Diaz-Torres *et al. Acta Neuropathologica Communications* (2024) 12:130
https://doi.org/10.1186/s40478-024-01841-9

Acta Neuropathologica Communications

RESEARCH Open Access

Macular structural integrity estimates are associated with Parkinson's disease genetic risk

Santiago Diaz-Torres[1,2], Samantha Sze-Yee Lee[3], Natalia S. Ogonowski[1,2], David A. Mackey[3], Stuart MacGregor[1,2], Puya Gharahkhani[1,2,4*†] and Miguel E. Renteria[1,2,4*†]

Abstract

Background Optical coherence tomography (OCT) is a non-invasive technique to measure retinal layer thickness, providing insights into retinal ganglion cell integrity. Studies have shown reduced retinal nerve fibre layer (RNFL) and ganglion cell inner plexiform layer (GCIPL) thickness in Parkinson's disease (PD) patients. However, it is unclear if there is a common genetic overlap between the macula and peripapillary estimates with PD and if the genetic risk of PD is associated with changes in ganglion cell integrity estimates in young adults.

Method Western Australian young adults underwent OCT imaging. Their pRNFL, GCIPL, and overall retinal thicknesses were recorded, as well as their longitudinal changes between ages 20 and 28. Polygenic risk scores (PRS) were estimated for each participant based on genome-wide summary data from the largest PD genome-wide association study conducted to date. We further evaluated whether PD PRS was associated with changes in thickness at a younger age. To evaluate the overlap between retinal integrity estimates and PD, we annotated and prioritised genes using mBAT-combo and performed colocalisation through the GWAS pairwise method and HyPrColoc. We used a multi-omic approach and single-cell expression data of the retina and brain through a Mendelian randomisation framework to evaluate the most likely causal genes. Genes prioritised were analysed for missense variants that could have a pathogenic effect using AlphaMissense.

Results We found a significant association between the Parkinson's disease polygenic risk score (PD PRS) and changes in retinal thickness in the macula of young adults assessed at 20 and 28 years of age. Gene-based analysis identified 27 genes common to PD and retinal integrity, with a notable region on chromosome 17. Expression analyses highlighted *NSF*, *CRHR1*, and *KANSL1* as potential causal genes shared between PD and ganglion cell integrity measures. *CRHR1* showed consistent results across multiple omics levels.

†Puya Gharahkhani and Miguel E. Renteria jointly supervised this study.

*Correspondence:
Puya Gharahkhani
puya.gharahkhani@qimrberghofer.edu.au
Miguel E. Renteria
miguel.renteria@qimrberghofer.edu.au

Full list of author information is available at the end of the article

Interpretation Our findings suggest that retinal measurements, particularly in young adults, could be a potential marker for PD risk, indicating a genetic overlap between retinal structural integrity and PD. The study highlights specific genes and loci, mainly on chromosome 17, as potential shared etiological factors for PD and retinal changes. Our results highlight the importance of further longitudinal studies to validate retinal structural metrics as early indicators of PD predisposition.

Keywords Parkinson's disease, Retina, Ganglion cell, Genetics, *NSF*, *CRHR1*, *KANSL1*

Introduction

Parkinson's disease (PD) is a chronic and progressive neurodegenerative disorder that affects 1% of the population over 60 years [1]. Motor symptoms, such as tremors, rigidity, and bradykinesia, traditionally characterise PD. However, non-motor symptoms are also manifested in the disease. Among these, ocular changes have gained attention as potential early indicators of PD [2, 3] and its progression [4].

The retina is an extension of the central nervous system and offers a unique and accessible window to understand neurodegenerative processes. Retinal ganglion cells (RGC), a type of neuron located near the inner surface of the eye's retina, play a crucial role in transmitting visual information from the retina to the brain. RGC atrophy and the associated thinning of retinal layers have been previously observed in prospective and cross-sectional studies for PD [5]. Recent studies have suggested that individuals with PD exhibit reductions in the retinal nerve fibre layer (RNFL) [6] and the ganglion cell inner plexiform layer (GCIPL) [7] thicknesses, as quantified using optical coherence tomography (OCT) imaging. Such findings highlight retinal structural integrity as a potential marker for PD. However, the molecular and genetic mechanisms driving the atrophy of RGC in PD are still unclear.

In addition to clinical observations, genetics could provide insights into PD aetiology. Genome-wide association studies (GWAS) have identified multiple loci associated with an increased risk of PD [8] and retinal ganglion cell measures [9]. Combining genetic association studies and OCT estimates, our study aimed to investigate whether genetic predispositions to PD, as captured by polygenic risk scores (PRS), are associated with cross-sectional and longitudinal structural retinal estimates in young adults. We further used a colocalisation approach to assess the overlap between macular GCIPL and RNFL with PD and to evaluate overlapping genes and common biological pathways associated with retinal neurodegeneration in PD using bulk and single-cell gene expression data.

Methods

Raine cohort dataset

This analysis utilised data from the Generation 2 (Gen2) participants of the Raine Study, a longitudinal health study that has been following the Gen2 cohort since their prenatal stages in 1989–1991 [10, 11]. Between 2010 and 2012, when participants were approximately 20 years old, they underwent a baseline eye examination. A follow-up examination occurred in 2018–2020 when the participants were around 28 [12]. Before each eye examination, participants received a detailed explanation of the procedure and provided informed written consent. Blood samples were obtained from participants when they were aged 14 or 17. Samples were analysed in 2010 for 1,592 participants using the Infinium HD Human660W-Quad Beadchip Array, and those from an additional 310 participants were analysed in 2013 using the Infinium OmniExpress-24 BeadChip Array, for a total of 1,902 participants.

Retinal integrity estimates

Participants underwent Spectral Domain OCT imaging (SD-OCT; Spectralis HRA+OCT, Heidelberg Engineering, Heidelberg, Germany) at the 20- and 28-year eye examinations (Fig. 1); further details outlining acquisition and processing protocols of the OCT measurements for the Raine Study are explained in Lee et al., 2020. Disc-centred 3.5-mm circular B-scans were conducted to obtain the pRNFL thickness(n=658). A 31-slice macula-centred scan covering a 6-mm diameter area was conducted to obtain the GCIPL(n=640) and overall macular thicknesses(n=520) based on the Early Treatment for Diabetic Retinopathy (ETDRS) grid; the study design is outlined in Fig. 2. Outcome estimates (i.e., pRNFL, GCIPL, and overall macular thickness) were averaged between the two eyes. Cross-sectional measures for these traits at ages 20 and 28 and the longitudinal change in thicknesses between the two-time points were regressed against the PRS of PD.

Parkinson's disease GWAS summary statistics

We leveraged GWAS summary statistics for a PD meta-analysis that included ~37.7 K cases, ~18.6 K UK Biobank proxy cases (having a first-degree relative with PD), and 1,417,791 controls, yielding a total sample size of 1,474,097. This dataset included samples of European ancestry from multiple cohorts, including the International Parkinson's Disease Genomics Consortium (IPDG), 23andMe Inc., and the UK Biobank. More information about the GWAS meta-analysis is available in the corresponding publication [8]. Summary-level data from the 23andMe cohort was obtained through

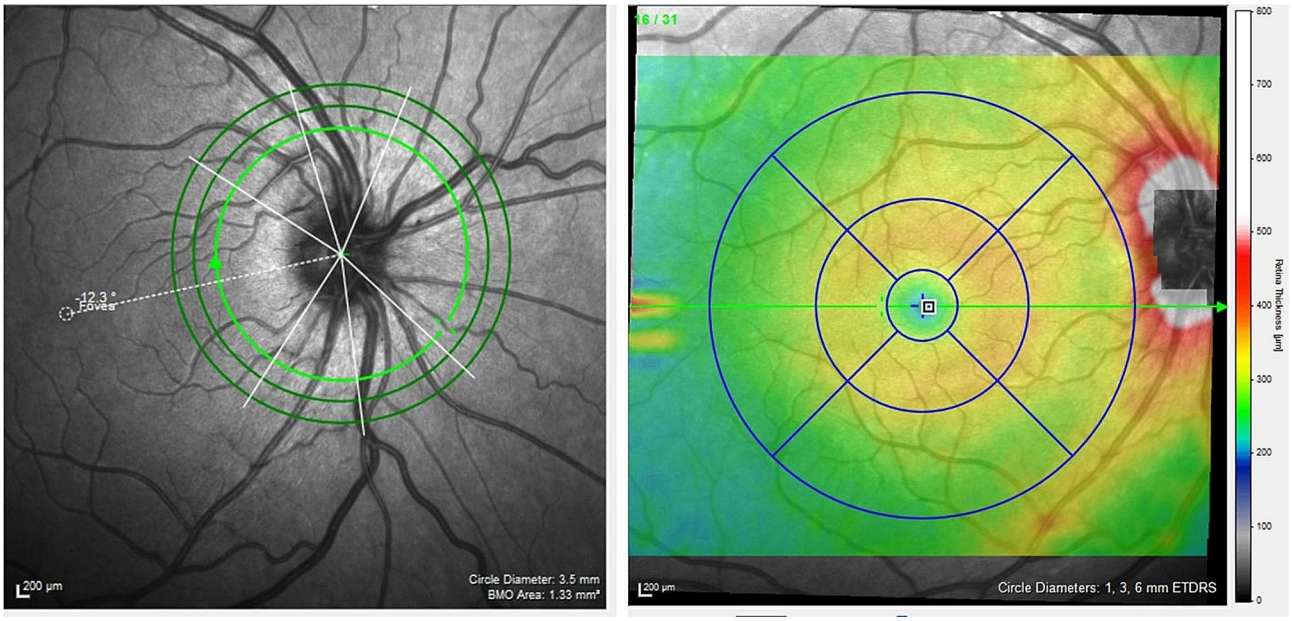

Fig. 1 Spectral Domain optical coherence tomography scans centred on the disc (left) and macular (right). The 3.5 mm-diametre disc-centred B-scan obtains measurements of the peripapillary retinal nerve fibre layer thickness. The 31-slice macular-centred scans cover a 6-mm diameter area

the corresponding application procedure (https://research.23andme.com/dataset-access/) and Institutional Data Transfer Agreement. Additionally, we obtained a version of the summary statistics excluding the 23andMe, Inc. cohort from corresponding authors [8].

Estimating polygenic risk scores for parkinson's disease

Polygenic risk scores (PRS) is a statistical method that adds the number of risk alleles a person carries weighted by their effect sizes to estimate an individual's genetic risk for developing a particular disease. PRS were used to evaluate the association between the genetic risk of PD and retinal integrity estimates. PRS estimates for Raine participants were derived using the GWAS summary statistics for PD described above [8] and PLINK 2.0 [13]. We selected 105 independent SNPs using the following parameters: --clump-r2 0.05, --clump-p1 5e-8, and --clump kb 1000. We employed a subset of the UK Biobank, comprising 5,000 healthy individuals, as a reference for linkage disequilibrium during the clumping process. Quality control measures excluded data with an SNP call rate below 0.95, a Hardy-Weinberg equilibrium p-value less than 10^{-6}, and a minor allele frequency under 0.01. Post-quality control, the genotype data from the Raine Study were imputed using the Haplotype Reference Consortium reference panel. PRS was estimated in individuals of European ancestry, as determined through principal component analysis, using the 1000 Genomes Project as the reference population. To further assess the reliability of genetic scoring approaches, we calculated the PRS of GCIPL analysis based on GWAS studies [9], aiming to determine if the model was robust enough to predict GCIPL structural estimates in the Raine Study. A linear model was employed to evaluate the association between the scores generated from genome-wide significant SNPs and retinal integrity measurements. Linear models were adjusted for age, sex, principal components 1–10, and genotyping array.

Linkage disequilibrium score regression and colocalisation

To evaluate the overlap between retinal integrity estimates and PD, we used macula RNFL and GCIPL GWAS published by Currant et al. [9] based on 31,434 participants from UK Biobank. The genetic correlation between these retinal ganglion cell integrity measures and PD was evaluated using Linkage Disequilibrium Score Regression (LDSC). LDSC is a method that estimates the genetic correlation between phenotypes by analysing GWAS summary statistics while considering factors such as overlapping samples and polygenicity [14]. We used the 1000 Human Genome Project reference panel for LDSC estimations.

We subsequently contrasted the genetic makeup of GCIPL, macula RNFL, and PD by analysing data from existing literature using the GWAS pairwise approach (GWAS-PW) [15]. The GWAS-PW methodology evaluates the genetic overlap across specific genomic regions by segmenting the genome into 1,703 regions, then calculating the probability for four models: the region is exclusive to the retinal integrity estimate, it is exclusive to PD, shared by both with a shared causal variant and shared by both but without a common causal variant. For

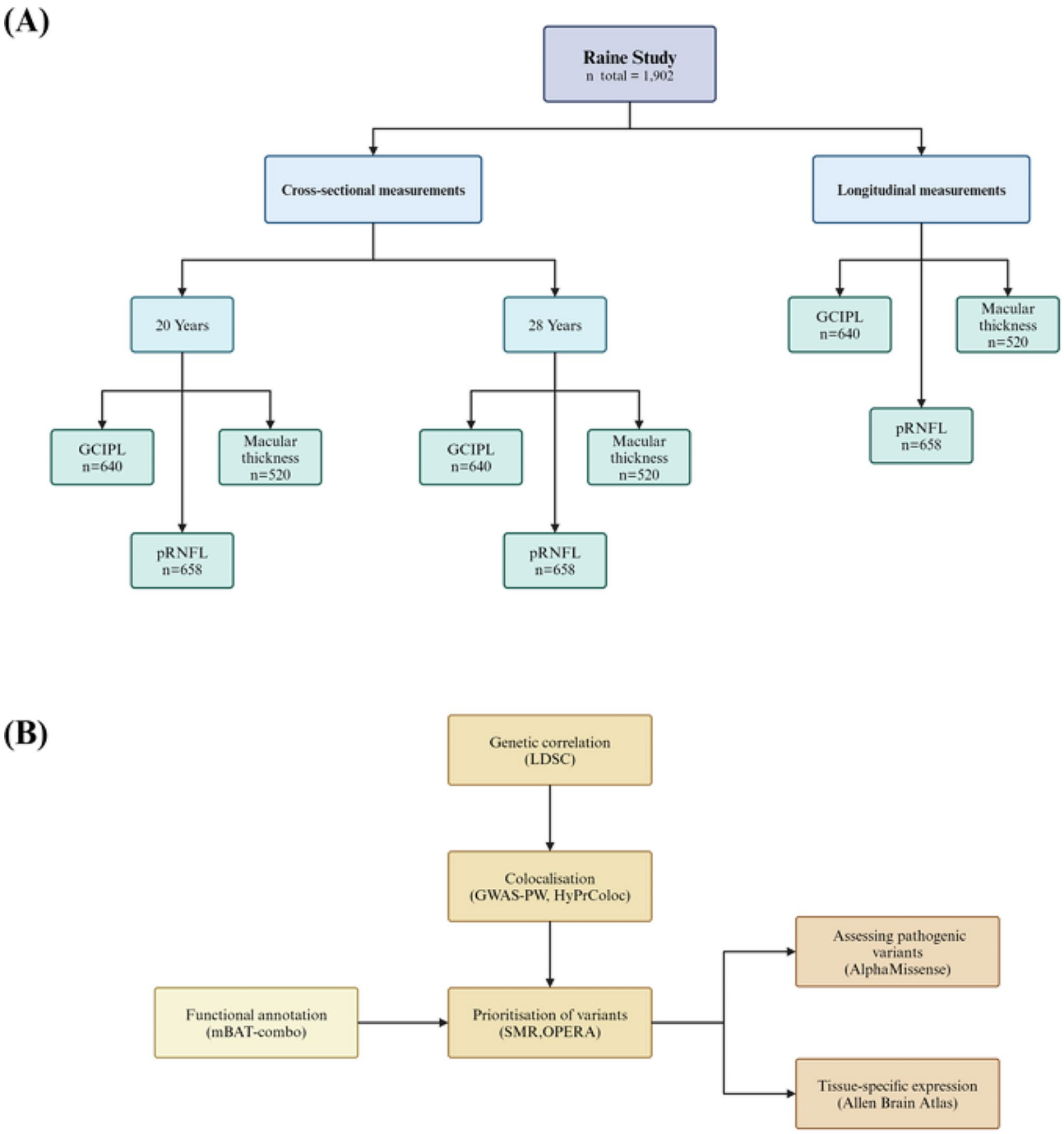

Fig. 2 (**A**) Polygenic risk scoring analysis in the Raine Study (Gen2), which included two time point measurements (20 and 28 years of age) and longitudinal changes of three OCT outcome variables: GCIPL, pRNFL, and overall macular thickness. (**B**) Study design to evaluate the genetic overlap between ganglion-cell structural estimates (i.e., macula RNFL and GCIPL) and Parkinson's disease

segments that suggested shared risk factors between retinal integrity estimates and PD, we used HyPrColoc. This deterministic Bayesian grouping method combines summary data to concurrently perform colocalisation among multiple traits.

Annotation and prioritisation of variants

Regions highlighted in the colocalisation analysis as regions with a shared causal variant were annotated by a gene-based association test, mBAT-combo v 1.94, a method recognised for its efficacy in identifying SNPs with masking effects [16]. Multiple testing was adjusted using the Bonferroni method, considering the total

number of genes evaluated in our study (α=0.05/6600 [genes], $p<7.57e-6$).

We then leveraged omics data to explore the functional relevance of the genes that were consistent between the gene-based and the colocalisation analyses. Firstly, we utilised the summary-data-based Mendelian Randomisation (SMR) version 1.3.1 [17] to discern potential causal associations based on peripheral blood gene expression data from 2,765 participants from the Consortium for the Architecture of Gene Expression (CAGE) [18] and retinal gene expression data from 453 participants [19]. We used single-cell RNA-sequencing data from 23 retinal ganglion cell sub-groups comprising 247,520 cells [20] and over a million neurons, both exposed and not exposed to rotenone-induced oxidative stress [21]. Neurons encompass a diverse range of cells: dopaminergic neurons, serotonin transporters, astrocyte-like cells, ependymal cells, and clusters undergoing neuronal differentiation. Additionally, to account for the multiple tests, we applied the Bonferroni correction technique, taking into account the effective number of independent genes being analysed (α=0.05/27 [genes], $p<0.001$).

Lastly, we assessed the multi-omic profile of genes that were consistent between single-cell and bulk tissue gene expression using Omics Pleiotropic Association (OPERA) version 1.0.0. OPERA is a Bayesian method [22] that aims to provide further interpretation of the biological mechanisms underlying GWAS signals and prioritise molecular phenotypes. This evaluation encompasses the single-cell RNA-sequencing data, a methylation profile derived from mQTL of peripheral blood samples from 1,980 individuals [23], and eQTL information from the peripheral blood of 2,765 subjects from the CAGE Consortium [18].

Regions prioritised through the gene-based analysis were evaluated for missense variants. Missense mutations lead to single amino acid changes that can affect protein folding and are usually pathogenic. In the context of PD, missense mutations in the leucine-rich repeat kinase 2 (LRRK2) gene have been associated with familial PD [24]. However, it is unclear if they have a broader effect and play a role in the thinning of the ganglion layers of the retina. We used AlphaMissense, a machine-learning approach that uses the sequence to predict the protein structure and evaluate the pathogenicity of missense variants [25].

Tissue-specific gene expression

The causal association between genes identified via functional annotation and PD-related alterations in visual cortex morphology were tested using the Allen Brain Atlas, which encompasses an extensive gene expression dataset specific to several brain regions [26]. Three brain models were employed, including a 55 and a 57-year-old male and a 49-year-old female. We chose these brain models due to their proximity to the age of onset for PD (40 to 65 years). Gene expression data were collected from 52 brain regions selected for their relevance to the retina and the vision system. These regions include the optic nerve, optic tract, optic chiasm, optic radiations, supraoptic decussation, oculomotor nerve, and occipital lobe in both hemispheres, as detailed in Supplementary Table 7. Fifteen brain regions with missing expression data were excluded from the analysis. The Allen Brain Atlas project facilitated gene expression quantification through fragment counts of RNA-Seq using quantitative PCR. Values were based on fluorescence or intensity measurements obtained from RNA microarrays.

Results

Association between polygenic risk scores and retinal integrity estimates

PD was nominally associated with longitudinal changes in GCIPL thickness between ages 20 and 28 (R^2=0.004, p-value=0.03) and longitudinal changes of the macular thickness in the inferior, temporal and inner nasal grids, as shown in Fig. 3. We further evaluate point estimates as a sensitivity analysis. Specifically, the PD polygenic score exhibited a nominal association with the thickness of the nasal pRNFL at age 20 years (R^2 = 0.03, p-value=0.028). However, this association was not sustained at age 28 (R^2 = 0.03, p-value=0.07). Furthermore, the PD polygenic score was significantly correlated with the retinal thickness at the nasal (R^2 = 0.01, p-value=0.001) and inferior (R^2 = 0.01, p-value=0.005) inner macula at the ETDRS grid. Results were consistent when assessing the association in pRNFL; as shown in Supplementary Table 1. We further evaluated the reliability of PRS models in predicting retinal structural estimates. The PRS for GCIPL predicted cross-sectional measurements at ages 20 and 28 ($p<0.001$), but it did not predict changes in the GCIPL layer between these two time points, as shown in Supplementary Fig. 1 to 3. The statistical significance threshold was adjusted to $p<0.01$ using the Bonferroni correction (0.05 divided into three main outcome measures: GCIPL, RNFL and overall macula thickness).

Linkage disequilibrium score regression and colocalisation

Linkage disequilibrium score regression showed no statistically significant association between PD and GCIPL (rg=0.04, $p>0.05$) or macula RNFL (rg=0.02, $p>0.05$). Further examination of all loci across the genome using the GWAS-PW identified three regions with the same causal variant shared between GCIPL and PD and two regions shared between macula RNFL and PD, as detailed in Table 1. A region on chromosome 17 (43056905–45875506; hg19) was consistently associated with GCIPL, macula RNFL, and PD. HyPrColoc analysis

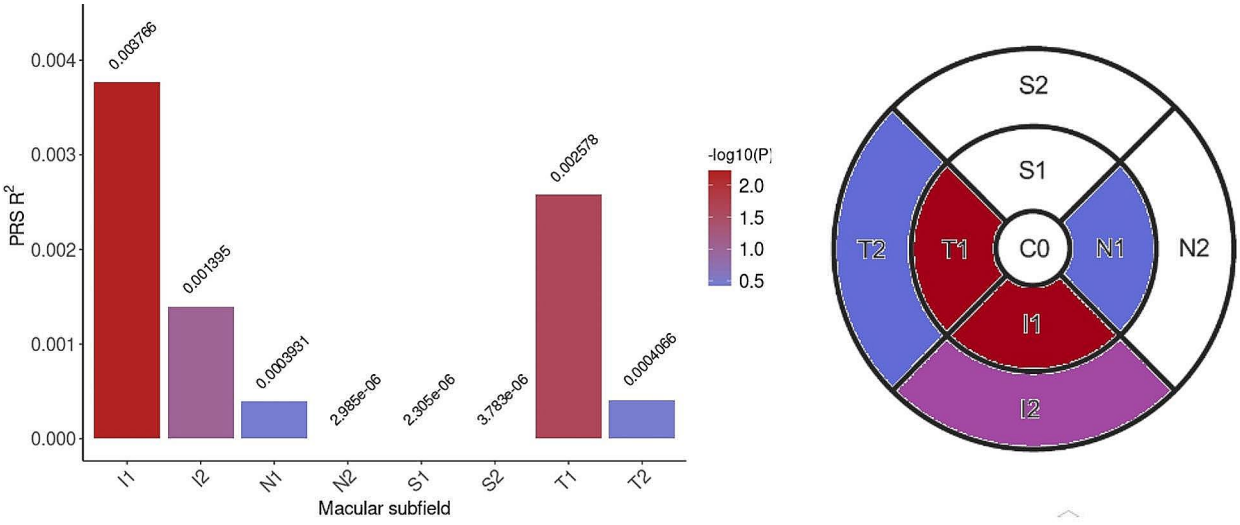

Fig. 3 The phenotypic variance explained (R^2) by the Parkinson's disease polygenic risk score for changes in retinal thickness from 20 to 28 years of age. The macular grid of the GCIPL layer is reported. Subfields are described as inferior (I), nasal (N), superior (S), temporal (T), inner (1), and outer (2)

Table 1 GWAS PW results evaluating the posterior probability (PPA) of four hypotheses: the region is exclusive to the retinal integrity estimate (1), it is exclusive to Parkinson's disease (2), it is shared by both with a shared causal variant (3), or it is shared by both without a common causal variant (4). Positions are in hg19

Trait 1	Trait 2	CHR	START (BP)	STOP (BP)	PPA 1	PPA 2	PPA 3	PPA 4
RNFL	PD	12	182,451	1,080,007	0.12	0.04	0.80	0.04
RNFL	PD	17	43,056,905	45,875,506	< 0.01	< 0.01	0.98	0.01
GCIPL	PD	17	43,056,905	45,875,506	0.01	0.02	0.95	0.02
GCIPL	PD	19	40,171,266	40,983,034	0.03	0.01	0.94	0.02
GCIPL	PD	21	41,389,527	43,321,426	< 0.01	< 0.01	0.98	0.01

on chromosome 17 indicated a high likelihood that the region 43,056,905–45,875,506, build hg19, is shared between ganglion integrity estimates and PD (PP = 0.97) and a candidate SNP (rs199453) likely shared between retinal estimates and PD (PP = 0.62).

Annotation and prioritisation of variants

Gene-based analysis using mBAT-combo on 6.600 genes identified 27 genes common to both PD and retinal integrity measurements. However, only seven genes (*CRHR1*, *SPPL2C*, *STH*, *MAPT*, *NSF*, *KANSL1*, and *LINC02210*) located on chromosome 17 remained statistically significant after corrections for multiple testing (see Supplementary Table 2). Rs199453 and rs117300236 were the most significantly associated SNPs in mBAT-combo analysis for the region containing genes WNT3 and NSF. Aggregates of the N-ethylmaleimide sensitive factor (*NSF*) have previously been linked to PD through the *LRRK2* [27] pathway, and *NSF* has been previously associated with another neurodegenerative disease, such as frontotemporal dementia [28].

Further analysis of the expression profile on peripheral blood using SMR highlighted the consistency between the *NSF* GWAS association in PD, GCIPL and macula RNFL, and eQTL data. However, the results were heterogeneous ($p > 0.05$ [HEIDI]) except for an association between *NSF* and GCIPL, as shown in Supplementary Table 3. Single-cell expression results showed a statistically significant association between the expression of *CRHR1* and *KANSL1* in PD, GCIPL and macula RNFL involving serotonin transporter neurons exposed to rotenone-induced oxidative stress, as per Supplementary Table 4.

Results for *CRHR1* were consistent with the multi-omics analysis. Rs12949256 was associated with DNA methylation at multiple promoter regions, as detailed in Supplementary Table 5, with a posterior probability of association greater than 0.9, reflecting a combined effect of changes in gene expression and methylation of *CRHR1* in macula RNFL and PD. Analysis of missense variants using AlphaMissense identified 25,173 variants within the seven regions prioritised by the GWAS PW analysis, as depicted in Supplementary Table 6. Of these loci, 10,737 are likely pathological. However, none of the variants highlighted by the eQTL and mQTL overlap with these pathological missense variants.

Tissue-specific gene expression

We focused on four key genes: N-ethylmaleimide sensitive factor (NSF), KANSL1 antisense RNA 1 (KANSL1-AS1), corticotropin-releasing hormone receptor 1 (CRHR1), and Wnt family member 3 (WNT3), given that these genes were highlighted as possible causal genes shared between ganglion cell integrity measurements and PD in the colocalisation and SMR analyses. Results were based on the highest match of probes for genes: *NSF* (probe number 1053554), *KANSL1-RNA1* (probe number 1016061), *CRHR1* (probe number 1011485), and *WNT3* (probe number 1050353). Results revealed a consistent gene expression pattern across the visual cortex regions for the four studied genes. Gene expression levels for *NSF*, *KANSL1-RNA1*, *CRHR1*, and *WNT3* across 52 visual regions, with mean values ranging from 7 to 9.6, were observed, as shown in Supplementary Table 7. However, since these results are based on three brain models, confirming the consistency of these findings in studies with a larger sample size is necessary.

Discussion

Our study offers a comprehensive overview of the potential genetic overlap between retinal structural integrity and PD. Our findings indicate that genetic susceptibility to PD likely influences retinal morphometric measurements of the RGC and longitudinal changes of macular retinal thickness in young adults. We observed significant associations between PD PRS and OCT measures. A higher PRS was nominally associated with a thinner pRNFL in young adults and a generally thinner retina at both 20 and 28 years of age. Additionally, the PRS of PD was linked with longitudinal changes in retinal thickness from ages 20 to 28. The temporal and inferior grids were identified as the areas most likely associated with retinal thinning in PD. This likely underscores the vulnerability of the RGC in these regions to neurodegenerative processes.

Our findings align with a potentiation pattern of neurodegeneration in the macula, as corroborated by both observational studies [5, 29] and comprehensive reviews [30]. Notably, the parafoveal region appears particularly susceptible to the neurodegenerative processes associated with PD [31, 32]. Furthermore, observational studies were done on patients who were on average over 60 [5], while our research highlights that structural changes in the macula are associated with a genetic predisposition to PD from a younger age. If our findings are sustained on other cohorts and under diverse ancestries, it might present avenues for screening patients at high risk of PD from a younger age through eye examination (i.e., OCT).

We further assessed the overlap between the genetic architecture of RGC and PD. Notably, there was a lack of genetic correlation and only a few regions highlighted as shared with the same causal variants through the colocalisation analysis between ganglion cell integrity measurements and PD. This suggests a pleiotropic effect, one gene influencing multiple traits, rather than a causal association with PD. This is consistent with the identification of a few shared genomic regions that are mainly located on chromosome 17, which shared causal variants between retinal integrity and PD. Previous studies evaluating the putative causal association between PD and RGC highlight a similar pleiotropic association between PD and RGC integrity estimates on chromosomes 12, 17, and 21. [33].

However, it is important to emphasise that the GWAS of RGC integrity estimates used for this analysis corresponds to a single-point thickness estimate. Thus, we are likely capturing the overlap between retinal structure (which corresponds more to a single time-point measurement) and not the decrease in retinal thickness that might be more closely associated with the neurodegenerative process. In line with this notion, some genes, such as WNT3, appear to be more related to the developmental processes of the brain and retina. It is necessary to emphasise this limitation of our study and to suggest that future studies adopt a prospective approach to further elucidate the causal relationship between PD and ganglion cell integrity over time, given the apparent association between RGC longitudinal estimates and the risk of PD, as highlighted in this study.

The prioritisation of specific genes, such as *CRHR1*, *KANSL1*, *NSF*, and others on chromosome 17, underlines the potential involvement of these loci in both RGC integrity estimates and PD. *NSF*, in particular, has been previously associated with PD through the *LRRK2* pathway; phosphorylation of the gene leads to the accumulation of *NSF* in toxic aggregates [26]. Furthermore, within retinal photoreceptor cells, *NSF* is observed to co-localise in the synaptic region, outer nuclear layer, and inner segments, indicating *NSF* involvement in the synaptic processing of photoreceptors [34].

Both *CRHR1* and *KANSL1* have been linked to PD through GWAS studies. *CRHR1* has been proposed as a potential drug target due to its interaction with several drugs, including hydrocortisone [29]. In mice, *CRHR1* seems to modulate the responses of RGCs through a potential autocrine action via corticotropin-releasing hormone [35], which has been shown in animal models to modulate dopamine release [36]. *KANSL1*, confirmed to be expressed in RGC [20], plays a key role in the development of PD [30]. *KANSL1* is a mitophagy regulator involved in the PINK1-mitophagy pathway in idiopathic PD [37]. This pathway serves as a critical control mechanism for mitochondrial health, helping to prevent the accumulation of dysfunctional mitochondria, which has been implicated in the progressive damage to

RGCs in other neurodegenerative diseases, such as glaucoma [38]. Consistently, in our analysis, these genes have been associated with PD and RGC integrity estimates through multi-omic and single-cell analyses. Additionally, they have been confirmed to be expressed in both retinal and brain tissue.

Our results suggest a shared genetic architecture between PD and retinal ganglion cell integrity. PRS was associated with ganglion cell integrity estimates over time in a cohort that comprises young adults who are unlikely to have thinned pRNFL due to other diseases such as glaucoma or macular degeneration. However, these findings warrant careful interpretation. The longitudinal nature of our analysis is constrained to two temporal data points. Comprehensive longitudinal studies encompassing broader age intervals and diverse cohorts are necessary to elucidate this relationship further. While the underlying mechanisms for these associations appear to be pleiotropic, we identified links between genes *CRHR1*, *KANSL1*, and *NSF* with both PD risk and RGC integrity measures. Further validation and functional characterization of these genes are encouraged, as this will elucidate shared pathways that could enhance our understanding of the disease etiology. Our findings further advance the understanding of the molecular interplay between retinal structure and PD, emphasising that structural integrity measurements could serve as potential markers for PD risk in young adults.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40478-024-01841-9.

Supplementary Material 1

Supplementary Material 2

Acknowledgements

We would like to acknowledge the Raine Study participants and their families for their ongoing participation in the study and the Raine Study team for study coordination and data collection. We also thank the NHMRC for their long-term contribution to funding the study over the last 30 years. The Pawsey Supercomputing Centre provided computation resources to conduct analyses required with funding from the Australian Government and the Government of Western Australia. Also, we would like to thank the research participants and employees of 23andMe, Inc. for making this work possible.

Authors' contributions

M.E.R. and P.G. conceived the study and designed the analyses with support from D.A.M. and S.M.; S.D-T. carried out the analyses with support from S.S.L. and N.S.O.; S.D.T. wrote the first draft of the manuscript and revised it based on input and feedback from all other co-authors.

Funding

The core management of the Raine Study is funded by The University of Western Australia, Curtin University, Telethon Kids Institute, Women and Infants Research Foundation, Edith Cowan University, Murdoch University, The University of Notre Dame Australia and the Raine Medical Research Foundation. The eye data collection of the Raine Study Gen2 20- and 28-year follow-ups were funded by the NHMRC (Grants 1021105, 1126494, and 1121979), the Ophthalmic Research Institute of Australia, Alcon Research Institute, Lions Eye Institute, the Australian Foundation for the Prevention of Blindness, and the Heart Foundation (Grant no. 102170). DM is supported by an NHMRC Practitioner Fellowship. PG is supported by an NHMRC Investigator grant. MER is supported by an Al & Val Rosenstrauss Fellowship from the Rebecca L Cooper Medical Research Foundation (F20231230). None of the funders had a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. SM was supported by NHMRC grants (Fellowship and Program grants, 1154543, 1150144).

Data availability

Full summary-level data for PD, including the 23andMe cohort, are available upon request through a Data Transfer Agreement and the appropriate application procedure (https://research.23andme.com/dataset-access/). Data are available from the Raine Study (www.rainestudy.org.au) for researchers who meet the criteria for access to de-identified data.

Declarations

Ethics

All eye assessments adhered to the principles outlined in the Declaration of Helsinki and received approval from the University of Western Australia Human Research Ethics Committee.

Competing interests

The authors report no relevant competing interests.

Author details

[1]QIMR Berghofer Medical Research Institute, Brisbane, QLD, Australia
[2]School of Biomedical Sciences, Faculty of Medicine, The University of Queensland, Brisbane, QLD, Australia
[3]Centre for Ophthalmology and Visual Science (incorporating the Lions Eye Institute), The University of Western Australia, Perth, WA, Australia
[4]School of Biomedical Sciences, Faculty of Health, Queensland University of Technology, Brisbane, Australia

Received: 18 March 2024 / Accepted: 29 July 2024
Published online: 13 August 2024

References

1. Tysnes O-B, Storstein A (2017) Epidemiology of Parkinson's disease. J Neural Transm 124:901–905. https://doi.org/10.1007/s00702-017-1686-y
2. Wolf J, Rasmussen DK, Sun YJ, Vu JT, Wang E, Espinosa C et al Liquid-biopsy proteomics combined with AI identifies cellular drivers of eye aging and disease in vivo. Cell 2023. https://doi.org/10.1016/j.cell.2023.09.012
3. Zhang Y, Zhang X, Yue Y, Tian T (2021) Retinal degeneration: a window to understand the origin and progression of Parkinson's Disease? Front Neurosci 15:799526. https://doi.org/10.3389/fnins.2021.799526
4. Rascunà C, Russo A, Terravecchia C, Castellino N, Avitabile T, Bonfiglio V et al (2020) Retinal thickness and Microvascular Pattern in Early Parkinson's Disease. Front Neurol 11:533375. https://doi.org/10.3389/fneur.2020.533375
5. Sung MS, Choi S-M, Kim J, Ha JY, Kim B-C, Heo H et al (2019) Inner retinal thinning as a biomarker for cognitive impairment in de novo Parkinson's disease. Sci Rep 9:11832. https://doi.org/10.1038/s41598-019-48388-7
6. El-Kattan MM, Esmat SM, Esmail EH, Deraz HA, Ismail RS (2022) Optical coherence tomography in patients with Parkinson's disease. Egypt J Neurol Psychiatry Neurosurg 58:1–8. https://doi.org/10.1186/s41983-021-00421-1
7. Murueta-Goyena A, Del Pino R, Galdós M, Arana B, Acera M, Carmona-Abellán M et al (2021) Retinal thickness predicts the risk of Cognitive decline in Parkinson Disease. Ann Neurol 89:165–176. https://doi.org/10.1002/ana.25944
8. Nalls MA, Blauwendraat C, Vallerga CL, Heilbron K, Bandres-Ciga S, Chang D et al (2019) Identification of novel risk loci, causal insights, and heritable risk for Parkinson's disease: a meta-analysis of genome-wide association studies. Lancet Neurol 18:1091–1102. https://doi.org/10.1016/S1474-4422(19)30320-5
9. Currant H, Hysi P, Fitzgerald TW, Gharahkhani P, Bonnemaijer PWM, Senabouth A et al (2021) Genetic variation affects morphological retinal phenotypes extracted from UK Biobank optical coherence tomography images. PLoS Genet 17:e1009497. https://doi.org/10.1371/journal.pgen.1009497

10. McKnight CM, Newnham JP, Stanley FJ, Mountain JA, Landau LI, Beilin LJ et al (2012) Birth of a cohort–the first 20 years of the Raine study. Med J Aust 197:608–610. https://doi.org/10.5694/mja12.10698
11. Dontje ML, Eastwood P, Straker L (2019) Western Australian pregnancy cohort (Raine) study: generation 1. BMJ Open 9:e026276. https://doi.org/10.1136/bmjopen-2018-026276
12. Lee SS-Y, Lingham G, Yazar S, Sanfilippo PG, Charng J, Chen FK et al (2020) Rationale and protocol for the 7- and 8-year longitudinal assessments of eye health in a cohort of young adults in the Raine Study. BMJ Open 10:e033440. https://doi.org/10.1136/bmjopen-2019-033440
13. Chang CC, Chow CC, Tellier LC, Vattikuti S, Purcell SM, Lee JJ (2015) Second-generation PLINK: rising to the challenge of larger and richer datasets. Gigascience 4:7. https://doi.org/10.1186/s13742-015-0047-8
14. Bulik-Sullivan BK, Loh P-R, Finucane HK, Ripke S, Yang J, Patterson N et al (2015) LD score regression distinguishes confounding from polygenicity in genome-wide association studies. Nat Genet 47:291–295. https://doi.org/10.1038/ng.3211
15. Pickrell JK, Berisa T, Liu JZ, Ségurel L, Tung JY, Hinds DA (2016) Detection and interpretation of shared genetic influences on 42 human traits. Nat Genet 48:709–717. https://doi.org/10.1038/ng.3570
16. Li A, Liu S, Bakshi A, Jiang L, Chen W, Zheng Z et al (2023) mBAT-combo: a more powerful test to detect gene-trait associations from GWAS data. Am J Hum Genet 110:30–43. https://doi.org/10.1016/j.ajhg.2022.12.006
17. Zhu Z, Zhang F, Hu H, Bakshi A, Robinson MR, Powell JE et al (2016) Integration of summary data from GWAS and eQTL studies predicts complex trait gene targets. Nat Genet 48:481–487. https://doi.org/10.1038/ng.3538
18. Lloyd-Jones LR, Holloway A, McRae A, Yang J, Small K, Zhao J et al (2017) The Genetic Architecture of Gene expression in Peripheral Blood. Am J Hum Genet 100:371. https://doi.org/10.1016/j.ajhg.2017.01.026
19. Ratnapriya R, Sosina OA, Starostik MR, Kwicklis M, Kapphahn RJ, Fritsche LG et al (2019) Retinal transcriptome and eQTL analyses identify genes associated with age-related macular degeneration. Nat Genet 51:606–610. https://doi.org/10.1038/s41588-019-0351-9
20. Daniszewski M, Senabouth A, Liang HH, Han X, Lidgerwood GE, Hernández D et al (2022) Retinal ganglion cell-specific genetic regulation in primary open-angle glaucoma. Cell Genom 2:100142. https://doi.org/10.1016/j.xgen.2022.100142
21. Jerber J, Seaton DD, Cuomo ASE, Kumasaka N, Haldane J, Steer J et al (2021) Population-scale single-cell RNA-seq profiling across dopaminergic neuron differentiation. Nat Genet 53:304–312. https://doi.org/10.1038/s41588-021-00801-6
22. Wu Y, Qi T, Wray NR, Visscher PM, Zeng J, Yang J (2023) Joint analysis of GWAS and multi-omics QTL summary statistics reveals a large fraction of GWAS signals shared with molecular phenotypes. Cell Genomics
23. Wu Y, Zeng J, Zhang F, Zhu Z, Qi T, Zheng Z et al (2018) Integrative analysis of omics summary data reveals putative mechanisms underlying complex traits. Nat Commun 9:918. https://doi.org/10.1038/s41467-018-03371-0
24. Bryant N, Malpeli N, Ziaee J, Blauwendraat C, Liu Z, Consortium AMPPD et al (2021) Identification of LRRK2 missense variants in the accelerating medicines partnership Parkinson's disease cohort. Hum Mol Genet 30:454–466. https://doi.org/10.1093/hmg/ddab058
25. Cheng J, Novati G, Pan J, Bycroft C, Žemgulytė A, Applebaum T et al (2023) Accurate proteome-wide missense variant effect prediction with AlphaMissense. Science 381:eadg7492. https://doi.org/10.1126/science.adg7492
26. Shen EH, Overly CC, Jones AR (2012) The Allen Human Brain Atlas: comprehensive gene expression mapping of the human brain. Trends Neurosci 35:711–714. https://doi.org/10.1016/j.tins.2012.09.005
27. Pischedda F, Cirnaru MD, Ponzoni L, Sandre M, Biosa A, Carrion MP et al (2021) LRRK2 G2019S kinase activity triggers neurotoxic NSF aggregation. Brain 144:1509–1525. https://doi.org/10.1093/brain/awab073
28. Diaz-Torres S, Ogonowski N, García-Marín LM, Bonham LW, Duran-Aniotz C, Yokoyama JS et al (2023) Genetic overlap between cortical brain morphometry and frontotemporal dementia risk. Cereb Cortex 33:7428–7435. https://doi.org/10.1093/cercor/bhad049
29. Abd Hamid MR, Wan Hitam W-H, Abd Halim S (2021) Retinal nerve Fiber layer and Macular Thickness in Parkinson's Disease patients. Cureus 13:e16224. https://doi.org/10.7759/cureus.16224
30. Lee J-Y, Martin-Bastida A, Murueta-Goyena A, Gabilondo I, Cuenca N, Piccini P et al (2022) Multimodal brain and retinal imaging of dopaminergic degeneration in Parkinson disease. Nat Rev Neurol 18:203–220. https://doi.org/10.1038/s41582-022-00618-9
31. Murueta-Goyena A, Romero-Bascones D, Teijeira-Portas S, Urcola JA, Ruiz-Martínez J, Del Pino R et al (2024) Association of retinal neurodegeneration with the progression of cognitive decline in Parkinson's disease. NPJ Parkinsons Dis 10:26. https://doi.org/10.1038/s41531-024-00637-x
32. Murueta-Goyena A, Del Pino R, Reyero P, Galdós M, Arana B, Lucas-Jiménez O et al (2019) Parafoveal thinning of inner retina is associated with visual dysfunction in Lewy body diseases. Mov Disord 34:1315–1324. https://doi.org/10.1002/mds.27728
33. Diaz-Torres S, He W, Thorp J, Seddighi S, Mullany S, Hammond CJ et al Disentangling the genetic overlap and causal relationships between primary open-angle glaucoma, brain morphology and four major neurodegenerative disorders. eBioMedicine 2023;92. https://doi.org/10.1016/j.ebiom.2023.104615
34. Holopainen JM, Cheng CL, Molday LL, Johal G, Coleman J, Dyka F et al (2010) Interaction and localization of the retinitis pigmentosa protein RP2 and NSF in retinal photoreceptor cells. Biochemistry 49:7439–7447. https://doi.org/10.1021/bi1005249
35. Walsh H, Rahmani P, Zhang K, Kim I-J, Justice NJ, Demb JB et al (2019) Anatomical and molecular characterization of CRH (corticotropin-releasing hormone) receptor 1-expressing cell populations in the mouse retina. Invest Ophthalmol Vis Sci 60:540–540
36. Payer D, Williams B, Mansouri E, Stevanovski S, Nakajima S, Le Foll B et al (2017) Corticotropin-releasing hormone and dopamine release in healthy individuals. Psychoneuroendocrinology 76:192–196. https://doi.org/10.1016/j.psyneuen.2016.11.034
37. Soutar MPM, Melandri D, O'Callaghan B, Annuario E, Monaghan AE, Welsh NJ et al (2022) Regulation of mitophagy by the NSL complex underlies genetic risk for Parkinson's disease at 16q11.2 and MAPT H1 loci. Brain 145:4349–4367. https://doi.org/10.1093/brain/awac325
38. Wang S, Long H, Hou L, Feng B, Ma Z, Wu Y et al (2023) The mitophagy pathway and its implications in human diseases. Signal Transduct Target Ther 8:304. https://doi.org/10.1038/s41392-023-01503-7

Publisher's Note