Disentangling the genetic overlap and causal relationships between primary open-angle glaucoma, brain morphology and four major neurodegenerative disorders

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Summary

Background Primary open-angle glaucoma (POAG) is an optic neuropathy characterized by progressive degeneration of the optic nerve that leads to irreversible visual impairment. Multiple epidemiological studies suggest an association between POAG and major neurodegenerative disorders (Alzheimer's disease, amyotrophic lateral sclerosis, frontotemporal dementia, and Parkinson's disease). However, the nature of the overlap between neurodegenerative disorders, brain morphology and glaucoma remains inconclusive.

Method In this study, we performed a comprehensive assessment of the genetic and causal relationship between POAG and neurodegenerative disorders, leveraging genome-wide association data from studies of magnetic resonance imaging of the brain, POAG, and four major neurodegenerative disorders.

Findings This study found a genetic overlap and causal relationship between POAG and its related phenotypes (i.e., intraocular pressure and optic nerve morphology traits) and brain morphology in 19 regions. We also identified 11 loci with a significant local genetic correlation and a high probability of sharing the same causal variant between neurodegenerative disorders and POAG or its related phenotypes. Of interest, a region on chromosome 17 corresponding to *MAPT*, a well-known risk locus for Alzheimer's and Parkinson's disease, was shared between POAG, optic nerve degeneration traits, and Alzheimer's and Parkinson's diseases. Despite these local genetic overlaps, we did not identify strong evidence of a causal association between these neurodegenerative disorders and glaucoma.

Interpretation Our findings indicate a distinctive and likely independent neurodegenerative process for POAG involving several brain regions although several POAG or optic nerve degeneration risk loci are shared with neurodegenerative disorders, consistent with a pleiotropic effect rather than a causal relationship between these traits.

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Research in context

Evidence before this study

We searched PubMed, ScienceDirect, Scopus, and Google Scholar up to July 12 of 2022 to identify published literature on the overlap between glaucoma and neurodegenerative conditions. The terms used for the search were ("primary open-angle glaucoma" or "Glaucoma" or "normal-tension glaucoma" or "high tension glaucoma" or "vertical cup-to-disc ratio" or "ganglion cell-inner plexiform layer" or "retinal nerve fiber layer" or "retina") AND ("neurodegeneration" or "cognitive decline" or "Parkinson*" or "Alzheimer*" or "amyotrophic*" or "dementia"), AND "brain morphology". We identified several epidemiological studies that suggested a potential risk of dementia in patients with glaucoma, where having glaucoma increases the risk of developing some specific types of dementia such as Alzheimer's disease. However, it was unclear from observational studies if the neurodegenerative disorders and glaucoma shared a causal association.

Added value of this study

Our study is a comprehensive assessment of the genetic and causal relationship between POAG, brain morphology, and major neurodegenerative disorders. The results of our study shed light on the neurodegenerative process of POAG linked to brain morphology by identifying several regions of the brain that causally affect the risk of POAG. This study also identified shared biological mechanisms including several regions of the genome that contribute to the risk of both glaucoma and other neurodegenerative conditions. Despite these shared biological mechanisms, this study did not identify a causal relationship between POAG and neurodegenerative diseases, suggesting that the previous observational studies that found an association were likely confounded.

Implications of all the available evidence

Our findings indicate that brain morphology in several regions causally influences the neurodegenerative process of POAG, providing further insights into the neuropathological etiology of the disease, and highlighting regions of the brain that could potentially serve as neuroimaging biomarkers of glaucoma. The shared risk loci identified in this study increase our understanding of the underlying shared molecular mechanisms, and provide avenues for development of common neuroprotective treatments for POAG and neurodegenerative diseases by targeting the loci that increase the risk of both conditions, or inform adverse effects of such treatments where a locus has an opposite direction of effect on these diseases.

Introduction

Primary open-angle glaucoma (POAG) is an optic neuropathy characterized by progressive degeneration of the optic nerve that leads to irreversible visual impairment.[1] Multiple epidemiological studies suggest an association between POAG and major neurodegenerative disorders, including conditions such as Alzheimer's disease (AD)[2] Parkinson's disease (PD),[3] amyotrophic lateral sclerosis (ALS)[4] and frontotemporal dementia (FTD).[5] However, the nature of the overlap between neurodegenerative disorders and glaucoma remains controversial; although some studies claimed an association between glaucoma and neurodegenerative disorders,[6–9] others identified no association.[10–12] Moreover, the findings vary across POAG subtypes; cognitive impairment was higher in normal-tension glaucoma (NTG), defined as POAG with normal intraocular pressure (IOP), compared with high-tension glaucoma (HTG), defined as POAG with an increased IOP.[13]

The progressive degeneration of the retinal ganglion cells in POAG is associated with IOP where an increase in the pressure in the eye damages the optic nerve.[14] Phenotypes that estimate neurodegenerative processes of the optic nerve, such as vertical cup-to-disc ratio (VCDR), and those that estimate the impact of neurodegeneration in the retina, such as measurements derived from optical coherence tomography (e.g., macular thickness (MT) and retinal nerve fiber layer (RNFL)), have been used as biomarkers of disease progression.[15–17] Several observational studies have suggested an association between these POAG-related phenotypes and neurodegenerative diseases. For example, an observational study in UK Biobank (UKBB) showed that a thinner RNFL is associated with cognitive decline.[15] However, confounding and reverse causation could bias observational studies and, hence, causality cannot be reliably inferred.

Magnetic Resonance Imaging (MRI) techniques that quantify the area, thickness and volume of the brain are used in the diagnosis of neurodegenerative disorders such as PD[18] and AD,[19] as morphological changes in the brain can delineate structural and functional alterations as a result of the neurodegenerative process.[20] As a neurodegenerative condition, POAG has been linked through MRI to the decrease of white matter and the visual cortex density,[21] as well as the reduction of cortical

thickness in the frontal pole and amygdala in observational studies.[22]

Although these findings suggest that there is a link between POAG, brain morphology, and neurodegenerative disorders, whether these relationships are causal and the degree of genetic overlap between these conditions remains unknown. Leveraging GWAS data from brain structure MRIs, POAG, its endophenotypes, and tension subtypes, and four major neurodegenerative disorders (AD, ALS, FTP, and PD), this study aimed to:

1) investigate the genetic overlap and infer causality between POAG, neurodegenerative disorders, and brain morphology,
2) identify morphological brain changes that may causally affect glaucoma, and
3) identify shared genetic mechanisms between glaucoma and neurodegenerative disorders.

Methods

We leveraged genome-wide association data from studies of MRI of the brain, POAG, and four major neurodegenerative disorders. While the majority of the data used in this study is publicly available, we believe that understanding the context of the cohorts mentioned in our study, from which the data is derived, is necessary for interpreting the results. Hence, we provide a general overview of the primary cohorts employed in this study, though it is important to note that each of these studies includes multiple cohorts, and detailed descriptions can be found in their respective publications.

Open-angle glaucoma and endophenotypes GWAS data

We used the summary statistics from a GWAS meta-analysis that include 34,179 POAG cases and 349,321 controls and a stratified meta-analysis on glaucoma tension subtype, with 3247 cases for NTG and 74,997 controls, and 5144 cases for HTG and 47,997 controls.[23] This study identified 127 genome-wide significant loci for POAG by combining GWAS data across ancestries and restricting glaucoma to POAG based on the ICD9/ICD10 criteria for most of the studies included in the meta-analysis. The only exception was the UK Biobank study, which included 7286 self-reported glaucoma cases.[23] A subset of the POAG GWAS based on individuals with European ancestry was used for analysis that required an LD estimate.

VCDR summary statistics were obtained from a GWAS of AI-graded VCDR in 282,100 images from UKBB and Canadian Longitudinal Study on Aging (CLSA).[24] Ganglion Cell-Inner Plexiform Layer (GCIPL) and macula-region Retinal Nerve Fiber Layer (mRNFL) summary statistics were obtained from a GWAS that identifies 46 loci associated with both phenotypes from 31,434 OCT images in UKBB.[25] IOP summary statistics were obtained from a GWAS of 126,069 participants of European descent from the UKBB and the International Glaucoma Genetics Consortium.[26] UKBB is a large prospective study that follows the health of approximately 500,000 participants aged between 40 and 69 years at baseline assessment in 2010.[27] CLSA is a longitudinal cohort study with 51,338 participants aged 45–85 years at enrollment. The baseline was completed in 2015, and participants are followed over a three-year period.

For macular thickness (MT), we performed a GWAS in the UKBB. Among the 409,694 UKBB participants of white European ancestry determined through genetic principal component analysis, we selected 29,880 individuals with the MT data available. We used BOLT-LMM v 2.3.3, a mixed-model association method,[28] to run the GWAS. We included sex, age, and 10 principal components as covariates in the model.

Neurodegenerative disorders summary statistics

We used GWAS summary statistics for four major neurodegenerative disorders: AD[29] from a GWAS meta-analysis of 78,709 cases and 565,403 controls, identifying 33 loci associated with AD. PD summary statistics included 55,306 cases and 1.4 million controls used to identify 37 associated loci.[30] ALS included 20,806 cases and 122,656 controls, which identified 15 risk loci,[31] and FTD included 2154 cases and 4308 controls, which identified three genome-wide significant loci.[32]

MRI summary statistics

GWAS summary statistics on derived brain morphology phenotypes processed through MRI were extracted from the Oxford Brain Imaging Genetic Server–BIG40 (accessible here https://open.win.ox.ac.uk/ukbiobank/big40/).[33] We used a total of 606 brain imaging-derived GWAS summary statistics; 164 GWAS summary statistics correspond to the T1 MRI method, 57 to the Subcortical Volumetric Segmentation (ASEG), 120 to the Subcortical Volumetric Sub-Segmentation and 265 to volume, area and mean thickness of Desikan-Killiany parcellation. We used T1, subcortical sub-segmentation and Desikan-Killiany parcellation as they are established and reliable techniques to measure the impact of neurodegenerative conditions on brain structure.

Genetic correlation

Genetic correlation between the brain imaging, neurodegenerative disorders and glaucoma-related phenotypes were assessed using Linkage Disequilibrium Score Regression (LD-Score regression; LDSC), a method that estimates the genetic correlation between phenotypes using GWAS summary statistics while accounting for confounding (e.g., sample overlap) and polygenicity,[34] using 1000 Human Genome Project reference panel. We used the package 'pheatmap' v

1.0.12 in R v 4.0.2 to visualize the genetic correlation between phenotypes. A k-means clustering algorithm implemented in pheatmap was used to identify clusters within the genetic correlations.

Multivariate analysis

We used genomic structural equation modelling implemented in the GenomicSEM package,[35] aiming to identify a shared genetic factor between neurodegenerative disorders (AD, ALS and PD) and POAG or its endophenotypes (VCDR, mRNFL, GCIPL and IOP). GenomicSEM is a multivariate method for the analysis of the joint genetic architecture of complex traits. We tested three different models and estimated the model fit using the maximum likelihood estimation in genomicSEM. The first model aimed to assess a common shared latent factor between POAG, or the main POAG-related phenotypes (VCDR and IOP) and the neurodegenerative disorders (AD, PD, and ALS). The second model was similar to the first model except that it also estimated the correlation between the residuals of the model by allowing a non-zero covariance between the residuals. The third model was used to assess the correlation of each independent neurodegenerative disease with POAG through a multiple regression model; models are shown in Supplementary Table S1. FTD was excluded from this analysis given a small sample size (N cases ~2 K).

Locus-specific analysis

We used the GWAS pairwise (GWAS-PW)[36] approach to identify shared causal risk loci between neurodegenerative disorders (AD, PD and ALS) and POAG or its endophenotypes. Regions of the genome with a posterior probability of association (PPA) over 0.5 for a shared causal variant were further assessed for local genetic correlation (see details below). GWAS-PW is a method that evaluates the genetic overlap over specific genomic regions by splitting the genome into 1703 segments and estimating the posterior probability of four different models: the region is unique to POAG, unique to a neurodegenerative disorder, shared with both with a common causal variant and shared with both without a common causal variant. To account for potential confounding due to sample overlap between GWASs, we used the correlation between effect sizes of single nucleotide polymorphisms (SNPs) on regions with a PPA <0.2, calculated in fGWAS,[37] as a proxy for sample overlap.

Regions of the genome that were selected as shared with a common causal variant through GWAS-PW were further assessed using Local Analysis of coVariant Annotation (LAVA), aiming to provide additional evidence supporting local genetic correlation and to show the direction of the association. LAVA is an integrated method for local correlation analysis and conditional genetic analysis.[38] For the regions with evidence of shared risk loci across multiple phenotypes, we used HyPrColoc, a deterministic Bayesian clustering algorithm that uses summary statistics to detect colocalization between multiple traits simultaneously[39].

Fine mapping

Regions of the genome that were consistently associated as sharing a causal variant in HyPrColoc were further assessed using expression quantitative trait loci (eQTL) in Summary-based Mendelian Randomization (SMR). In our implementation of SMR, we leveraged eQTL data from the mRNA levels analysis of 2765 individuals from the Consortium for the Architecture of Gene Expression (CAGE) with 36,778 transcript expression traits in peripheral blood,[40] and 449 individuals from the GTEx consortium with 7051 transcript expression traits in brain tissue.[41]

Mendelian randomization

We estimated the causal relationship between the above phenotypes using the GCTA-GSMR framework (also known as Generalized Summary-data-based Mendelian Randomization, GSMR) implemented through the GCTA v 1.91 software.[42] This method relies on only GWAS summary statistics for estimating MR effect sizes; however, it has the advantage of accounting for correlated SNP instruments through modelling of LD from a pre-specified reference panel and can statistically test for heterogenous SNP-outliers through the HEIDI-outlier test. To select independent instrumental variants, we use the following parameters: –clump-r2 0.001, –gwas-thresh 5e-8 and –clump kb 1000 –heidi-thresh 0.01.

As a sensitivity analysis, for significant MR results (the multiple-testing adjusted $p < 2.4e\text{-}5$; see details below) obtained from GSMR, we used the IVW MR method implemented in the 'TwoSampleMR' package v 0.5.5,[43] as IVW combines Wald estimates for each instrumental variable in a multiplicative random effect model, which creates an unbiased estimate even when few instrumental variables are present. We selected instrumental variables based on clumping using PLINK, with the same parameters used for GSMR: –clump-r2 0.001, –clump-p1 5e-8, –clump kb 1000. If the IVW estimate showed evidence for a nominal causal association, we further re-assessed the MR relationship using a series of alternative MR models, including MR-Egger, weighted-median, simple- and weighted-mode and the MR-PRESSO framework.[44] Multivariate mendelian randomization (MVMR) was used to evaluate blood pressure[45] and cerebrospinal fluid volume[33] as possible confounders of the association between POAG-related phenotypes and MRI measurements.

We used the Open Target Genetics platform (https://genetics.opentargets.org/) to query public GWAS databases for a collection of phenotypes associated with individual SNP instruments (used in our MR analysis) to

identify SNPs with potential pleiotropic effects. Open Target is an integrative platform that aggregates functional genomics and GWAS data to make a strong connection between associated loci and likely causal genes.[46] To leverage better statistical power for MR analyses performed using very few SNPs (n ≤ 2), we relaxed the clumping threshold in these MR experiments to the following parameters: r2 = 0.01 and p < 5e-6 to increase the number of SNPs instruments and repeated the analyses using alternative MR models. We calculated the proportion of phenotypic variance (PVE) explained by SNPs based on the formula below and used the traits where SNPs collectively explained at least 1% of the phenotypic variance. Here, beta refers to the estimated SNP effect obtained from GWAS, SE to standard error for beta estimates, MAF to minor allele frequency, and N to the sample size specific to each instrumental variant.

$$R^2 = \frac{2\beta^2 MAF(1-MAF)}{2\beta^2 MAF(1-MAF)+(SE(\beta))^2 2N\ MAF(1-MAF)}$$

Observational validation

We tested the phenotypic association between brain structural measurements based on MRI and the traits with robust MR results through linear regression, and logistic regression for binary outcomes, to validate the MR findings by providing phenotypic support for those associations in the UK Biobank. The phenotypic measurements used for IOP and MT were the average values between the left and right eye; IOP UKBB fields 5254 and 5254, MT fields 27,800 and 27,801. We extracted individuals with glaucoma using any of the following case definitions: 1) individuals with an ICD10 diagnosis of any type of glaucoma, 2) individuals who answered "glaucoma" to the question 'Has a doctor told you that you have any of the following problems with your eyes diagnosis?' 3) individuals who answered "glaucoma" to the question 'In the touch screen, you selected that you have been told by a doctor that you have other serious illnesses or disabilities, could you now tell me what they are? (non-cancer illness)'. As NTG status was not available in UKBB, we used a proxy trait where NTG was created as a subset of glaucoma cases with an IOP below 21 mmHg. Regression analyses were done only for 'trait-pairs' (eye-brain) regions that had robust MR findings (i.e., consistent evidence of association using alternative MR models). Importantly, self-reported sex was added as a covariate in the regression models to account for potential sex differences in brain morphology.

Multiple testing correction

Due to the high correlation between brain regions, we adopted a less conservative approach to prevent overcorrection in the event of multiple testing. We used matSpD,[47] a spectral decomposition method based on eigenvalues to estimate the number of independent tests. Based on the algorithm by Li and Ji (2005), incorporated in matSpD, we obtained 95 independent variables for 606 brain regions tested. Given that we used 11 glaucoma and neurodegenerative-related phenotypes, 95 independent variables for brain structure, and 2 methods (i.e. LDSC and GSMR), we set the adjusted p-value threshold for statistical significance to p < 2.4e-5 based on 0.05/(11 phenotypes x 95 independent variables x 2 methods).

Role of funders

The funders of the study did not have any involvement in the design of the study.

Results

This study aimed to evaluate the relationship between neurodegenerative conditions, POAG, and related phenotypes. Additionally, we assessed the brain morphometry associated with POAG. We employed LD score regression and Mendelian randomization frameworks to evaluate genetic correlation and causal relationships. The Mendelian randomization framework was further validated by observational analysis. Further, to identify specific loci shared between POAG and neurodegenerative conditions, we used a genetic colocalization framework (GWAS pairwise). We also used factor analysis to identify common latent factors between POAG and neurodegenerative diseases. Our study provides valuable insights into the potential shared genetic factors between POAG and neurodegenerative conditions, as well as the associated brain morphometry.

Genetic correlation

Brain regions and POAG phenotypes

Only two MRI phenotypes based on the T1 method had statistically significant genetic correlation with POAG phenotypes after multiple testing corrections. Frontal pole volume (rg = 0.2, se = 0.04, p = 1.9e-5 [LDSC]) and the total volume of gray matter (rg = 0.15, se = 0.03, p = 2.1e-5 [LDSC]) were genetically correlated with IOP. Several other brain structures, such as total brain volume and volume of white matter, showed genetic correlations at p < 0.05 with glaucoma endophenotypes (Supplementary Figures S1 and S2). However, none of these correlations reached the statistical significance threshold after correcting for multiple testing (p < 2.4e-5 [matSpD]).

Neurodegenerative disorders and POAG phenotypes

We identified a positive genetic correlation at nominal significance (p < 0.05) between neurodegenerative disorders and two glaucoma endophenotypes; AD was correlated with IOP (rg = 0.08, se = 0.04, p = 0.04

[LDSC]) and ALS with GCIPL (rg = 0.18, se = 0.09, p = 0.04 [LDSC]), as shown in Supplementary Table S2. However, we did not identify any significant genetic correlation between neurodegenerative disorders and POAG phenotypes after correction for multiple testing.

Shared risk loci between neurodegenerative disorders and POAG endophenotypes

K-means clustering

The genetic correlations between neurodegenerative disorders and POAG phenotypes were clustered into two major components based on the K-means clustering algorithm: 1) Eye pressure component with IOP, POAG, NTG, and HTG grouping together. 2) Neurodegenerative components with retinal structural-related phenotypes (i.e., VCDR, GCIPL, and mRNFL) and neurodegenerative disorders (AD, ALS, FTD, and PD) clustering together (Supplementary Figure S3).

Multivariate analysis

We performed three models (see the Methods section) to identify a common shared latent factor between POAG or related phenotypes and neurodegenerative diseases (AD, ALS and PD) using the genomic structural equation modelling implemented in the GenomicSEM package. The first model identified a common latent factor significantly loaded onto AD (r = 0.42, p = 0.03 [GenomicSEM]), ALS (r = 0.71, p = 0.03 [GenomicSEM]), and PD (r = 0.18, p = 0.03 [GenomicSEM]), but not POAG (r = –0.01, p > 0.05 [GenomicSEM]); complete results are shown in Supplementary Table S3. The results from the second model were similar when we allowed for correlation between the residuals of the model. The third model using multiple regression did not identify a significant correlation between POAG and each of the neurodegenerative diseases. These results indicate that there is no significant correlation between these traits averaged across the whole genome.

Locus-specific analysis

Results of GWAS-PW identified 36 regions of the genome that shared a common causal variant between POAG or POAG-related phenotypes and neurodegenerative diseases. Of these, we prioritized 11 regions that also had a statistically significant local genetic correlation in LAVA (Table 1). These loci showed different directions of association across traits; while some increased the risk of both neurodegenerative diseases and POAG or its endophenotypes, the others had an opposite direction of effect on these traits (Supplementary Table S4).

Interestingly, one region between 43,056,909 bp and 45,875,506 on chromosome 17 was consistently associated with a common causal variant between POAG-related phenotypes (GCIPL, IOP, and mRNFL) and neurodegenerative diseases (AD and PD). Further tests in this region using HyPrColoc showed a 0.56 probability of a shared causal variant (rs199449, closest gene *WNT3*) between AD, PD, IOP, GCIPL, and mRNFL in the *MAPT* region. Consistently, results from SMR based on peripheral blood eQTL data showed a significant causal association between multiple genes within the *MAPT* region (*APR2, ARL17B, C17orf69, DCAKD, DQ577523, ITGB3, LOC644297, LRRC37A4, MGC57346, NMT1, NSF*), and AD, PD, IOP, GCIPL, mRNFL, and POAG; as shown in Supplementary Table S5.

Mendelian randomisation

Brain regions and POAG phenotypes

The results from GSMR based on the T1 method showed 17 associations that were consistent with a causal relationship between brain volumes and glaucoma-related phenotypes, 26 based on ASEG and 30 based on Desikan-Killiany parcellation after correction for multiple testing (Supplementary Tables S6–S8). Most of the associations (64 out of 73) showed brain morphology as the causal factor for POAG or glaucoma-associated traits. The association of seven T1 volumes, four ASEG volumes, and nine Desikan-Killiany regions remained consistent with a causal relationship in the sensitivity analyses ($p < 0.05$) using IVW and other MR methods (Fig. 1 and Supplementary Table S9), with no evidence of reverse causality via bidirectional MR or horizontal pleiotropy (p value > 0.05 [Egger intercept]). Results from one T1 volume (Optic-chiasm) and two Desikan-Killany regions (right lateral orbitofrontal volume and right pericalcarine volume) remained consistent in IVW but inconsistent using other MR methods.

Of the 11 significant reverse associations (POAG phenotypes affecting brain regions), nine remained significant in sensitivity analyses: the effect of IOP on four brain volumes (left frontal pole, left frontal orbital cortex, left lateral orbitofrontal, and right lateral orbitofrontal) and two areas (right lateral orbitofrontal and right pars orbitalis), the effect of mRNFL on the left parahippocampal volume, and GCIPL on the volume of the optic-chiasm and right fimbria (Fig. 2). The effect of IOP in these associations remained consistent after accounting for blood pressure and cerebrospinal fluid volume in MVMR (Supplementary Table S10).

Neurodegenerative disorders and POAG phenotypes

We observed a nominally significant causal positive relationship between AD and POAG; results from the GSMR analysis are shown in Supplementary Table S11. AD was also found to have a nominally significant negative causal relationship with NTG, HTG, GCIPL, and mRNFL (Supplementary Table S11). None of these results remained significant after multiple testing corrections.

Overlap of causal brain regions between neurodegenerative conditions and POAG phenotypes

A higher risk of AD was causally associated with 17 brain structures, which remained significant after multiple

Trait 1	Trait 2	CHR	START (BP)	STOP (BP)	PPA	rg (LAVA)	p (LAVA)
POAG	PD	1	7,247,376	9,365,093	0.94	−0.35	0.013
mRNFL	AD	2	64,625,913	65,933,279	0.91	0.56	6.04E-04
mRNFL	AD	2	54,685,226	56,202,116	0.52	−0.94	0.033
POAG	PD	4	74,592,493	77,130,320	0.77	−0.46	1.14E-03
mRNFL	PD	12	182,451	1,080,007	0.8	0.75	6.05E-03
mRNFL	PD	12	46,024,786	47,714,786	0.69	0.58	0.022
POAG	AD	16	68,841,409	71,049,984	0.56	0.79	7.90E-04
mRNFL	PD	17	43,056,905	45,875,506	0.98	−0.91	1.21E-11
GCIPL	PD	17	43,056,905	45,875,506	0.95	−0.62	2.91E-08
IOP	PD	17	43,056,952	45,875,506	0.66	−0.38	3.56E-06
POAG	AD	17	43,056,952	45,875,506	0.57	−0.68	3.66E-04
POAG	AD	19	44,744,147	46,102,690	0.67	−0.91	4.81E-10
POAG	AD	19	46,102,801	47,148,853	0.87	−0.47	0.022
GCIPL	PD	21	41,389,527	43,321,426	0.99	0.51	2.58E-07

Table 1: **Shared regions between neurodegenerative disorders and POAG or POAG-related phenotypes (mRNFL, GCIPL and IOP), based on the GWAS-PW posterior probability of a shared region with a common causal variant (PPA) and local correlation using LAVA.**

testing corrections. Of these, only four subcortical brain regions (amygdala, right and left accumbens and a thalamic region known as PuA) overlapped with the causal brain regions for POAG and related phenotypes. Out of these four subcortical regions, only the amygdala showed significant association with VCDR that also survived the sensitivity tests (b = 0.02, se = 0.01 [IVW]). There was no evidence of reverse causality via bidirectional MR or heterogeneity (i^2 = 52.9, p > 0.05 [IVW]). However, given the null effect of AD on VCDR (beta = –0.001, se = 0.0009), a cascade effect (AD affecting the amygdala volume and the volume of the amygdala influencing VCDR) was ruled out. These results do not support strong evidence for overlap of the causally associated brain regions between AD and glaucoma traits.

Observational validation

The phenotypic associations supported all the causal associations obtained in the MR analyses, with the exception of four regions: the phenotypic association between MT and the volume of the optic chiasm, NTG and cerebrospinal fluid, glaucoma and middle temporal thickness, and pars opercularis; as shown in Supplementary Table S12.

Discussion

We identified 11 locally correlated loci between POAG-related phenotypes and neurodegenerative disorders and 19 brain regions causally associated with POAG and endophenotypes. Our findings highlighted a shared risk locus on chromosome 17, *MAPT*, between neurodegenerative disorders and almost all of the POAG endophenotypes.

The genetic overlap and causal relationship between brain morphology and POAG

Elevated IOP is known to be a major risk factor for glaucoma, while other related phenotypes such as mRNFL and GCIPL are used as biomarkers of the disease progression. Previous studies of structural brain alterations in POAG showed abnormalities in the frontal pole[22] and a reduced gray matter volume,[48] both of which have been previously linked to ocular hypertension.[49] Consistently, our results showed a significant genetic correlation between the frontal pole volume and the total volume of gray matter with IOP. Although this study did not investigate the underlying biological mechanisms, the relationship between IOP and brain structural measurements could be downstream of specific morphometric or pressure abnormalities in the brain (e.g., intracranial pressure) that are correlated with the vascular hypertension process in the eye. However, the association of IOP remained after we accounted for the possible confounders of the association between IOP and brain morphological measurements using intracranial pressure-related traits (i.e., blood pressure and cerebrospinal fluid volume). We should also note that several of the above associations showed a bidirectional relationship that did not survive the multiple testing threshold; thus, future studies with a larger sample size are necessary to clarify the biological nature of these associations.

Other glaucoma-related phenotypes, such as mRNFL and GCIPL, have been associated with brain alterations across the greater hippocampal region in elderly adults without dementia[50] and a reduced thickness in ganglion cell layer of the retina, which has been linked to brain lesions.[51] The results from our study confirmed a causal genetic relationship, supported by the MR analysis between mRNFL and the parahippocampal region and between GCIPL and the volume of two subcortical structures, the optic-chiasm and the right fimbria (a region of the hippocampus). These findings are in concordance with clinical studies that have shown a decrease in the functional connectivity of the visual

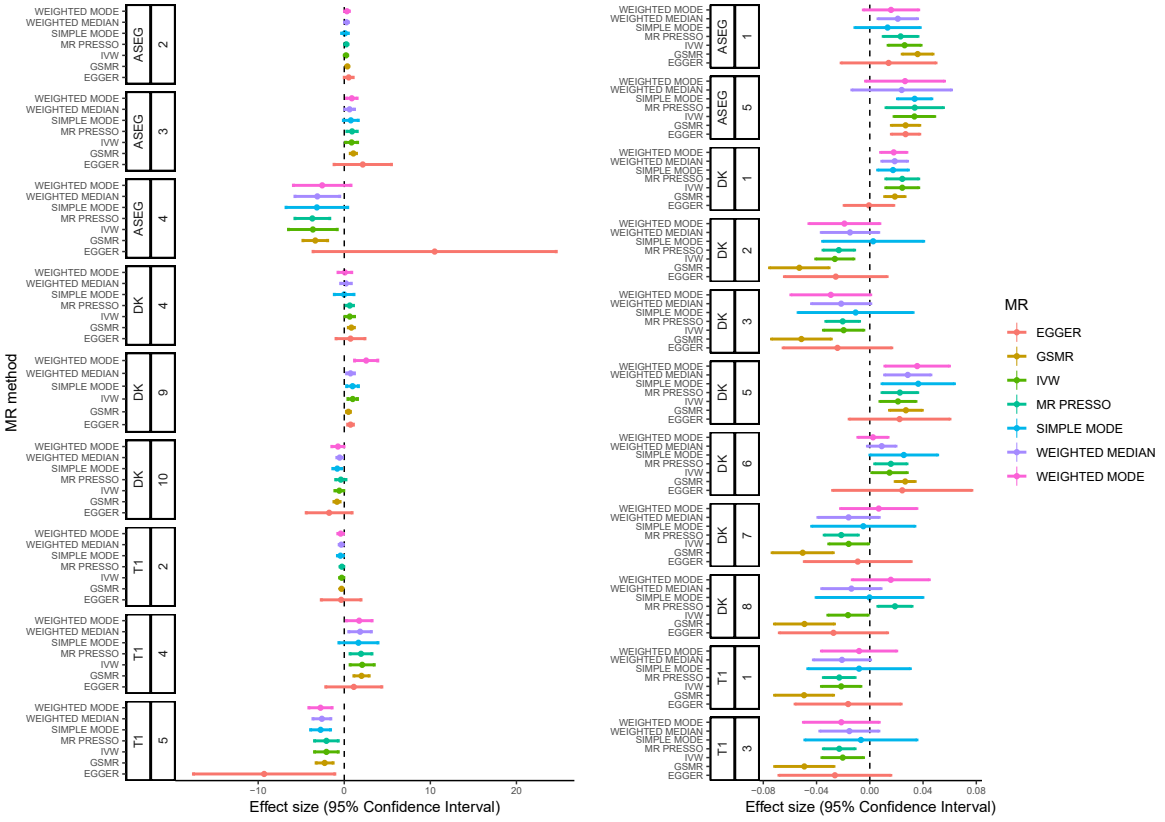

Fig. 1: Forest plot of Causal association between glaucoma endophenotypes and MRI structural brain measurements based on different MR methods. Estimated effects (beta) are presented as per unit change of the exposure with a 95% confidence interval; log (OR) for binary traits. DK–corresponds to the Desikan-Killiany parcellation method; DK-1) effect of the left supramarginal volume on the vertical cup to disc ratio (VCDR), DK-2) intraocular pressure (IOP) effect on the left lateral orbitofrontal volume, DK-3) intraocular pressure (IOP) effect on the right lateral orbitofrontal volume, DK-4) effect of the right pericalcarine volume on the ganglion cell-inner plexiform layer (GCIPL), DK-5) effect of the retinal nerve fiber layer (mRNFL) on the left parahippocampal volume, DK-6) effect of the left precuneus area on VCDR, DK-7) effect of IOP on the right lateral orbitofrontal area, DK-8) effect of IOP on the pars orbitalis area, DK-9) effect of the right middle temporal thickness on primary open-angle glaucoma (POAG), DK-10) effect of the right pars opercularis thickness on POAG. T1–corresponds to the T1 MRI method; T1-1) IOP effect on the volume of the left frontal pole, T1-2) effect of the volume of the left subcallosal cortex on IOP, T1-3) IOP effect on the volume of left frontal orbital cortex, T1-4) effect of the of the volume of the left I-IV cerebellum on macular thickness (MT), T1-5) effect of the volume of the right Heschl's gyrus on mRNFL. ASEG–corresponds to the ASEG method; ASEG-1) effect of GCIPL on the right fimbria, ASEG-2) effect of the volume of the right putamen on IOP, ASEG-3) effect of the volume of cerebrospinal fluid on normal-tension glaucoma (NTG), ASEG-4) effect of the volume of the optic-chiasm on MT, ASEG-5) effect of GCIPL on the volume of the optic-chiasm.

cortex, which encompasses the middle temporal,[52] and structural brain abnormalities in the supramarginal gyrus[53] in patients with POAG. Our findings support a distinctive and causal neurodegenerative process in glaucoma that involves morphological brain changes that lead to the decrease of retinal ganglion cells and retinal nerve fibers.

Morphological brain changes that causally affect both neurodegenerative disorders and glaucoma

We did not identify strong evidence of a causal overlap between neurodegenerative disorders and POAG that involves common brain morphology. However, through MR analysis we identified that AD causes a smaller volume of the amygdala and a smaller amygdala causes increased VCDR, although we ruled out the same causal pathway between these traits given that we did not identify a causal relationship between AD and VCDR. Nonetheless, some clinical studies have shown evidence of an association between the amygdala and retinal structural measurements.[54] Given that the causal (MR) association between AD and the amygdala is broadly consistent with previous studies,[55–57] the most plausible explanation is that the causal association of the amygdala on VCDR might be mediated through a separate causal pathway (independent of its effect on AD).

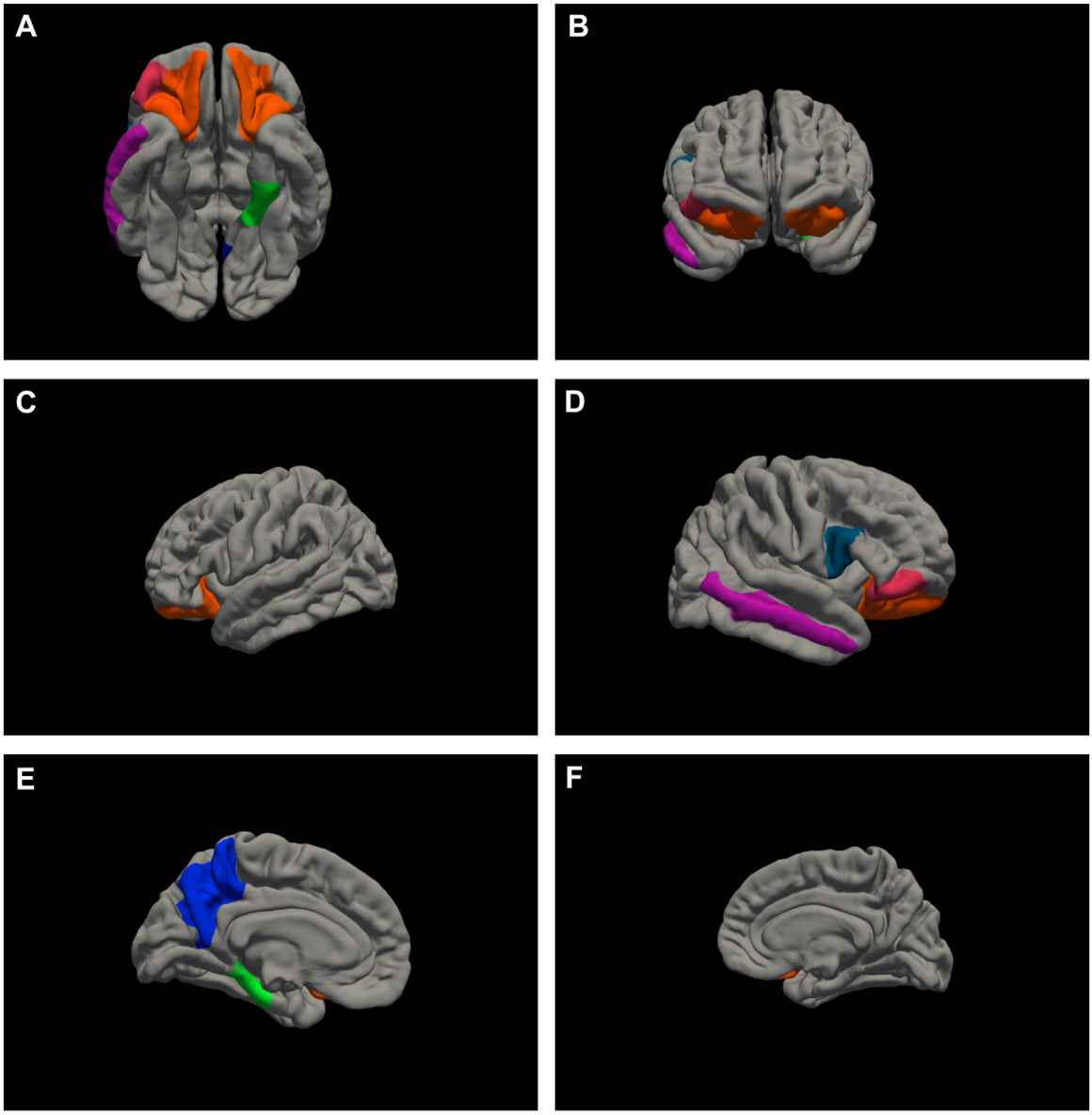

Fig. 2: Cortical brain regions associated with primary open angle glaucoma or glaucoma endophenotypes, based on the Desikan Killiany atlas. Lateral orbitofrontal region is highlighted in orange, parahippocampal in green, precuneus in blue, pars orbitalis in pink, middle temporal gyrus in purple, and pars opercularis in indigo blue. A) ventral image of the brain, B) frontal image of the brain, C) lateral image of the left hemispherium, D) lateral image of the right hemispherium, E) internal image of the right hemispherium, F) internal image of the left hemispherium.

Shared genetic mechanisms between glaucoma and neurodegenerative disorders

There was limited evidence of a causal association between POAG-related phenotypes and neurodegenerative disorders, suggesting that the overall nature of the overlap between neurodegenerative disorders and glaucoma is likely pleiotropic. However, we observed nominal causal associations between AD and GCIPL/mRNFL, consistent with previous observational studies that have found an association between retinal morphology and cognitive decline.[15,58] Hence, we cannot rule out a small to modest causal relationship between AD and GCIPL/mRNFL. Further studies with larger sample sizes are required to confirm such a causal relationship.

Colocalization analysis identified several shared risk loci between neurodegenerative disorders and glaucoma and related traits. Of interest, the region containing the microtubule-associated protein tau (*MAPT*) was causally associated with POAG, related phenotypes and

neurodegenerative disorders. *WNT3* in this region is the closest gene to the most likely causal variant, which has been previously associated with cognitive performance[59] and PD[30] through GWAS studies and as an inhibitor of the glucocorticoid receptor (GR) in mice.[60] *WNT3* is reported to be associated with AD,[61] PD[62] and glaucoma.[63] *WNT3* as an antagonist of the GR receptor is likely denoting a shared biological mechanism between neurodegenerative diseases that is likely linked to the vascular and inflammatory processes of glaucoma. However, the results based on the SMR analysis pointed to multiple genes within the *MAPT* region that are likely causally associated with both POAG and neurodegenerative traits; *WNT3* was not present in the peripheral blood eQTL data, therefore we could not narrow down to the most likely causal gene based on our available data.

Final remarks

This study has some limitations that should be acknowledged. First, given the extensive multiple testing performed, we had limited statistical power to identify genetic and causal associations. Thus, a non-significant association in our study does not necessarily warrant a lack of association. Additionally, given that we did not have access to individual-level data, we could not analyze age or sex as specific factors in our study design. Moreover, most of the GWAS data available for this study were driven by individuals with European ancestry, making it necessary to explore other ethnic groups to investigate whether our findings replicate in more diverse ancestries. We also acknowledge that replication of our results in an independent cohort is essential to confirm the validity of our findings. While we performed several analyses to ensure the robustness and consistency of our results, including sensitivity analyses using various MR approaches and support from phenotypic association, further validation in other populations and cohorts is needed. Therefore, future studies should investigate the identified genetic loci in other populations and cohorts to confirm and extend our findings.

To our knowledge, this study comprehensively examined the genetic overlap between glaucoma, brain morphology and neurodegenerative diseases. We presented compelling evidence of shared genetic association for several loci such as the *MAPT* on chromosome 17 as common causal loci between neurodegenerative disorders and POAG-related traits. In addition, our study identified 19 brain regions causally associated with POAG and endophenotypes. Further interrogation of these loci and brain structures will continue to unveil the mechanisms involved in the neurodegenerative process of glaucoma and help in the development of focal neuroprotective treatments.

Contributors

S.D.T wrote the manuscript, performed all the data analysis, and participated in study design. W.H performed GWAS analysis for macular thickness. W.H, J.T, S.S, S.M, C.H, P.H, L.P, A.K, A.H, J.C, D.M, J.W, C.V.D, M.K.L, J.S.O, S.M and P.G revised the manuscript and contributed to the study design. P.G supervised the study, revised the manuscript, and provided guidance during the whole project. S.D.T and P.G accessed and verified the underlying data reported in this manuscript. All authors have read and approved the final version of the manuscript.

Data sharing statement

The summary statistics of POAG and related phenotypes obtained from GWAS are publicly available and can be accessed through the original publications mentioned in our manuscript. Additionally, the GWAS for neurodegenerative disorders are also publicly available, and a reference for each of the publications is provided in our manuscript. The brain morphology phenotypes obtained through MRI were extracted from the Oxford Brain Imaging Genetic Server–BIG40, which can be accessed at https://open.win.ox.ac.uk/ukbiobank/big40/. The UK Biobank data can be obtained through the UK Biobank Access Management System, which is available at https://www.ukbiobank.ac.uk/. The GTEx expression data for peripheral blood and brain tissue can be accessed through the GTEx PORTAL at https://gtexportal.org/home/.

Declaration of interests

J.W. is a consultant for Allergan, Editas, Maze, Regenxbio and has received sponsored research support from Aerpio Pharmaceuticals Inc. L.R.P. is a consultant for Eyenovia, Twenty, and CharacterBio. A.P.K. is a consultant to Aerie, Allergan, Google Health, Novartis, Reichert, Santen and Thea. S.M. hold stock at Seonix Bio Ltd. S.D.T is supported by the QIMR Statistical Genetics PhD scholarship. All remaining authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ebiom.2023.104615.

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