) that cosegregate with the disease in families.³⁰ However, glaucoma is a complex disorder caused by the contribution of

several genetic and environmental risk factors; only 3%–5% of late-onset POAG cases are attributed to single-genes.^{31,32} More recently, genome-wide association studies (GWASs) have shed light on the genetic architecture of POAG by identifying a large number of genetic variants associated with the disease. For example, using a GWAS meta-analysis of the UK Biobank and GERA cohort, more than 70 nucleotide polymorphisms (SNPs) have been either identified or replicated for POAG at a genome-wide level of significance.³³ However, the variance explained by these significant SNPs was about 3%, that is, far below the h^2 estimated using a family study ($h^2 = 81\%$).³³ Furthermore, GWASs identify genetic variants without providing definitive information on the likely causal genes and functional mechanisms underlying the statistical associations.³⁴ This calls for further post-GWAS bioinformatic analysis for ranking the genes in order of their relevance/causality based on different types of biological evidence, including gene expression and DNA methylation data.

The role of autonomic dysfunction and vascular factors

Glaucoma is multifactorial in etiology - several theories have been proposed to explain the underlying mechanisms. The mechanical theory focuses on the mechanical stress due to IOP, i.e., elevated IOP, the most important modifiable risk factor for glaucoma, is directly responsible for the damage of the scleral membrane and axon of the optic nerve head.³⁵ The vascular theory hypothesizes that glaucoma is a consequence of insufficient blood supply to the optic nerve head, either due to high IOP or other factors, such as hypertension (HTN) and low blood pressure (BP).^{36,37} However, current results are conflicting, at least partially due to the fact that direct and convincing evidence is lacking. For example, the findings of the Rotterdam³⁸ and the Blue Mountains Eye Studies³⁹ showed a positive association between POAG and BP. In contrast, the progression of glaucoma has also been linked to low nocturnal SBP,^{40,41} and in the Barbados Eye Study,⁴² a 10-mmHg increase in systolic BP (SBP) was associated with a lower incidence of POAG, whereas diastolic BP (DBP), pulse pressure (PP), and mean arterial pressure (MAP) measures failed to show a significant association. In another US study, J- or U-shaped relationships were suggested, but only in individuals not taking antihypertensive medication.⁸ This apparent controversy has led to a new hypothesis, the involvement of autonomic nervous dysfunction. Autonomic control together with a related phenomenon, autoregulation, maintains a relatively constant level of blood flow into the eye despite changes in blood pressure and changes in intraocular pressure.⁴³ In normal-tension glaucoma patients (glaucoma without elevated IOP), a predominance of sympathetic activity was associated with an unstable blood supply and

reduced perfusion pressure to the optic nerve head, and a faster rate of central visual field loss.^{10,44-46} However, there is a paucity of data investigating the role of autonomic dysfunction in large population-based studies.

Myopia

A relationship between glaucoma and myopia has been suggested, as the eyeball elongation in myopia is thought to affect the integrity of the retinal ganglion cells. Myopia (short-sightedness) is a common refractive error that causes the image to focus in front of the retina resulting in poor distance vision. Myopia can be corrected with glasses or refractive surgery, but more importantly, it increases the risk of other eye diseases including glaucoma, myopic macular degeneration, and retinal detachment.⁴⁷ Although the rate differs significantly between countries and ethnicities, the global burden of myopia is dramatically increasing worldwide, currently affecting 22.9% of the world's population.⁴⁸ The prevalence is about 30% in Europe,⁴⁹ whereas, in some parts of East and Southeast Asia, myopia has reached an epidemic level affecting 80-90% of young adults.⁵⁰ Based on the extrapolation of the current trend, myopia is projected to affect half of the world population by 2050.⁴⁸

Population-based cohort data provide a unique opportunity to understand pathways linking exposures across individuals' life to disease outcomes. As such, there is a rapid shift from small-scale epidemiological and genetic studies into mega-cohorts with hundreds of thousands of participants. This improves the power to understand the natural history of diseases and the identification of novel markers of disease across an individuals' life course. However, ophthalmic examination in such mega-cohorts is challenging, time-consuming, and costly. This calls for alternative data collection tools for capturing myopic cases with reasonably high accuracy. Questionnaire surveys offer the opportunity to gather vast amounts of data, as such, a few studies⁵¹⁻⁵² have attempted to use questions related to age and/or reason for first glass use to determine myopia status. However, these studies used different questions for their myopia definition, and because of this, systematic comparison/synthesis of questions seems lacking thus far.

Thesis outline

The research questions addressed in this thesis are summarized in **Box 1**. Part I (**Chapter 2-4**) deals with the role of genes and underlying molecular pathways leading to glaucoma pathogenesis. In **Chapter 2**, I developed a systematic review and meta-analysis protocol,

a guide for summarising h^2 evidence through meta-analysis. It gives guidance on: how to systematically search data, the inclusion criteria to be undertaken, quality control procedures to be performed, methods of data extraction and analysis, and how to assess heterogeneity and bias between studies. In **Chapter 3**, I applied the protocol developed in **Chapter 2**. I systematically extracted all available h^2 estimates of glaucoma and ten glaucoma-related endophenotypes (intraocular pressure, anterior chamber size, central corneal thickness, cup-to-disc ratio, disc size, cup size, corneal hysteresis, retinal nerve fiber layer thickness, cup shape, and peripapillary atrophy) from the literature and summarized the evidence by meta-analysis. I also performed subgroup and meta-regression analyses to identify sources of heterogeneity among h^2 estimates.

In **Chapter 4**, I prioritized the most likely causal genes for glaucoma and explored the underlying biological processes involved in glaucoma pathogenesis. For this, I used the most recent and largest POAG genome-wide association study (GWAS) summary statistics¹³ and performed systematic gene-prioritization analyses. Next, I performed functional and tissue enrichment analyses to find overrepresented pathways and tissues within the prioritized genes. In addition, I conducted tissue enrichment analysis and assessed whether prioritized genes are overrepresented in ocular tissues including, choroid, ciliary body, and trabecular meshwork. I also examined pleiotropy and genetic correlations of POAG with other traits and diseases that were associated with glaucoma in previous studies.

In Part II (**Chapter 5**), I assessed the relationship of heart rate variability, a proxy measure of autonomic nervous system regulation, and blood pressure with glaucoma. For this chapter, I used phenotypic data from the Lifelines cohort study and biobank,⁵³ a multidisciplinary population-based cohort study of the Northern Netherlands. Glaucoma was defined according to a previously described algorithm in Lifelines, which was based on self-report of glaucoma diagnosis and treatment in combination with the National Eye Institute Visual Functioning standard questionnaire.⁵⁴

Part III (**Chapter 6**) deals with myopia. I used population-based Lifelines cohort data⁵³ to assess whether myopic cases can be identified using refractive error-related questions. Therefore, I developed and validated a questionnaire-based myopia proxy that can be used in large-scale population-based epidemiology. For this, I first performed principal component analysis (PCA) to responses of refraction-status questions posed to Lifelines participants. Next, by actually measuring the refractive state in a subset of Lifelines participants, I performed logistic regression using myopia as dependent and the principal

components as independent variables. Specificity, sensitivity, and the classification threshold were estimated under the receiver operating characteristic (ROC) curve. Finally, I explored the value of the proxy by determining the prevalence of myopia and using it as an outcome measure for analyses with well-known myopia risk factors, being educational attainment and a polygenic risk score (PRS) of myopia.

For the systematic review and meta-analysis, I used data from large biomedical and life science literature databases (e.g. PubMed and EMBASE) to increase our understanding of the proportion of glaucoma (and closely related traits) variance due to variation in genetic factors. Similarly, I utilized the largest POAG GWAS summary statistics-based data¹³ as well as different types of bioinformatics databases (DEPICT,⁵⁵ GeneMANIA,⁵⁶ and IPA (www.ingenuity.com)) to prioritize the most likely causal genes and molecular mechanisms underlying glaucoma pathogenesis. Furthermore, I used data from the Lifelines cohort to assess the role of autonomic dysfunction and blood pressure in glaucoma, as well as to build and validate myopia proxy using refractive error-related questions.

Box 1 Research questions



Part I Heritability of glaucoma and underlying pathogenic mechanisms

Chapter 2

Which approach is most appropriate for carrying out a systematic review and meta-analysis of heritability studies of glaucoma: which key terms should be used for the data search; which in- and exclusion criteria should be applied; how should bias and heterogeneity be tested, which quality

Chapter 3

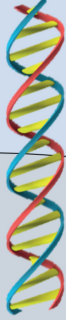
Given that glaucoma and its related endophenotypes are heritable, what are the pooled heritability estimates? What are the sources of heterogeneity in glaucoma and related endophenotype heritability estimates?

Chapter 4

Which genes are likely causal for glaucoma based on several lines of evidence? Which molecular functions and pathways are most relevant to glaucoma? In which tissues are glaucoma related genes overrepresented? Which diseases and traits have genetic overlap with glaucoma?



Part III Myopia

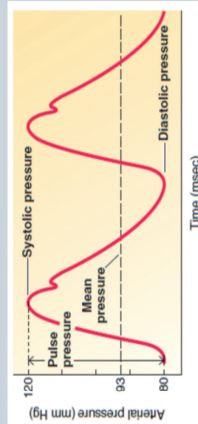
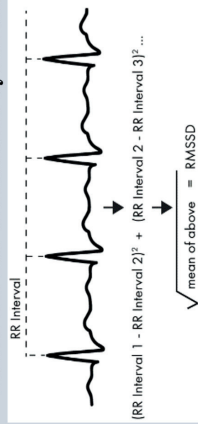


Chapter 6

Can distance and near vision-related questions be used to build a proxy that captures myopic cases in the general population? If so, which question or combination of questions provide reasonably high precision? Can the risk of previously known myopia risk factors, such as educational attainment and a myopia polygenic risk score (PRS) be confirmed when the proxy is applied in a large population-based study? If so, does the risk estimate agree with previous evidence?



Part II The role of autonomic dysfunction and vascular factors



Chapter 5

Is glaucoma associated with autonomic dysfunction (represented by heart rate variability [root mean square of successive differences, RMSSD]) in the general population? Do high and low blood pressure (BP) measures increase the risk of glaucoma? What is the risk of hypertension in glaucoma? Is the risk of BP on glaucoma confounded by anti-hypertensive medication or socio-demographic factors? Do anti-hypertensive medications increase or decrease the risk of glaucoma, is this effect confounded by BP?

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PART 1

Heritability of glaucoma and
underlying pathogenic mechanisms

