Correlations between intraocular pressure, blood pressure and primary open-angle glaucoma common genetic variants: a multi-cohort analysis

Supplementary data

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Supplementary Note

LD score estimation

Estimates of heritability and co-heritability derived by the LD score regression method should be taken with caution as it is sensitive to genomic control (GC)[1] correction applied on the GWAS summary statistics.[2] Indeed, for blood pressure phenotypes, which underwent double GC correction, estimates of heritability were substantially lower than those reported by twin studies.[3] For example h^2 for DBP was 0.109 (SD=0.0102), while the consensus value from the literature is 0.3–0.5.[4] This specific estimate is even smaller than the 0.24 value reported in studies using raw genetic data but also focusing on common variants.[5] While difference between the later estimates and twin studies corresponds to the so-called missing heritability,[6] the additional gap with the LD score estimate likely reflects an underestimation due to the application of genomic control to the GWAS. However, note that while this might slightly impact genetic correlation between POAG and DBP, this should not impact heritability estimates of glaucoma phenotypes (POAG, HTG and NTG) and IOP, which were performed on non-GC corrected summary statistics.

The Erasmus Rucphen Family (ERF) Study

The Erasmus Rucphen Family (ERF) Study is a family-based study in a genetically isolated population in the Southwest of the Netherlands and is being studied for various traits,[7] including glaucoma.[8] This young, genetic isolate is characterized by minimal immigration and high inbreeding due to social and religious reasons. Participants of the ERF study are descendants of 20 couples who have lived in this area since the second half of the 19th century. These 20 couples are related through previous generations and had at least 6 children baptized in

the community church between 1880 and 1900. In total, over 3,000 participants were included with age varying between 18 and 86 years old. The cross-sectional examinations took place between 2002 and 2005, including a medical history, anthropometrical measurements, cardiovascular assessment, an ophthalmic examination, cognitive function and blood was drawn for DNA and clinical chemistry. IOP was measured twice per eye with Goldmann applanation tonometry (Haag-Streit, Bern, Switzerland). If the two measurements in one eye differed, a third measurement was performed, and the median value was recorded. Blood pressure was measured twicw on the right arm in a sitting position after at least 5 minutes of rest, using an automated device (OMRON 711, Omron Healthcare, Bannockburn, IL, USA). The average of these two measurements was used for analysis. The medical ethics committee of the Erasmus Medical Center (Rotterdam, The Netherlands) approved this study and written consent was obtained from all subjects. All investigations were carried out in accordance with the Declaration of Helsinki.

SOLAR analysis in ERF

To estimate the genetic correlation between BP traits (i.e. SBP, DBP, MAP and PP) and IOP we performed bivariate analyses implemented in SOLAR (Sequential Oligogenic Linkage Analysis Routines) version 6.6.2,[9] which performs genetic analyses for family-based data using variance components.[10] Bivariate analyses decompose phenotypic correlations (ρ_P) between two traits into genetic (ρ_G) and environmental (ρ_E) correlations accounting for kinship. By comparison of the log-likelihood of the model estimating ρ_G and a model in which ρ_G is constrained to zero, or to either 1 or −1, the significance of ρ_G was tested. The magnitude of ρ_G is a measurement of shared genetic variance between traits, in this case, IOP and BP traits. All the

analyses were adjusted for age and sex; participants with IOP or blood pressure lowering medication were set to "missing".

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Supplementary Table 1. Genome-Wide Association Study sample sizes for various traits of interest

	#SNPs	Cases	Controls	Sample size
POAG	6 425 680	3 853	33 480	37 333
HTG	6 351 916	1 774	33 480	35 254
NTG	6 270 260	725	33 480	34 205
IOP	2 440 635	-	-	27 558
DBP	2 673 125	-	-	69 899
SBP	2 650 286	-	-	69 909
MAP	2 585 157	-	-	29 182
PP	2 585 509	-	-	74 079

POAG=primary open-angle glaucoma; HTG=high tension glaucoma; NTG=normal tension glaucoma; DBP= diastolic blood pressure; SBP=systolic blood pressure; MAP=mean arterial blood pressure; PP= pulse pressure.

Details of phenotype definitions**,** genotyping panels and imputation methods may be found in the GWAS reports.[11-13]

Supplementary Table 2. p-values for association of intraocular pressure (upper 8-member panel) and diastolic blood pressure SNPs (lower 27-member panel) in relation to primary open angle glaucoma (POAG), high-tension glaucoma (HTG) and normal tension glaucoma (NTG) in the NEIGHBORHOOD study.

HGVS Names	Gene	Freq	Study	POAG	HTG	NTG
chr1:g.165718979C>A	*TMCO1*	0.87	IOP	**5.9×10^{-13}**	**1.3×10^{-12}**	0.065
chr3:g.171992387G>A	*FNDC3B*	0.16	IOP	**1.5×10^{-3}**	**0.0067**	0.055
chr7:g.116150095C>A	*CAV1*	0.29	IOP	**5.3×10^{-5}**	**0.010**	2.2×10^{-3}
chr9:g.107695848G>A	*ABCA1*	0.57	IOP	**1.2×10^{-7}**	**3.1×10^{-5}**	3.6×10^{-4}
chr9:g.136131415C>T	*ABO*	0.08	IOP	0.32	0.66	0.092
chr11:g.47468545C>T	*RAPSN*	0.71	IOP	**0.019**	**0.029**	0.10
chr11:g.48004369C>T	*PTPRJ*	0.14	IOP	0.41	0.17	0.78
chr17:g.10031183A>G	*GAS7*	0.65	IOP	**5.0×10^{-9}**	**3.0×10^{-7}**	**0.027**
chr15:g.75077367C>A						
chr12:g.111884608T>C	*CYP1A1–ULK3*	0.64	DBP	0.92	0.38	0.58
chr4:g.81164723C>T	*SH2B3*	0.48	DBP	**6.2×10^{-6}**	**1.2×10^{-4}**	0.11
chr20:g.57751117A>G	*FGF5*	0.28	DBP	0.69	0.62	0.19
chr1:g.11862778A>G	*GNAS–EDN3*	0.87	DBP	0.99	0.37	0.13
chr4:g.103188709C>T	*MTHFR–NPPB*	0.85	DBP	0.16	0.094	**0.044**
chr20:g.10969030A>G	*SLC39A8*	0.08	DBP	**0.023**	0.17	0.24
chr6:g.26091179C>G	*JAG1*	0.54	DBP	0.40	0.86	0.41
chr15:g.91437388A>T	*HFE*	0.86	DBP	0.72	0.35	1.00
chr11:g.100593538G>C	*FURIN–FES*	0.67	DBP	**0.016**	**0.0023**	0.82
chr10:g.18707448T>C	*FLJ32810–TMEM133*	0.71	DBP	0.53	0.44	0.57
chr12:g.90060586G>A	*CACNB2(39)*	0.65	DBP	0.87	0.90	0.16
chr17:g.47402807C>T	*ATP2B1*	0.17	DBP	0.68	0.81	0.49
chr3:g.41877414T>C	*ZNF652*	0.36	DBP	0.24	0.071	0.74
chr5:g.157845402C>T	*ULK4*	0.83	DBP	0.90	0.21	0.59
chr10:g.104846178T>C	*EBF1*	0.36	DBP	0.70	0.83	0.056
chr10:g.63467553G>C	*CYP17A1–NT5C2*	0.91	DBP	0.44	0.12	0.33
chr3:g.169100886T>C	*C10orf107*	0.17	DBP	0.32	0.62	0.05
chr5:g.32815028A>G	*MECOM*	0.48	DBP	0.43	0.38	0.95
chr6:g.31616366G>A	*NPR3–C5orf23*	0.4	DBP	0.93	0.15	0.41
chr4:g.156645513C>A	*BAT2–BAT5*	0.37	DBP	0.35	0.24	0.59
chr10:g.18419972G>C	*GUCY1A3–GUCY1B3*	0.24	DBP	0.47	0.96	0.75
chr11:g.16902268C>T	*CACNB2(59)*	0.43	DBP	0.64	0.86	0.99
chr12:g.115387796T>C	*PLEKHA7*	0.28	DBP	0.53	0.79	0.77
chr1:g.113216543A>G	*TBX5–TBX3*	0.7	DBP	0.080	**0.01**	0.57
chr3:g.27537909T>C	*MOV10*	0.25	DBP	0.18	0.83	0.21
chr11:g.10350538G>A	*SLC4A7*	0.78	DBP	0.33	0.07	0.84
chr1:g.165718979C>A	*ADM*	0.12	DBP	0.19	0.19	0.19

Freq = frequency of allele associated with higher intraocular pressure or lower diastolic blood pressure.
All information comes from genome build 19.

Supplementary Table 3. Association of diastolic blood pressure SNPs with intraocular pressure in the International Glaucoma Genetics Consortium.

rsid	beta	SD	P-value
rs17367504	-0.017	0.032	0.60
rs2932538	0.068	0.029	**0.018**
rs419076	0.000	0.024	1.00
rs13082711	-0.009	0.030	0.76
rs3774372	-0.013	0.032	0.68
rs13139571	0.026	0.028	0.36
rs1458038	0.011	0.026	0.68
rs13107325	-0.084	0.057	0.14
rs11953630	-0.009	0.026	0.73
rs1173771	-0.023	0.024	0.34
rs1799945	-0.012	0.038	0.75
rs805303	-0.028	0.025	0.26
rs11191548	-0.035	0.038	0.36
rs4373814	-0.020	0.024	0.40
rs1813353	0.037	0.026	0.16
rs4590817	0.008	0.037	0.82
rs7129220	-0.080	0.047	0.089
rs381815	0.004	0.028	0.88
rs633185	-0.029	0.026	0.26
rs3184504	-0.041	0.027	0.12
rs10850411	0.023	0.026	0.38
rs17249754	0.017	0.031	0.58
rs1378942	-0.039	0.026	0.14
rs2521501	0.038	0.031	0.22
rs12940887	-0.050	0.026	0.052
rs1327235	0.022	0.024	0.36
rs6015450	0.006	0.043	0.88

SD=standard deviation

Supplementary Table 4. Genetic correlation between IOP and BP traits estimated in the Erasmus Rucphen Family Study (n= 2 519)

	ρ_G	se	p-value
SBP	-0.042	0.106	0.69
DBP	-0.051	0.107	0.63
MAP	-0.042	0.108	0.70
PP	-0.025	0.126	0.84

ρ_G = genetic correlation; se= standard error; SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP= mean arterial pressure; PP=pulse pressure

NB: These data excluded patients using glaucoma or blood pressure medications as well as outliers with values ± 4 standard deviations from the mean

Supplementary Table 5. Partitioning of heritability for glaucoma traits using genomic data from the IGGC and NEIGHBORHOOD.

Cell line		Enrichment				Enrichment p-value				Coefficient p-value			
	% SNPs	*IOP*	*POAG*	*HTG*	*NTG*	*IOP*	*POAG*	*HTG*	*NTG*	*IOP*	*POAG*	*HTG*	*NTG*
CILIARY BODY	8.77%	2.04	1.95	2.20	2.75	**0.012**	0.072	**0.046**	0.15	0.88	0.56	0.65	0.25
COCHLEA	26.15%	1.86	1.48	1.31	1.14	**2.6×10^{-5}**	**0.019**	0.22	0.80	0.069	0.74	0.22	0.65
CORNEA	11.09%	2.15	1.54	1.87	1.78	**2.9×10^{-4}**	0.090	0.058	0.36	0.22	0.86	0.62	0.72
LENS	7.39%	2.20	1.73	2.23	2.13	**5.2×10^{-3}**	0.14	**0.021**	0.41	0.40	0.84	0.54	0.99
OPTIC NERVE	15.99%	1.77	1.20	1.51	1.19	**4.1×10^{-3}**	0.53	0.19	0.79	0.68	0.11	0.57	0.46
RETINA	22.58%	1.35	1.35	1.35	1.68	0.053	0.14	0.21	0.29	0.098	0.33	0.37	0.88
RETINA-PERICYTE	21.18%	1.61	1.80	1.67	1.77	**2.7×10^{-3}**	2.5×10^{-3}	0.034	0.26	0.92	0.075	0.67	0.79
RPE-CHOROID	30.90%	1.54	1.49	1.49	1.88	**3.5×10^{-4}**	0.010	0.029	0.086	0.51	0.87	0.92	0.17
TRABECULAR MESHWORK	15.70%	1.76	1.75	1.72	1.08	**2.3×10^{-3}**	**7.8×10^{-3}**	0.059	0.93	0.34	0.054	0.16	0.65

Abbreviations: IOP=intraocular pressure; POAG=primary open-angle glaucoma; HTG=high tension glaucoma; NTG=normal tension glaucoma; RPE=retinal pigment epithelium

Enrichment is defined as the tissue specific proportion of heritability divided by the available GWAS SNPs falling into the same tissue category. % SNPs refers to the representation of ocular tissue specific SNPs in the available GWAS. The enrichment p-value allows for inferences about the contributions tissue specific subset SNPs to heritability without accounting for other functional categories, while the coefficient p-value addresses the question of whether a category is still significant after accounting for the other functional categories. The most significant enrichment observed was for the contribution of trabecular meshwork genes to POAG (enrichment=1.75; enrichment p-value=7.8×10^{-3}; coefficient p-value=0.054).

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