Genetics and epidemiology of glaucoma and myopia

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CHAPTER 8

Summary

Nederland samenvatting

Glaucoom is een chronische oogaandoening die schade veroorzaakt aan de kop van de oogzenuw. De oogzenuw bestaat uit een groep zenuwvezels die een visueel signaal van het oog naar het brein stuurt. Hiermee kunnen visuele signalen worden omgezet naar de objecten die we zien. Glaucoom wordt vaak 'de stille dief van het zicht' genoemd, omdat het ziekteverloop lang asymptomatisch blijft totdat het plotseling ernstig is. Hierdoor worden patiënten veelal laat gediagnosticeerd, of wordt glaucoma onderzocht wanneer significant gezichtsverlies reeds is opgetreden; tot 50% van de gevallen van glaucoom wordt niet gedetecteerd en blijft onbehandeld. Een regulier en compleet oogonderzoek is belangrijk om glaucoom vroeg te detecteren en verdere progressie van deze ziekte af te remmen.

Leeftijd, verhoogde oogdruk en etniciteit zijn belangrijke risicofactoren, alsook een familiegeschiedenis van glaucoom, wat suggereert dat glaucoom een erfelijke oogziekte is. Familie- en tweelingstudies zijn uitgevoerd om het belang van genen en de omgeving bij het risico op glaucoom te bepalen. Deze studies bevestigen dat glaucoom en gerelateerde onderliggende kenmerken (bijvoorbeeld oogdruk, dikte van het hoornvlies) een genetische component bevatten. Erfelijkheid is de proportie van individuele verschillen in een kenmerk of ziekte die verklaard wordt door genetische factoren.

Bijziendheid (myopie) is ook een risicofactor voor de ontwikkeling en de progressie van glaucoom. Myopie is een focusfout van het oog die ervoor zorgt dat het beeld gevormd wordt vóór het netvlies (de retina), resulterend in een vervaagd zicht. Hoewel lage tot matige myopie niet zorgwekkend is, wordt hoge myopie geassocieerd met een verhoogd risico op verblindende oogcomplicaties zoals glaucoom, myopische maculadegeneratie, en retinale onthechting. De wereldwijde prevalentie van myopie is sterk aan het toenemen; 22.9% van de wereldbevolking heeft myopie en men voorspelt dat dit percentage is verdubbeld in 2050.

In Deel I van deze these (**Hoofdstukken 2 tot en met 4**) bestudeerde ik de rol van genen en onderliggende moleculaire mechanismen die ten grondslag liggen aan de pathogenese van glaucoom. In **Hoofdstuk 2** heb ik een protocol voor een systematische review opgesteld. Dit protocol bevat een beschrijving over hoe erfelijkheidsstudies naar glaucoom en gerelateerde kenmerken samengevat moeten worden. In **Hoofdstuk 3** paste ik dit protocol van Hoofdstuk 2 toe, dat wil zeggen, ik heb systematisch alle beschikbare erfelijkheidsschattingen van glaucoom en nauw verwante kenmerken uit de literatuur geëxtraheerd en het bewijs door middel van meta-analyse samengevat. Op

basis van familie-gebaseerde studies bleek dat glaucoom voor 65 tot 81 procent erfelijk is. De erfelijkheid van kenmerken verwant aan glaucoom varieerde tussen de 43% voor oogdruk tot 81% voor centrale corneadikte. De hoge erfelijkheid betekent dat mensen met een familiegeschiedenis van glaucoom een hoger risico op glaucoom hebben dan de rest van de populatie. Deze bevindingen onderstrepen het belang van het screenen van familieleden van glaucomapatiënten in een klinische setting, aangezien populatie-gebaseerde screening van glaucoma niet kosteneffectief kan zijn. In **Hoofdstuk 4** heb ik mij beziggehouden met bio-informatische prioritering en functionele annotatie van genen voor glaucoom op basis van eerder geïdentificeerde genetische varianten en bio-informatische databases. Ik prioriteerde 142 genen die hoogst waarschijnlijk glaucoom veroorzaken. Van deze 142 genen waren 64 genen niet eerder gerelateerd aan glaucoom. Bovendien wezen mijn bevindingen op het gebied van functionele verrijking uit dat de extracellulaire matrix, transformerende groeifactor-β signaaloverdracht, cardiovasculaire ontwikkeling en bloedvatontwikkeling de meest oververtegenwoordigde routes zijn in de pathogenese van POAG. De bevindingen in **Hoofdstuk 3** en **Hoofdstuk 4** verdiepen ons begrip over hoe genen de pathogenese van glaucoma initiëren en zouden kunnen helpen bij de ontwikkeling van genetische tests voor vroege diagnose of gepersonaliseerde behandeling van glaucoom.

Deel II (in **Hoofdstuk 5**) betreft de beoordeling van het risico op autonome disregulatie en bloeddruk in glaucoom. Ik onderzocht de relatie tussen hartslagvariabiliteit, een proxy maat voor de regulatie van het autonome zenuwstelsel, en bloeddruk en glaucoom. Mijn bevindingen toonden aan dat glaucoompatiënten een significant lagere hartslagvariabiliteit en een hogere bloeddruk hadden. Op basis van onze resultaten stellen we dat lage hartslagvariabiliteit en hoge bloeddruk belangrijke parameters kunnen zijn bij screening voor glaucoom, bovenop traditionele risicofactoren (verhoogde oogdruk, familiegeschiedenis, leeftijd en etniciteit).

Populatie-gebaseerde cohortdata bieden een unieke kans om mechanismen achter de relatie tussen blootstellingen gedurende de levensloop en ziekte-uitkomsten zoals myopie. Oogonderzoeken zijn echter kostbaar in zulke megacohorten. Om dit probleem te ondervangen ontwikkelde en valideerde ik een proxy voor myopie in deel III (**Hoofdstuk 6**). Gebaseerd op zelf-gerapporteerde antwoorden op vijf vragen over zicht en de reden voor en leeftijd van het eerste gebruik van een bril kon ik redelijk nauwkeurig myopische personen identificeren. De waarde van de proxy werd verkend door het bepalen van de prevalentie van myopie en de associatie van de proxy met opleidingsniveau en een genetische risicoscore voor myopie. Niet alleen gaf de proxy een realistische

prevalentieschatting van myopie, maar ook bleek dat de effecten van opleidingsniveau en genetisch risico op myopie consistent waren met de resultaten van eerdere studies die direct gemeten data over refractiefouten gebruikten.

Het is belangrijk om gevallen van glaucoom nog beter te kunnen detecteren. Daarom kunnen studies die genen willen vinden voor glaucoom voortborduren op de resultaten van dit proefschrift, met als uiteindelijk doel een efficiënte screening en gepersonaliseerde gezondheidszorg op basis van genetische profielen. De kosteneffectieve en minder tijdrovende proxy voor myopie kan toekomstige studies over myopie in een grootschalige populatie-gebaseerde setting ondersteunen.

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About the author

Nigus Asefa was born in 1984 in Alamata, Ethiopia. In 2003, he completed his Secondary School in Alamata (*Tadagiwa* Ethiopia Secondary School) and in the same year, he moved to Addis Ababa for his undergraduate study. During his childhood, he was interested in studying health, and in 2007, he got his Bachelor's degree in Pharmacy from Addis Ababa University. His professional career started as a hospital pharmacy head in Lemlem Karl Hospital (Maychew), where he was responsible for administrating the pharmacy unit and maintaining pharmaceutical stock, i.e., ordering and purchasing pharmaceutical and medical supplies, and laboratory reagents. After a year and a half, he left the hospital and moved to academics where he works for most of his time. From March 2009 to September 2012, he has taught several pharmacy courses, including pharmacology and pharmaceutics to low- and middle-level health professionals. This has triggered his sense of engagement in research and in 2014, he has received his Masters of Public Health (MPH) from Mekelle University. His master's thesis focused on identifying the risk factors of road traffic crashes among taxi drivers and was published in a peer-reviewed journal. The publication of his master's thesis has promoted his academic growth, boosted his confidence, and encouraged him for more research work. After completing his master's study, he resumed his teaching career at Dr. Tewelde Health College (2014-2016) and later at Mekelle University (2016-2017). Nigus also received an Advanced Diploma in Sexual and Reproductive Health Rights (SRHR) from Lund University (2017, Sweden).

In March 2017, he moved to The Netherlands and started his PhD study at the University of Groningen, University Medical Center Groningen, under an EU-sponsored project called European Glaucoma Research Training (EGRET). In his PhD study, Nigus found a strong influence of genetic factors on glaucoma and its endophenotypes and provided the most accurate heritability estimates through meta-analysis. He identified 142 'likely' causal genes for glaucoma and their functional pathways leading to glaucoma pathogenesis. He found an association of glaucoma with low heart rate variability and high blood pressure, and also developed and validated a questionnaire-based myopia (short-sightedness) proxy. Nigus presented his work at several national and international conferences. Nigus's future is to engage in epidemiological studies that have an impact on improving human health and quality of life.