Common genetic variants associated with open-angle glaucoma

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Received December 19, 2010; Revised March 4, 2011; Accepted March 16, 2011

Open-angle glaucoma (glaucoma) is a major eye disorder characterized by optic disc pathology. Recent genome-wide association studies identified new loci associated with clinically relevant optic disc parameters, such as the optic disc area and vertical cup–disc ratio (VCDR). We examined to what extent these loci are involved in glaucoma. The loci studied include ATOH7, CDC7/TGFBR3 and SALL1 for optic disc area, and CDKN2B, SIX1, SCYL1/LTBP3, CHEK2, ATOH7 and DCLK1 for VCDR. We performed a meta-analysis using data from six independent studies including: the Rotterdam Study (n = 5736), Genetic Research in Isolated Populations combined with Erasmus Rucphen Family study (n = 1750), Amsterdam Glaucoma Study (n = 296) and cohorts from Erlangen and Tübingen (n = 1363), Southampton (n = 702) and deCODE (n = 36 151) resulting in a total of 3161 glaucoma cases and 42 837 controls. Of the eight loci, we found significant evidence (P = 1.41 × 10^-8) for the association of CDKN2B with glaucoma [odds ratio (OR) for those homozygous for the risk allele: 0.76; 95% confidence interval (CI): 0.70–0.84], for the role of ATOH7 (OR: 1.28; 95% CI: 1.12–1.47) and for SIX1 (OR: 1.20; 95% CI: 1.10–1.31) when adjusting for the number of tested loci. Furthermore, there was a borderline significant association of CDC7/TGFBR3

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and SALL1 (both \( P = 0.04 \)) with glaucoma. In conclusion, we found consistent evidence for three common variants (CDKN2B, ATOH7 and SIX1) significantly associated with glaucoma. These findings may shed new light on the pathophysiological protein pathways leading to glaucoma, and point to pathways involved in the growth and development of the optic nerve.

**INTRODUCTION**

Open-angle glaucoma (from here on called glaucoma) is a chronic neurodegenerative disease that leads to progressive damage to retinal ganglion cells and nerve fibers, resulting in visual field loss (1). Glaucoma is recognized as the commonest cause of irreversible blindness worldwide. However, the etiology of glaucoma remains obscure. Risk factors for glaucoma include old age, elevated intraocular pressure, myopia, African descent and positive family history (2,3). Only three causative genes have been established (MYOC, OPN and WDR36) for late-onset glaucoma (4). High-risk variants in these genes are predominantly observed in familial cases of glaucoma, but their frequency in sporadic patients from the general population is low (3−5%) (4).

One of the first signs of glaucoma is damage to the optic disc (optic nerve head), visible as an increased excavation (cupping). The optic disc cupping occurs more in the vertical direction, which is commonly quantified as the vertical cup-disc ratio (VCDR) (1,5). An increased VCDR is a significant determinant of the risk of developing glaucoma (6−8). Recently, we identified new loci involved in the optic disc area as well as VCDR: ATOH7, CDC7/TGFB3 and SALL1 for optic disc area, and CDKN2B, SIX1, SCYL1/LTB3, CHEK2, and DCLK1, in addition to ATOH7, for VCDR (Table 1) (9). When considering the function of the proteins these genes encode for, two protein pathways emerge (Fig. 1) (9). To further elucidate the relation of genes implicated in the optic disc area and VCDR to glaucoma, we examined to what extent these loci are involved in glaucoma. For this purpose, we performed a meta-analysis using data from six independent studies comprising of Caucasian persons: the Rotterdam Study (n = 5736), Genetic Research in Isolated Populations combined with Erasmus Rucphen Family (ERF) study (n = 1750), Amsterdam Glaucoma Study (AGS) (n = 296), and cohorts from Erlangen and Tübingen (n = 1363), Southampton (n = 702) and deCODE (n = 36 151) resulting in a total of 3161 glaucoma cases and 42 837 controls.

**RESULTS**

Table 2 summarizes the general characteristics of the cases and controls for all cohorts. Cases of GRIP and Southampton were significantly older (\( P < 0.001 \)) than their controls. As expected, in all studies, the intraocular pressure and intraocular pressure-lowering treatment were increased in glaucoma cases.

All studies showed marginal evidence for association (\( P < 0.003; \) adjusted for multiple testing) of rs1900004 (close to ATOH7), rs1063192 (CDKN2B) and rs10483727 (close to SIX1) with glaucoma for the homozygous effect (Fig. 2). For rs1900004 (ATOH7) as well as rs10483727 (SIX1), we found significant odds ratios (ORs) for glaucoma of 1.28 [95% confidence interval (CI): 1.12−1.47; \( P = 2.49 \times 10^{-3} \)) and 1.20 (95% CI: 1.10−1.31; \( P = 7.65 \times 10^{-3} \)), respectively, for those homozygous for the T-allele. For rs1063192 (CDKN2B), we found evidence for association with glaucoma in persons heterozygous and homozygous for the G-allele. The OR for the heterozygous ones was 0.85 (95% CI: 0.77−0.94; \( P = 0.002 \)) and for the homozygous 0.76 (95% CI: 0.70−0.84; \( P = 1.41 \times 10^{-3} \)). The latter translates into a 1.32 increase in risk for the C-allele. Testing for heterogeneity showed no significant differences across the studies (\( I^2 < 22.5\% \)).

We could not find evidence for a significant association for the other loci with glaucoma when adjusting for multiple testing. Nonetheless, the associations of the homozygous effect for rs1192415 (CDC7/TGFB3) and rs1362756 (close to SALL1) with glaucoma were borderline significant (\( P = 0.044 \) and \( P = 0.040 \), respectively). However, rs1192415 (CDC7/TGFB3) is a rare single nucleotide polymorphism (SNP), which appeared to be monomorphic in the Southamp-ton cohort. For this SNP, findings were inconsistent through the other studies. Finally, we evaluated whether the findings were robust when ignoring specific recessive effects for those hetero- and homozygous. The allelic effect showed significant evidence for rs1063192 (CDKN2B) and rs10483727 (SIX1); see Supplementary Material, Table S1) with glaucoma.

**DISCUSSION**

The present study yielded one significant gene (CDKN2B) involved in glaucoma in those heterozygous as well as those homozygous. The minor allele of the corresponding SNP (rs1063192) was genome-wide significantly associated with a lower VCDR and a reduced risk of glaucoma (9). In addition, there was also significant evidence for a role of ATOH7 and SIX1 in glaucoma when adjusting for multiple testing. For these genes, the effect appeared to be recessive, although the association remained significant when testing a multiplicative model for SIX1. Those homozygous for the minor allele had an increased risk of glaucoma. The three genes showed consistent evidence for a recessive effect through all cohorts. The other five regions (CDC7/TGFB3, SALL1, SCYL1/LTB3, CHEK2 and DCLK1) that were previously reported to be associated with either the optic disc area or VCDR could not be significantly related to glaucoma. None of the genes was identified before in genome-wide association studies (GWAS) on glaucoma (10,11).

The region of CDKN2B has been implicated in other diseases (e.g. diabetes, myocardial infarction and gliomas) (12−14). Different variants have been associated with different disorders. The variant associated with glaucoma in our study was earlier implicated in glioma (14). Glioma and glaucoma appear to share the same risk allele. Most of the risk
variants at this locus are in non-coding regions. The consistent association with several diseases suggests these variants act by influencing the expression of nearby genes. The SNP associated with glaucoma in the current study is highly correlated with increased CDKN2B antisense RNA (ANRIL) expression. Thus, the SNP is involved in regulating CDKN2B levels in blood and other tissues, suggesting that modulation of ANRIL expression may mediate disease susceptibility (15).

At present, little is known about the function of ANRIL in general and in neuronal tissue specifically. ATOH7 has been implicated in eye development before and points to a role of early development of the optic nerve (see further). Recently, ATOH7 has also been associated with optic nerve hypoplasia in humans (16). Deficiency of ATOH7 in mice may result in a critical reduction in retinal ganglion cells (17).

SIX1 acts within a network of genes that trigger eye organogenesis (18). These findings combined with the current findings are of interest and may shed new light on the etiology of glaucoma.

Increased intraocular pressure is the predominant risk factor for glaucoma. About half of the glaucoma patients have a statistically normal intraocular pressure. Earlier, we showed that adjustment for intraocular pressure did not alter the findings for the investigated SNPs (Table 1), in that the association with the VCDR remained significant (9). This suggests that

### Table 1. Loci investigated in the current study

<table>
<thead>
<tr>
<th>Most significant SNP</th>
<th>MA</th>
<th>MAF</th>
<th>Chromosome location</th>
<th>Position</th>
<th>Nearest gene (symbol; name)</th>
<th>Distance (b)</th>
<th>Quantitative trait associated with GWAS</th>
<th>Direction of effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs1900004</td>
<td>T</td>
<td>0.22</td>
<td>10q21.3–q22.1</td>
<td>69 670 887</td>
<td>ATOH7; atonal homolog 7</td>
<td>9021</td>
<td>Optic disc area/VCDR</td>
<td>−/−</td>
</tr>
<tr>
<td>rs1192415</td>
<td>G</td>
<td>0.22</td>
<td>1p22</td>
<td>91 849 685</td>
<td>CDC7/TGFBR3; cell division cycle 7 homolog/transforming growth factor, beta receptor III</td>
<td>116 719</td>
<td>Optic disc area</td>
<td>+</td>
</tr>
<tr>
<td>rs1362756</td>
<td>C</td>
<td>0.28</td>
<td>16q12.1</td>
<td>50 015 791</td>
<td>SALL1; sal-like 1</td>
<td>1 154 095</td>
<td>Optic disc area</td>
<td>+</td>
</tr>
<tr>
<td>rs1063192</td>
<td>G</td>
<td>0.44</td>
<td>9p21</td>
<td>21 993 367</td>
<td>CDKN2B; cyclin-dependent kinase inhibitor 2B</td>
<td>0</td>
<td>VCDR</td>
<td>−</td>
</tr>
<tr>
<td>rs10483727</td>
<td>T</td>
<td>0.44</td>
<td>14q22–23</td>
<td>60 142 628</td>
<td>SIX1; sine oculis-related homeobox 1 homolog</td>
<td>39 878</td>
<td>VCDR</td>
<td>+</td>
</tr>
<tr>
<td>rs17146964</td>
<td>G</td>
<td>0.20</td>
<td>11q13</td>
<td>65 005 721</td>
<td>SCY1/LTBP3; SCY1-like 1/latent transforming growth factor beta binding protein 3</td>
<td>43 403</td>
<td>VCDR</td>
<td>−</td>
</tr>
<tr>
<td>rs1547014</td>
<td>T</td>
<td>0.26</td>
<td>22q12.1</td>
<td>27 430 711</td>
<td>CHEK2; CHK2 checkpoint homolog</td>
<td>0</td>
<td>VCDR</td>
<td>−</td>
</tr>
<tr>
<td>rs1926320</td>
<td>C</td>
<td>0.25</td>
<td>13q13</td>
<td>35 550 617</td>
<td>DCLK1; doublecortin-like kinase 1</td>
<td>0</td>
<td>VCDR</td>
<td>+</td>
</tr>
</tbody>
</table>

SNP, single nucleotide polymorphism; MA(F), minor allele (frequency); GWAS, genome-wide association study; VCDR, vertical cup–disc ratio.

**Figure 1.** Overview of the biological interaction of the investigated genes in relation to open-angle glaucoma (left part: developmental pathway; right part: TGFβ-signaling/growth pathway; genes associated with open-angle glaucoma in the present study are in bold).
other mechanisms independent of intraocular pressure explain these associations. When we combine current findings with previous ones, two pathways emerge that may be relevant in addition to intraocular pressure (Fig. 1). One pathway related to growth, including CDKN2B and ATOH7 involved through the TGFβ pathway, which has been implicated before in the pathogenesis of glaucoma (19–21), and the other pathway related to development, including SIX1.

Only three out of the eight loci that were previously associated with the optic disc area and VCDR were significantly associated with glaucoma in the current study. It remains to be determined whether other genes associated with the VCDR will be relevant when studying larger samples. Only ATOH7 was significantly associated with the optic disc area, but also had an independent effect on the VCDR (9).

So far, only one genome-wide significant gene has been identified and consistently replicated for glaucoma using GWAS (11). It is of interest that this gene (CAV1) interacts with CAV2 through CAV2A (www.ingenuity.com). Nevertheless, in the present study, the gene showing the strongest association in terms of P-values is CAV2B. This gene reaches genome-wide significance ($P < 5 \times 10^{-8}$) in our study. At present, there is no interaction known of this gene with CAV1. Identification of the causal variant in the region is needed to increase our knowledge of the causal pathways.

Although this is one of the largest studies on the genetics of glaucoma, the power to detect genes with small effects is still limited. Furthermore, one of the major problems in glaucoma in general is the lack of standardized clinical criteria, which will remain a problem in future research. Despite this hampering our findings, the consistency in ORs suggests that this problem may have primarily affected the statistical power rather than heterogeneity of glaucoma cases.

In conclusion, the present study reveals three common variants implicated in glaucoma and supports the hypothesis of the involvement of the TGFβ pathway in glaucoma. Further exploration of our findings may include expression and translational studies. The role of these genes in non-white populations (such as some African populations with a markedly higher prevalence of glaucoma) remains to be established. Nonetheless, we could relate three of the eight loci to glaucoma, opening new avenues to improve our understanding for this common form of sight-threatening disease.

**MATERIALS AND METHODS**

**Study populations**

The first cohort, the Rotterdam Study (RS-I), is a prospective population-based cohort study of 7983 residents aged 55 years and older living in Rotterdam, the Netherlands (22). RS-I was previously included in the gene discovery study (9). In this paper, we included cases and controls from RS-I. The second study included glaucoma cases from the Genetic Research in Isolated Populations (GRIP; $n = 104$) and controls from the ERF study. For GRIP, medical records in three local hospitals were assessed to identify patients with glaucoma. ERF is a family-based study in a genetically isolated population in the southwest of the Netherlands with over 3000 participants aged 18–86 years (23,24). Participants of GRIP were
ascertained independently of ERF, but lived in the same region. The third study, the AGS, included 148 cases and 148 controls collected from eye clinics, meetings of the glaucoma patients’ association, nursing homes and fairs for the elderly from all over the Netherlands. The fourth study included participants from Erlangen and Tübingen, Germany, comprising 986 glaucoma cases and 377 controls. Cases and controls were recruited from the same geographic regions. For the fifth study, from Southampton, glaucoma cases and controls (n = 470 and 232, respectively) were collected from specialist glaucoma and general clinics at the Southampton Eye Unit, UK. Finally, in deCODE, the sixth study, 1265 glaucoma cases were recruited from the Reykjavik Eye Study (25) and Icelandic glaucoma clinics. Controls (n = 34,886) were selected among individuals who had participated in the various genetic programs at deCODE. The present study included a total of 3161 glaucoma cases and 42,837 controls, all of Caucasian ethnicity. All measurements in these studies were conducted after the respective relevant medical ethics committees had approved the study protocols, and all participants had given a written informed consent in accordance with the Declaration of Helsinki.

Ophthalmic examination

The ophthalmic assessment in RS-I included a medical history, autorefraction, keratometry, Goldmann applanation tonometry, visual field testing [Humphrey Field Analyzer II 740 (HFA; Carl Zeiss, Oberkochen, Germany)] and optic nerve head imaging with Topcon ImageNet System (Topcon Corporation, Tokyo, Japan) of both eyes after pharmacologic mydriasis. In GRIP, visual fields were tested with standard automated perimetry by means of the HFA 24-2 SITA Standard test program or the Octopus 101 (Haag Streit) G2 program with TOP strategy. The ophthalmic assessment in ERF was similar to RS-I, but no visual field testing was included, medical records were checked for any glaucoma pathology (L.M.E.v.K. and H.G.L.) and optic nerve head imaging was done with Heidelberg Retina Tomograph 2 (HRT; Heidelberg Engineering, Dossenheim, Germany). In AGS, all persons underwent ophthalmoscopy and biomicroscopy with a 90 diopter lens, and digital stereo images of the optic nerve head were taken after mydriatic drops. Participants from Erlangen and Tübingen underwent standardized clinical examinations for glaucoma at the Ophthalmology Department of the University of Erlangen-Nuremberg and at the University Eye Hospital in Würzburg and Tübingen, respectively. The examination included optic nerve head imaging (HRT 1 and 2; or biomicroscopy with Goldmann lens and a Haag-Streit slit lamp), and 24 h Goldmann applanation tonometry profile with five measurements (26,27). Patients from Southampton were examined by an experienced glaucoma specialist at the Southampton University Hospital Eye Unit. Biomicroscopy was performed and visual fields were measured using HFA 24-2 and HFA 30-2. Examination of participants from deCODE included biomicroscopy and visual field testing using the Octopus 123 perimeter (Haag-Streit, Köniz, Switzerland). Details have been described elsewhere (25).

Criteria for glaucoma

In RS-I, glaucoma diagnosis was primarily based on the presence of glaucomatous visual field loss, and not on the VCDR. The visual field of each eye was screened using a 52-point...
supra-threshold test that covered the central visual field with a radius of 24° (28,29), and tested the same locations as used in the Glaucoma Hemifield Test. In participants in whom visual field loss was reproducible on a second supra-threshold test, Goldmann kinetic perimetry or full-threshold HFA testing with 24-2 grid was performed on both eyes by a skilled perimetrist. Details about the classification process have been described before (8,28). Cases had to have an open anterior chamber angle and no history or signs of secondary glaucoma or manifest exfoliation were allowed.

In GRIP, the diagnosis of glaucoma was made by the ophthalmologist in attendance and verified by a glaucoma specialist (H.G.L.). The diagnosis was based on the glaucomatous appearance of the optic disc, combined with a matching glaucomatous visual field defect and open angles upon gonioscopy. Visual field test results had to be reliable and reproducible. Patients with any other disease that could cause visual field defects were excluded.

In AGS, glaucoma cases had to have glaucomatous optic neuropathy with corresponding glaucomatous visual field loss in at least one eye or a VCDR ≤ 0.6 on ophthalmoscopy and fundus photography. Details of the glaucoma cases from Southampton have been reported previously (32). In brief, diagnosis was made on the basis of characteristic glaucomatous visual field loss/glaucomatous optic disc damage/increased intraocular pressure. Patients presenting with narrow-angle, developmental or secondary glaucoma or any other known abnormalities of the anterior segment were excluded. Controls had no history of glaucoma and were not on any treatment to lower intraocular pressure.

Finally, in deCODE, glaucoma was based on glaucomatous optic neuropathy and glaucomatous visual field loss (11). Cases had to have an open anterior chamber angle on gonioscopy. Exfoliation syndrome was specifically looked for and if detected the participant was excluded. Controls with a reported history of glaucoma were excluded from the control group.

Laboratory analysis
In the RS-I, DNA was genotyped using the Illumina Infinium II HumanHap550chip v3.0® array according to the manufacturer’s protocols (33,34). After exclusion of participants for reasons of low-quality DNA, a total of 5974 participants were available with genotyping data from RS-I, of whom 5736 had reliable optic disc measurements and visual fields.

In ERF and GRIP, DNA was genotyped on four different platforms (Illumina 6k, Illumina 318K, Illumina 370K and Affymetrix 250K), which were then merged. A total of 2385 had genotyping data, of which 1646 from ERF had reliable optic disc data. For the AGS study, the SNPs were characterized by using TaqMan®. The Erlangen and Tübingen cohorts were genotyped using selected pre-developed TaqMan® Genotyping Assays (Applied Biosystems, Foster City, CA, USA), following the manufacturer’s instructions. Genotyping of Southampton cases and controls was carried out using KASPar chemistry (KBioscience, Hoddesdon, UK). Finally, in deCODE, samples were assayed with the Illumina HumanHap300 or HumanHapCNV370 bead chips (Illumina, SanDiego, CA, USA).

Statistical analyses
Within each study logistic regression, analyses were used to examine the associations between the top SNPs (Table 1) and glaucoma adjusted for age and gender. With these logistic regression models, we calculated ORs with corresponding 95% CIs. The minor allele of the SNPs was considered the risk allele. Next, we performed meta-analyses using fixed-effects models to calculate the joint effect through the six independent cohorts for the heterozygous and homozygous effect of the SNPs. To adjust for multiple testing, we used Bonferroni’s correction; a P-value of 0.003 [0.05/8 SNPs/2 (for hetero- and homozygous effect)] or smaller was considered statistically significant. Heterogeneity of the meta-analyses was measured by calculating I² (35). Finally, as a secondary analysis, we ran an allelic analysis assuming the risk associated with the genotype is multiplicative to the number of risk alleles. All statistical analyses were performed using SPSS version 15.0.0 for Windows (SPSS Inc., Chicago, IL, USA; 2006), and R statistical package version 2.11.1 for Mac (www.r-project.org).

SUPPLEMENTARY MATERIAL
Supplementary Material is available at HMG online.

ACKNOWLEDGMENTS
We thank Pascal Arp, Mila Jhamai, Dr Michael Moorhouse, Jeannette Vergeer, Martin Verkerk and Sander Bervoets for their help in creating the GWAS database, and Dolinda Pottuit and Raph de Haas for their help in analyzing the optic disc images. The authors are grateful to the study participants, the staff from all involved studies and the participating general practitioners, pharmacists and others who contributed.

Conflict of Interest statement. None declared.

FUNDING
The Rotterdam Study is funded by the Erasmus Medical Center and the Erasmus University, Rotterdam, the Netherlands Organization for Health Research and Development (ZonMw), the Research Institute for Diseases in the Elderly (RIDE), the
Ministry of Education, Culture and Science, the Ministry for Health, Welfare and Sports, the European Commission (DG XII) and the Municipality of Rotterdam. The generation and management of GWAS genotype data for the Rotterdam Study is supported by the Netherlands Organization of Scientific Research NWO Investments (no. 175.010.2005.011, 911-03-012). This study is funded by the Research Institute for Diseases in the Elderly (014-93-015; RIDE2), the Netherlands Genomics Initiative (NGI)/Netherlands Organization for Scientific Research (NWO)/Netherlands Consortium for Healthy Aging (NCHA) project no. 050-060-810. The genetic study in the Erasmus Rucphen (ERF) Study were supported by the Center for Medical Systems Biology (CMSB) of NGI.


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