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

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Abstract:

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 datasets 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), $p=1.8\times10^{-27}$) 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=2 519) study using Sequential Oligogenic Linkage Analysis Routines (SOLAR). LD score regression revealed high genetic correlation between IOP and POAG (48.5%, $p=2.1\times10^{-5}$); 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, while BP has limited shared genetic correlation with IOP or POAG.

Key words: intraocular pressure; blood pressure; primary open-angle glaucoma; genetic correlations; shared heritability; LD score regression.

Introduction:

Primary open angle glaucoma (POAG) is an intraocular pressure (IOP)-related, chronic optic neuropathy that is a leading cause of blindness worldwide.[1] Randomized controlled trials (RCTs) indicate that treatments designed to lower IOP slow disease progression.[2] Compared to an IOP of 16 mm Hg or less, an IOP of 35 mm Hg is associated with a 39-fold increased risk of POAG (ref. 3). 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.[4]

The relationship between BP and POAG is more complex. In pooled analyses, every 10 mm Hg increase in systolic blood pressure (SBP) was associated with a 1% increased risk of POAG while every 5 mm Hg increase in diastolic blood pressure (DBP) was associated a 2% increased risk of POAG (ref. 4). However, observational studies report a robust inverse relation between ocular perfusion pressure (OPP) and POAG, where OPP is calculated as either mean arterial pressure, SBP or DBP minus IOP (ref. 5-7). Since a lower BP in the context of higher IOP may result in poor optic nerve perfusion, glaucoma drugs are frequently scrutinized for their effects on both IOP and OPP (ref. 8, 9). Finally, post-hoc analysis of two RCTs found that lower OPP was associated with glaucoma progression (ref. 10-11).

Several common gene variants have been identified for IOP (ref. 12) and BP (ref. 13). IOP variants, like *TMCO1* (ref. 14) and *CAV1* (ref.15) are also associated with POAG, and a multi-locus IOP genetic panel was associated with POAG (ref. 16) Nevertheless,

more data regarding IOP genetic variants in relation to POAG subtypes defined by IOP at disease presentation is needed. Furthermore the relations between BP and IOP single nucleotide polymorphisms (SNPs) and between BP and POAG SNPs are not known. The International Glaucoma Genetics Consortium (IGGC), the International Consortium of Blood Pressure (ICBP), and the National Eye Institute Glaucoma Human Genetics Collaboration Heritable Overall Operational Database (NEIGHBORHOOD) contain genome-wide data for IOP, BP traits and POAG, respectively. We use these datasets to explore genetic correlations focusing first on genome-wide significant loci (those with p-value for association $<5\times10^{-8}$) for IOP and BP in relation to POAG. Second, we examined the co-heritability between IOP BP traits, and POAG across the genome using linkage disequilibrium (LD) score regression.[17-19] Finally, we compared our genome-wide estimate of heritability between IOP and BP to an estimate based solely on direct measures of these traits and pedigree information in the Erasmus Rucphen Family (ERF) study.

Methods

The NEIGHBORHOOD: A Genome-Wide Association Meta-analysis for POAG

The NEIGHBORHOOD dataset included 37 333 participants of European ancestry (3 853 cases and 33 480 controls) enrolled as part of 8 independent studies from the United States for a genome-wide meta-analysis of POAG. Additional details regarding the cohort composition and analyses performed are described in the original paper.[20] All participants had genome-wide genotype data (each contributing dataset underwent site-specific genotyping, quality control and imputation of untyped variants using the 1000 Genomes Project reference panel[21]) and POAG phenotype data. Sample and genotype call rate was ≥95% for each site, and variants with minor allele frequencies (MAF) <5% or imputation

quality scores <0.7 were removed. For each study, logistic regression for POAG overall, as well as high tension glaucoma (HTG) and normal tension glaucoma (NTG) subtypes, adjusted for age, sex, nominally significant principal components of genotype and study-specific covariates was performed. The HTG and NTG subtypes were defined by maximum known IOP ≥ 22 mm Hg and < 22 mm Hg, respectively. Finally, meta-analysis study-specific results were performed using the inverse variance–weighted method and p-values were corrected using genomic control.[22]

The IGGC and ICBP: Genome-Wide Association Studies for IOP and BP

Briefly, the IGGC performed a GWAS for IOP that included 35,296 multi-ancestry participants from 18 studies;[12] 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.[13] Participants from both consortia had genome-wide data for approximately 2.5 million genotyped or imputed SNPs (**Supplementary Table 1**).

The Erasmus Rucphen Family study: a pedigree with IOP and BP data

The ERF study is an independent family-based cohort containing 2 519 participants with simultaneous IOP and BP measurements.[23] Details regarding the ERF and how IOP and BP were measured are available in the **Supplemental 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.[24,25] The genetic correlation

between IOP and BP estimated solely from kinship was compared to genome-wide

measures of genetic correlation for these traits as described below.

Genetic Risk Score Analyses

For each IOP and DBP locus with MAF >0.05 reported to have at least one genome-wide significant (i.e., $p<5\times10^{-8}$) associated SNP in the IGGC and ICBP respectively, we selected the most significant variant based on it's 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).[7,26] We evaluated the effect of IOP and DBP genome-wide significant SNPs in relation to POAG, HTG and NTG in the NEIGHBORHOOD using GRS's that aligned alleles associated with increasing IOP and decreasing DBP. GRS's 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[27], 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 $\boldsymbol{\beta} = \left(\beta_{G_1}, \beta_{G_2}, \dots \beta_{G_m}\right)$ represents the reported effect of the m selected SNP and $\boldsymbol{\sigma_\beta^2} = \left(\sigma_{\beta_{G_1}}^2, \sigma_{\beta_{G_2}}^2, \dots \sigma_{\beta_{G_m}}^2\right)$ represents the variance of each estimate, under the assumption of independence between the SNPs, χ_{GRS}^2, the chi-squared for the GRS effect on POAG over all SNPs G_i, $i = 1\dots m$, can be derived as:

$$\chi_{GRS}^2 = \frac{\left(\sum_m \frac{w_i \times \beta_{G_i}}{\sigma_{\beta_{G_i}}^2}\right)^2}{\sum_m \frac{w_i^2}{\sigma_{\beta_{G_i}}^2}}$$

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, since it is difficult to define homogenous weight between the IGGC 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, mean arterial pressure (MAP) and pulse pressure (PP)) 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 $z_{1j}z_{2j}$ for a SNP j equals (ref 17):

$$\mathbb{E}[z_{1j}z_{2j}] = \frac{\sqrt{N_1 N_2}\rho_g}{M}l_j + \frac{\rho N_s}{\sqrt{N_1 N_2}}$$

where ρ_g is the genetic covariance, M is the number of SNPs analyzed, N_1, N_2 and N_s are the sample size for phenotype 1, phenotype 2, and the overlapping sample size, respectively; and ρ, is the correlation between the two phenotypes. Finally, l_j, the LD score of a variant j is the sum of r_{kj}^2, the squared correlation between the SNP j and all SNPs $k = 1 \dots M$, and is expressed as $\sum_k r_{kj}^2$. It follows that the genetic correlation, the parameter of interest, can be estimated using the slope from the regression of $z_{1j}z_{2j}$ 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 ~1.2M common SNPs from the HapMap 3 panel, as these variants have r^2 for imputation > 0.9 in most studies. Moreover, LD Score of these variants, derived using a European ancestry panel, was readily available as part of the LD Score software. Finally, for binary traits the LD score estimates are based on a liability threshold model (LTM) (ref. 19). In brief, the LTM assumes binary traits are determined by an unobserved normally distributed liability. Individuals whose liability is above a given threshold τ are cases while others are controls. For a population prevalence K, the threshold τ can be derived as $\tau = \text{CDF}^{-1}(1 - K)$, where CDF is the standard normal cumulative distribution function. Hence, this derivation requires the population and sample prevalence of the disease. In this analysis, we assumed that the population prevalence of POAG, HTG and NTG equaled 0.01, 0.007 and 0.003, respectively based on the Rotterdam Study,[28] which consist of European derived Caucasians.

The LD score regression also allows estimating h_g^2, the genome-wide heritability explained by common variants. However this estimate might be biased downward when genomic control (GC) correction has been applied to the summary GWAS statistics. As non-GC corrected GWAS was available for POAG and IOP phenotypes, we used these data to estimate h_g^2. In brief the LD score has a linear relationship with SNP χ_j^2, with a slope proportional to heritability:

$$\text{E}[\chi_j^2] \sim \frac{Nh_g^2}{M} l_j + Na + 1$$

where N and M are the study sample size and the number of SNPs analyzed and a measures the contribution of confounding biases, such as cryptic relatedness and population stratification. As for the genetic correlation analyses, estimates of heritability were derived using only the ~1.2M 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 (www.neibank.nei.nih.gov). For each tissue selected, we included genes matching a known gene in the UCSC database with a clone count ≥1. The tissue included "ciliary" (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 (552 genes), retina pericyte (574 genes), retinal pigment epithelium - choroid (1,146 genes) and trabecular meshwork (394 genes). Since a prior report found no relation between hearing loss and POAG (ref. 29) we included the cochlea as a reference tissue (1797 genes). Using this information we constructed tissue-specific annotation where each SNP within 50kb of the start and end site of the selected genes defined a category. We estimated the proportion of heritability explained by each category using the following formula, as implemented in the LD score software:

$$E[\chi_j^2] \sim N \sum_C \tau_C l_{j,C} + Na + 1$$

where C indexes categories and τ_C represents the per-SNP contribution to heritability of category C, referred further as the heritability coefficient. As recommended,[19] we also

included for each analysis a set of 53 (overlapping) baseline annotation regions including a range of functional categories (e.g. coding, UTR, promoter and intronic regions, etc.) that allow for more accurate estimation of enrichment.

In practice we performed a single analysis including all tissue-specific and baseline annotation regions, thus estimating all τ_C jointly. For each category, we reported the fold-enrichment, i.e., the ratio of the proportion of total heritability explained to the proportion of SNPs falling into that category, and its associated *p*-value. We also report the significance of each τ_C separately. While the enrichment estimates and its *p*-value allow for inferences to be made on the contribution of these variants to the heritability for each category, the later *p*-value addresses the question of whether the category contributes to the outcome after accounting for other functional categories.

Data access URL:

http://jass.pasteur.fr/RawData.html

Results
IOP and BP Genome-Wide Significant Variants in Relation to POAG
Five of 8 genome-wide significant IOP SNPs showed nominally significant positive association with the glaucoma phenotypes (POAG, HTG and NTG) in NEIGHBORHOOD (**Figure 1 and Supplemental Table 2**). The strongest association was observed for hg19 chr1:g:165718979C>A (*TMCO1*; p=5.9x10^{-13}, p=1.3x10^{-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=4.76x10^{-4}).

Five out of the 27 genome-wide DBP SNPs showed nominal significance with at least one glaucoma phenotype but the direction of effects were inconsistent (**Figure 1** and

Supplementary Table 2) in NEIGHBORHOOD. Specifically, 3 DBP SNPs (in *SLC39A8, MTHFR-NPPB and TBX5-TBX3*) were positively related with at least one glaucoma trait while 2 DBP SNPs (in *SH2B3* and *FURIN-FES*) were negatively related with glaucoma traits. None of these associations remain significant after Bonferroni correction with the exception of rs3184504 (*SH2B3)*, which displayed strong negative associations with POAG and HTG (**Supplementary Table 2**; $p=6.2\times10^{-6}$ and $p=1.2\times10^{-4}$, respectively). Interestingly, the *SH2B3* locus is in high LD with hg19 chr12:g.111932800C>T (*ATXN2*, $r^2=0.90$ in CEU samples from the 1000 genomes project[21]), which was associated with POAG in a recent report.[20] Only 1 DBP SNP was nominally associated with IOP (*MOV10*, p=0.018, **Supplementary Table 3**).

The GRS of IOP-increasing SNPs showed strongly significant positive correlation with POAG and its subtypes (OR=1.18, $p=1.8\times10^{-27}$; OR=1.20, $p=1.1\times10^{-20}$; and OR=1.18; $p=6.2\times10^{-9}$, for POAG, HTG and NTG, respectively; **Table 1**). However there was no relation between the GRS for DBP-decreasing SNPs and POAG or its subtypes (p=0.93, p=0.97, and $p=0.96$, for POAG, HTG and NTG, respectively). The significance of the positive association between the GRS of OPP-lowering alleles (the combined effect of IOP-increasing alleles and DBP-lowering alleles) and the various glaucoma phenotypes (OR=1.04, $p=7.4\times10^{-7}$; OR=1.04, $p=1.6\times10^{-5}$; and OR=1.04, $P=6.1\times10^{-3}$ for POAG, HTG and NTG, respectively) was markedly attenuated when compared to the association between the GRS for IOP-increasing alleles and glaucoma phenotypes.

Genetic correlations and heritability between IOP, BP traits and Glaucoma Traits using data from the IGGC, ICBP and NEIGHBORHOOD

The genetic correlation between BP phenotypes using LD score regression was very high (e.g., the genetic correlation between DBP and SBP was 0.884, $p<10^{-300}$), in agreement with previous studies (**Table 2**) (ref. 30). IOP showed strong genetic correlation with POAG (0.485; SE = 0.110; p=2.1×10^{-5}) and HTG (0.548; SE = 0.116; p=9.6×10^{-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≥0.32). We also reported estimates of h_g^2 for our glaucoma phenotypes explained by common SNPs. Applying the LD score regression we obtained h_g^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_g^2 estimates (e.g., h_g^2 increased from 0.102 to 0.122 for POAG).

Since 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 NEIGBORHOOD and IGGC

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% to 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^{-9}; **Table 1**). Overall, significant variants from this analysis were already known to be associated with POAG phenotypes. chr7:g.116150095C>A (*CAV1/CAV2* intergenic region) is a known POAG SNP (ref. 15); chr1:g.165718979C>A (*TMCO1)*, chr17:g.10031183A>G (*GAS7)*, and chr9:g.107695848G>A (*ABCA1)* were identified by the NEIGHBORHOOD GWAS (ref. 20) ; and chr3:g.171992387G>A (*FNDC3B)* 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.

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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 relation 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 (ref. 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**), but between IOP and BP parameters, (≤ 0.005; p$\geq$0.58; **Table 2**) or between BP parameters and POAG (≤ 0.023; p$\geq$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 $\pm$ 0.16; p=9.6×10^{-4} **Table 2**). Conversely, while 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 $\pm$ 0.20; 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 heritably between NTG and HTG (0.24 $\pm$ 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 in relation to POAG.[36] In fact, in the Rotterdam Study, the relation between OPP and incident open-angle glaucoma was null when adjustment for baseline IOP was made.[37] Our agnostic genomic approach is consistent with epidemiologic data suggesting that IOP is more important than BP in predicting POAG risk across a range of presenting IOPs. Epidemiological research is clear that there is a modest positive relation between BP and IOP (ref. 4) but our data suggests 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 ($h^2 = 0.11$) (ref. 38) but lower than a contemporary estimate using GWAS data ($h^2 = 0.42$) (ref. 39). 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 (1 105) was considerably less than in our dataset (3 853). On the other hand, IOP has a reported heritability of 0.56 (ref. 40) 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,[41] season of year,[42] central corneal thickness (CCT) (ref. 43), variation in IOP measurement methodology[44] and other factors. CCT, a highly heritable trait ($h^2 = 0.95$) (ref. 45), was collected in IGGC but there is no agreed upon algorithm to adjust IOP based upon the CCT.[46] 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 while 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 datasets 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 genomic control correction,[17] 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 datasets 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.

Web Resources:
The LD-score regression analyses were performed using the implementation of the LD score method provided at: https://github.com/bulik/ldsc.

Supplementary information is available at the EJHG website.

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Figure Legends

Figure 1: Association of Intraocular Pressure and Diastolic Blood Pressure Gene Variants with primary open-angle glaucoma (POAG; n=3 853 cases) and the high-tension glaucoma (HTG; n=1 774 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**.

Figure 2: Heritability enrichment of selected glaucoma-related traits in various ocular tissues and the cochlea in NEIHBORHOOD and the International Glaucoma Genetics Consortium

See text for how tissue-specific SNP sets were assembled. Tissue categories with percent available GWAS SNPs are represented on the vertical axis. Heritability enrichment (E) estimates are presented on the horizontal axis along with tissue-specific heritability p-values.   These p-values, as opposed to the E p-values, are provided here because they represent a more conservative estimate of significance that simultaneously accounts for all tissue categories. E estimates for IOP are derived from the IGGC while similar estimates for HTG and NTG are from the NEIHBORHOOD. For a complete list of tissue-specific E values, E p-values and tissue specific heritability p-values for all glaucoma traits, see **Supplementary Table 5.** NB: Ciliary refers to ciliary body. RPE=retinal pigment epithelium. IOP=intraocular pressure, HTG=high-tension glaucoma, NTG=normal tension glaucoma.