Genetic correlations between intraocular pressure, blood pressure and primary open-angle glaucoma: a multi-cohort analysis


Primary open-angle glaucoma (POAG) is the most common chronic optic neuropathy worldwide. Epidemiological studies show a robust positive relation between intraocular pressure (IOP) and POAG and modest positive association between IOP and blood pressure (BP), while the relation between BP and POAG is controversial. The International Glaucoma Genetics Consortium (n = 27 558), the International Consortium on Blood Pressure (n = 69 395), and the National Eye Institute Glaucoma Human Genetics Collaboration Heritable Overall Operational Database (n = 37 333), represent genome-wide data sets for IOP, BP traits and POAG, respectively. We formed genome-wide significant variant panels for IOP and diastolic BP and found a strong relation with POAG (odds ratio and 95% confidence interval: 1.18 (1.14–1.21), P = 1.8 × 10−27) for the former trait but no association for the latter (P = 0.93). Next, we used linkage disequilibrium (LD) score regression, to provide genome-wide estimates of correlation between traits without the need for additional phenotyping. We also compared our genome-wide estimate of heritability between IOP and BP to an estimate based solely on direct measures of these traits in the Erasmus Rucphen Family (ERF; n = 2519) study using Sequential Oligogenic Linkage Analysis Routines (SOLAR). LD score regression revealed high genetic correlation between IOP and POAG (48.5%, P = 2.1 × 10−5); however, genetic correlation between IOP and diastolic BP (P = 0.86) and between diastolic BP and POAG (P = 0.42) were negligible. Using SOLAR in the ERF study, we confirmed the minimal heritability between IOP and diastolic BP (P = 0.63). Overall, IOP shares genetic basis with POAG, whereas BP has limited shared genetic correlation with IOP or POAG.

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INTRODUCTION

Primary open-angle glaucoma (POAG) is an intraocular pressure (IOP)-related, chronic optic neuropathy that is a leading cause of blindness worldwide. Randomized controlled trials (RCTs) indicate that treatments designed to lower IOP slow disease progression. Compared with an IOP of 16 mm Hg or less, an IOP of 35 mm Hg is associated with a 39-fold increased risk of POAG. A more modest but consistent positive association between blood pressure (BP) and IOP also exists. Specifically, a meta-analysis of epidemiological surveys found that every 10 mm Hg increase in systolic blood pressure (SBP) or 5 mm Hg increase in diastolic blood pressure (DBP) was associated with 0.26 mm Hg and 0.17 mm Hg increases in IOP, respectively. 

or 5 mm Hg increase in diastolic blood pressure (DBP) was associated found that every 10 mm Hg increase in systolic blood pressure (SBP) but consistent positive association between blood pressure (BP) and

in the context of higher IOP may result in poor optic nerve perfusion,

control and imputation of untyped variants using the 1000 Genomes Project

the genome using linkage disequilibrium (LD) score regression. 

The NEIGHBORHOOD data set included 37333 participants of European ancestry (3853 cases and 33480 controls) enrolled as part of eight independent studies from the United States for a genome-wide meta-analysis of POAG. The NEIGHBORHOOD: a genome-wide association meta-analysis

Additional details regarding the cohort composition and analyses performed are

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studies; however, to reduce the potential impact of population structure, our analysis only considered the meta-analysis results of 27 558 individuals of European ancestry from 14 studies. The ICBP performed a GWAS for BP traits that included 69 395 individuals of European ancestry from 29 studies. Participants from both consortia had genome-wide data for ~2.5 million genotyped or imputed SNPs (Supplementary Table 1).

The ERF study: a pedigree with IOP and BP data

The ERF study is an independent family-based cohort containing 2519 participants with simultaneous IOP and BP measurements. Details regarding the ERF and how IOP and BP were measured are available in the Supplementary note. We used SOLAR (Sequential Oligogenic Linkage Analysis Routines) to decompose the phenotypic correlation between IOP and BP into genetic and environmental components while accounting for kinship calculated from the pedigree file. The genetic correlation between IOP and BP estimated solely from kinship was compared with genome-wide measures of genetic correlation for these traits as described below.

Genetic risk score analyses

For each IOP and BP locus with MAF >0.05 reported to have at least one genome-wide significant (ie, \( P<5 \times 10^{-8} \)) associated SNP in the IGGC and ICBP, respectively, we selected the most significant variant based on its \( P \)-value for association. We chose to focus on DBP loci for our genetic risk score (GRS) analysis because two studies showed the strongest association between lower diastolic OPP (DBP minus IOP) and POAG as opposed to other OPP parameters (systolic OPP and mean arterial OPP). We evaluated the effect of IOP and DBP genome-wide significant SNPs in relation to POAG, HTG and NTG in the NEIGHBORHOOD using GRSs that aligned alleles associated with increasing IOP and decreasing DBP. GRSs are conventionally derived using individual level genotype data and then tested for association with the outcome of interest using standard linear or logistic regression. However as proposed by Aschard, such a test can be performed using summary statistics data. In brief, one can collect summary statistics for the SNPs that form the GRS and use an inverse variance-weighted sum meta-analysis of individual SNP effect estimates. If \( \mathbf{b} = (\hat{\beta}_G, \hat{\beta}_b, \ldots, \hat{\beta}_m) \) represents the reported effect of the \( m \) selected SNP and \( \mathbf{s} = (s^2, s^2, \ldots, s^2) \) represents the variance of each estimate, under the assumption of independence between the SNPs, \( \chi^2 \), the \( \chi^2 \) for the GRS effect on POAG over all SNPs \( \hat{\gamma}_ij \), can be derived as:

\[
\chi^2_G = \sum_{i=1}^{m} w_i x_i^2 / \sum_{i=1}^{m} w_i^2
\]

where \( w_i \) is the weight assigned to SNP \( G_i \) (commonly, the marginal genetic effect estimate). For unweighted GRSs, as performed in the present study, we set all weights to one. We chose unweighted GRSs for all analyses, as it is difficult to define homogenous weight between the IGCC and ICBP when merging IOP and DBP SNPs, respectively, to form the OPP panel, which represented the combined effect of IOP-increasing gene variants and DBP-decreasing gene variants in relation to POAG.

Genetic correlation and heritability

We used genome-wide summary statistics results across all SNPs for IOP and BP parameters (DBP, SBP, MAP, and pulse pressure) to derive the genetic correlation between those traits and glaucoma phenotypes (POAG, HTG, and NTG) using LD score regression. In brief, given genome-wide summary statistics of two phenotypes, defined as two vectors of \( z \)-scores, \( z_1 \) and \( z_2 \), and assuming a polygenic model, the expected value of the product \( z_1z_2 \) for a
SNP $j$ equals $^{17}$

$$E[z_{j,z_2}] = \frac{\sqrt{N_1 N_2 \rho_{kj}}}{M} + \rho_N \frac{N_1}{\sqrt{N_1 N_2}}$$

where $\rho_{kj}$ is the genetic covariance, $M$ is the number of SNPs analyzed, $N_1$, $N_2$ and $\rho_N$ are the sample size for phenotype 1, phenotype 2, and the overlapping sample size, respectively; and $\rho$ is the correlation between the two phenotypes.

Finally, $I_p$, the LD score of a variant is the sum of $r_{ik}^2$, the squared correlation between the SNP $j$ and all SNPs $k = 1, \ldots, M$, and is expressed as $\sum r_{ik}^2$. It follows that the genetic correlation, the parameter of interest, can be estimated using the slope from the regression of $z_{j,z_2}$ on LD Score.

As recommended, we applied the LD score on genetic variants that passed a stringent filter, removing SNPs with poor imputation quality ($r^2$ for imputation <0.9), MAF <5% and SNPs whose effect estimates were derived with <66% of the total sample. $^{18}$ As this information was only partly available in studies we analyzed, we instead used the systematic filtering proposed for use with the LD score regression software. It specifies analyzing only SNPs that are part of the ~1.2 M common SNPs from the HapMap 3 panel. Finally, for binary traits the LD score estimates are derived using a European ancestry panel, which was readily available as part of the ~1.2 M common SNPs from the HapMap 3 panel. Finally, for binary traits the LD score estimates are derived using a European ancestry panel, which was readily available as part of the ~1.2 M common SNPs from the HapMap 3 panel.

Partitioning POAG and IOP heritability

To gain further insight into the heritability of glaucoma-related traits, we also estimated how heritability partitioned across gene sets expressed in eye tissues. To do so, we leveraged publicly available gene expression data from human eye tissues provided by the National Eye Institute (https://neibank.nei.nih.gov/index.shtml). For each tissue selected, we included genes matching a known gene in the UCSC database with a clone count $\geq 1$. The tissue included ‘cornea’ (referring to the anterior segment uveal tract responsible for generating aqueous humor, 201 genes), cornea (259 genes), lens (135 genes), optic nerve (349 genes), retina (203 genes), and trabecular meshwork (129 genes). The tissue relatedness and population stratification. As for the genetic correlation analyses, estimates of heritability were derived using only the ~1.2 M common SNPs from the HapMap 3 panel.

Figure 1 Association of intraocular pressure and diastolic blood pressure gene variants with primary open-angle glaucoma (POAG; n = 3853 cases) and the high-tension glaucoma (HTG; n = 1774 cases) and normal tension glaucoma (NTG; n = 725 cases) subtypes in the NEIGHBORHOOD consortium (n=37 333 total participants). Odds ratios and 95% confidence intervals (indicated with error bars) for association between 8 intraocular pressure loci (upper panel), and 27 diastolic blood pressure loci (bottom panel) and POAG (a), HTG (b), and NTG (c). SNPs with nominally significant associations are highlighted in red. $P$-values can be found in Supplementary Table 2. The full colour version of this figure is available at European Journal of Human Genetics online.
RESULTS

IOP and BP genome-wide significant variants in relation to POAG

Eight of five genome-wide significant IOP SNPs showed nominally significant positive association with the glaucoma phenotypes (POAG, HTG, and NTG) in NEIGHBORHOOD (Figure 1 and Supplementary Table 2). The strongest association was observed for hgt9 chr1: g:165718979C = A (TMCO1; \( P = 5.9 \times 10^{-13} \), \( P = 1.3 \times 10^{-12} \), and \( P = 0.065 \), for POAG, HTG, and NTG, respectively). Many of those associations remained significant after Bonferroni correction accounting for the 105 tests performed (Supplementary Table 2; \( P = 4.76 \times 10^{-4} \)).

One of the 27 genome-wide DBP SNPs showed nominal significance with at least one glaucoma phenotype but the direction of

| Table 1 Polygenetic risk scores for intraocular pressure (IOP), diastolic blood pressure (DBP) and the combined ocular perfusion pressure (OPP) panels in relation to primary open-angle glaucoma (POAG; \( n = 3 \) 853 cases) and its high-tension glaucoma (HTG; \( n = 1 \) 774 cases) and normal tension glaucoma (NTG; \( n = 725 \) cases) subtypes in the NEIGHBORHOOD consortium (\( n = 37 \) 333)

<table>
<thead>
<tr>
<th>Association studied</th>
<th>Odds Ratio</th>
<th>95% lower bound</th>
<th>95% upper bound</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IOP SNPs–POAG</td>
<td>1.18</td>
<td>1.14</td>
<td>1.21</td>
<td>( 1.8 \times 10^{-27} )</td>
</tr>
<tr>
<td>DBP SNPs–POAG</td>
<td>1</td>
<td>0.98</td>
<td>1.01</td>
<td>0.93</td>
</tr>
<tr>
<td>OPP SNPs–POAG</td>
<td>1.04</td>
<td>1.02</td>
<td>1.05</td>
<td>( 7.4 \times 10^{-7} )</td>
</tr>
<tr>
<td>IOP SNPs–HTG</td>
<td>1.2</td>
<td>1.15</td>
<td>1.25</td>
<td>( 1.1 \times 10^{-20} )</td>
</tr>
<tr>
<td>DBP DBP–HTG</td>
<td>1</td>
<td>0.98</td>
<td>1.02</td>
<td>0.47</td>
</tr>
<tr>
<td>OPP SNPs–HTG</td>
<td>1.04</td>
<td>1.02</td>
<td>1.06</td>
<td>( 1.6 \times 10^{-5} )</td>
</tr>
<tr>
<td>IOP SNPs–NTG</td>
<td>1.18</td>
<td>1.12</td>
<td>1.25</td>
<td>( 6.2 \times 10^{-5} )</td>
</tr>
<tr>
<td>DBP SNPs–NTG</td>
<td>1</td>
<td>0.97</td>
<td>1.03</td>
<td>0.96</td>
</tr>
<tr>
<td>OPP SNPs–NTG</td>
<td>1.04</td>
<td>1.01</td>
<td>1.07</td>
<td>0.0061</td>
</tr>
</tbody>
</table>

Abbreviation: SNPs, single-nucleotide polymorphisms. NB: DBP allele variants coded as allele associated with lower diastolic blood pressure and IOP allele variants coded as allele with higher intraocular pressure so as to mimic the OPP term. Polygenic risk scores are unweighted. Bold values represent \( p \)-values < 0.05.

Genetic correlations between intraocular pressure, blood pressure and glaucoma

The genetic correlation between BP phenotypes using LD score regression was very high (eg, the genetic correlation between DBP and SBP was 0.884, \( P < 10^{-300} \), in agreement with previous studies (Table 2). IOP showed strong genetic correlation with POAG (0.485; \( SE = 0.110 \); \( P = 2.1 \times 10^{-5} \) and HTG (0.548; \( SE = 0.116 \); \( P = 9.6 \times 10^{-4} \)). Possibly owing to a smaller number of documented NTG cases (\( n = 725 \)), the genetic correlations between IOP and NTG (0.210; \( SE = 0.198 \); \( P = 0.28 \)) and between HTG and NTG (0.241; \( SE = 0.290 \); \( P = 0.41 \)) were not statistically significant. Conversely, we did not observe any genetic correlations between IOP and BP phenotypes, nor between BP phenotypes and POAG (\( P \geq 0.32 \)). We also reported estimates of \( h_{IOP}^2 \) for our glaucoma phenotypes explained by common SNPs. Applying the LD score regression we obtained \( h_{IOP}^2 \) of 0.102 (SE = 0.021), 0.099 (SE = 0.033), 0.165 (SE = 0.082), and 0.116 (SE = 0.018) for POAG, HTG, NTG, and IOP, respectively. In sensitivity analysis, doubling POAG prevalence from 1 to 2% did not appreciably alter \( h_{IOP}^2 \) estimates (eg, \( h_{IOP}^2 \) increased from 0.102 to 0.122 for POAG).

As IOP and BP traits were not measured in the ICBP and IGGC respectively, we sought to validate our estimate of shared heritability of these traits in the ERF study where IOP and BP were directly measured in defined pedigrees (see Supplementary note). Shared heritability estimates using purely family-based data were not significantly different from zero between IOP and the four BP phenotypes (\( P = 0.63 \); Supplementary Table 4), supporting our LD score regression results.
Partitioning of glaucoma trait heritability with ocular tissue genes using data from the NEIGHBORHOOD and iGGG.

Overall, after accounting for the strong overlap between the various ocular tissue SNP sets and the heterogeneous representation of these SNP collections in the available GWAS (7.4–30.9%), we find no significant enrichment of heritability for IOP and glaucoma traits in any ocular tissue gene set (Figure 2). Supplementary Table 5 provides further detail regarding heritability partitioning between IOP, glaucoma traits and ocular tissue genes.

**DISCUSSION**

In this large multi-cohort study of European ancestry we found strong associations between genome-wide significant IOP SNPs and POAG, as expected for an IOP-related optic neuropathy. In fact, even the association between the IOP GRS and NTG, where the highest known IOP was <22 mmHg, was highly significant (OR=1.18; P=6.2×10^{-5}; Table 1). Overall, significant variants from this analysis were already known to be associated with POAG phenotypes. chr7:g.116150995C>A (CAVI/CAV2 intergenic region) is a known POAG SNP,\(^{13}\) chr1:g.165718979C>A (TMCO1), chr17:g.10031183A>G (GAS7), and chr9:g.107695848G>A (ABCA1) were identified by the NEIGHBORHOOD GWAS;\(^{10}\) and chr3:g.17992387G>A (FNDCH8) has been associated with POAG as part of studies that used NEIGHBORHOOD data.\(^{12,31}\) However, we found weak, inconsistent relations between genome-wide significant DBP SNPs and POAG. Finally, we found minimal genome-wide shared genetic heritability between IOP and BP traits and these results were replicated in the ERF study.

We formed a SNP panel that combined DBP and IOP variants in an effort to mimic OPP (a measure of DBP minus IOP), a popularly derived biomarker felt to reflect optic nerve perfusion.\(^{5,7}\) We found that the relationship between OPP and POAG appeared to be driven by the IOP variants. The only BP SNP showing an association signal with POAG after correction for multiple comparisons (see Table 1 and Supplementary Table 2) was chr2:g.111884608T>C (SH2B3). Interestingly, this variant encodes a missense amino-acid change and has already been found associated with other outcomes such as type 1 diabetes\(^{32}\) and autoimmune hepatitis type 1,\(^{33}\) suggesting that this association is driven by a pleiotropic biological mechanism independent of the other variants.

The shared heritability across the genome between IOP and POAG was high (0.49; SE=0.11; P=2.1×10^{-5}; Table 2), between IOP and BP parameters, (50.005; P=0.58; Table 2) or between BP parameters and POAG (≤0.023; P=0.42; Table 2) the shared genome-wide heritability was minimal. Taken collectively, our work suggests that, unlike IOP, BP is not in the causal pathway of POAG from a genetic perspective. Furthermore, the genetic correlation between IOP and HTG across the genome was also high (0.55±0.16; P=9.6×10^{-4}; Table 2). Conversely, although an IOP GRS was significantly associated with NTG, an estimate of genetic correlation between IOP and NTG across the genome suggests a lower heritability (0.21±0.2; P=0.28; Table 2), though this estimate is unstable due to the smaller sample size (n=725 NTG cases). Finally, across the genome, there was non-significant shared heritability between NTG and HTG (0.24±0.29; P=0.41; Table 2). To date, only the CDKN2BAS region unequivocally appears to be shared between these two glaucoma phenotypes,\(^{34,35}\) underscoring the need to carefully phenotype POAG for known maximum IOP and to perform additional high-throughput genotyping, particularly for NTG.

Investigators have pointed out that it is impossible to dis-entangle the BP and IOP components of OPP when considering the latter term
that this is not mediated by the examined genetic factors. The mechanism by which higher BP might be associated with higher IOP is unknown but could represent the pleotropic effects of multiple environmental influences.

Our estimate for heritability of POAG is consistent with a prior classic twin study \((h^2 = 0.11)\) but lower than a contemporary estimate using GWAS data \((h^2 = 0.42)\). The sample size for the classic twin study was small. In the latter study, cases and controls were drawn from different sources and the number of cases (1105) was considerably less than in our data set (3853). On the other hand, IOP has a reported heritability of 0.56\(^4\) but our estimate from the IGGC based on common variants is 0.12. The missing IOP heritability could be partially related to imprecision in phenotyping as IOP measurements vary by time of day,\(^4,1\) season of year,\(^2\) central corneal thickness (CCT),\(^3\) variation in IOP measurement methodology\(^4\) and other factors. CCT, a highly heritable trait \((h^2 = 0.95)\),\(^3\) was collected in IGGC but there is no agreed upon algorithm to adjust IOP based upon the CCT.\(^8\) In the IGGC, the other variables effecting IOP variability were not systemically adjusted for in the collection of this glaucoma-related trait.

Study limitations include our candidate SNP analyses, which focused on selected genome-wide significant variants. These variants together capture only a small proportion of the total genetic component of those traits, and more extensive panels might show different characteristics. For example future work might compare SNP effects for variants showing only suggestive genome-wide significance or for variants annotated for functional characteristics. A recent meta-analysis\(^47\) uncovered an additional 31 BP loci but many of these are rare variants and assessing the more common ones in relation to IOP and glaucoma traits will not change our results about shared genetic correlation across the genome. Nonetheless, it is still possible that there is a small subset of BP genetic markers related to IOP and glaucoma traits. Next, for co-heritability estimates, whereas we did not observe genetic correlation between BP traits and glaucoma traits, isolated shared genetic loci between BP parameters and glaucoma traits may exist when very large data sets are considered. Furthermore, our findings are derived from individuals of European ancestry and it is not clear if they apply to other ethnicities. Finally, as previously discussed, the LD score regression approach is sensitive to GC correction,\(^1\) which was applied to the BP meta-analysis. This may result in a slight underestimation of genetic correlation between BP and POAG traits, though our replication analysis in the ERF study confirmed that if any correlation exists, its magnitude is likely very low. The LD score regression also relies on the assumption that the single SNP effect sizes are normally distributed. While violation of this assumption does not bias the regression, it would increase the standard error, making heritability and co-heritability estimates unstable.

In summary, using the largest data sets available to date for IOP, BP, and POAG we confirm a strong genetic link between IOP and POAG but we cannot detect any substantial shared genetic effect between BP and IOP, nor between BP and POAG. Thus, if BP contributes to POAG by altering optic nerve perfusion, it does so via non-genetic effects or genetic influences we could not detect.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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regression analyses were performed using the implementation of the LD score method provided at https://github.com/bulik/lscd.


Supplementary Information accompanies this paper on European Journal of Human Genetics website (http://www.nature.com/ejhg)