

1 ***Eye-brain connections revealed by multimodal retinal and brain imaging genetics in***
2 ***the UK Biobank***

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4 **Running title: Genetics of eye-brain connections**

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1 **Abstract**

2 As an anatomical extension of the brain, the retina of the eye is synaptically connected to
3 the visual cortex, establishing physiological connections between the eye and the brain.
4 Despite the unique opportunity retinal structures offer for assessing brain disorders, less
5 is known about their relationship to brain structure and function. Here we present a
6 systematic cross-organ genetic architecture analysis of eye-brain connections using retina
7 and brain imaging endophenotypes. Novel phenotypic and genetic links were identified
8 between retinal imaging biomarkers and brain structure and function measures derived
9 from multimodal magnetic resonance imaging (MRI), many of which were involved in the
10 visual pathways, including the primary visual cortex. In 65 genomic regions, retinal
11 imaging biomarkers shared genetic influences with brain diseases and complex traits, 18
12 showing more genetic overlaps with brain MRI traits. Mendelian randomization suggests
13 that retinal structures have bidirectional genetic causal links with neurological and
14 neuropsychiatric disorders, such as Alzheimer's disease. Overall, cross-organ imaging
15 genetics reveals a genetic basis for eye-brain connections, suggesting that the retinal
16 images can elucidate genetic risk factors for brain disorders and disease-related changes
17 in intracranial structure and function.

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19 **Keywords:** Brain MRI; Brain disorders; Fundus photography; GWAS; OCT; Retinal imaging;
20 Transfer Learning; Visual pathways; UK Biobank.

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1 The retina of the eye is the only part of the central nervous system that can be visualized
2 without surgical intervention. As a key component of the visual pathway, the retina is
3 synaptically connected to the visual cortex through the optic nerve, thalamus, and optic
4 radiations. There are anatomical, physiological, and embryological similarities between
5 the retina and the brain, in terms of cell types, vasculature, and immune responses¹. The
6 eye develops from the forebrain during the third week of gestation². The retina is
7 embryonically formed as part of the diencephalon, which later becomes the thalamus,
8 thus being developmentally related to specific brain regions. Consequently, the retina has
9 been considered a unique window into altered brain structure/function^{1,3} and brain
10 disorders⁴, such as Alzheimer's disease⁵⁻⁸, Parkinson's disease⁹, stroke^{10,11}, cerebral small
11 vessel disease¹², schizophrenia¹³, cognitive decline^{11,14,15}, and many others. For example,
12 it has been extensively studied that retinal neurodegeneration can be used as an easily
13 accessible biomarker to identify individuals at high risk of developing Alzheimer's disease
14 or those with preclinical Alzheimer's disease^{6,8,16-18}. Retinal abnormalities have also been
15 frequently reported in Parkinson's disease, and animal models have demonstrated that
16 similar molecular mechanisms underlie Parkinson's disease pathology and
17 neurodegeneration in parkinsonian eyes⁹. However, except for a few pairs of diseases,
18 such as primary open-angle glaucoma and Alzheimer's disease¹⁹, little is known about the
19 shared genetic effects underlying eye-brain relationships and parallel pathological
20 changes between the two organs.

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22 The retina and brain images provide well-defined clinical endophenotypes for disorders
23 of the eye and brain. Both color fundus photography and optical coherence tomography
24 (OCT) are popular retinal imaging modalities. Retinal images serve as the gold standard
25 screening for age-related macular degeneration²⁰, diabetic retinopathy²¹, and all other
26 pathologies involving the retina. These images offer a color picture of the back of the eye,
27 including the retina, optic nerve head, and retinal vasculature. Retinal OCT imaging shows
28 a high-resolution view of the cross-sectional structure of the retina²². In neurologic
29 conditions, OCT imaging allows the assessment of the retinal layers' thickness and
30 structural changes caused by the modification of neuronal and retinal glial cells²³. In
31 addition, magnetic resonance imaging (MRI) captures both structural and functional
32 characteristics of the brain, resulting in a wide range of clinical applications in neurological

1 and neuropsychiatric disorders²⁴. Recent large-scale genome-wide association studies
2 (GWAS) have shown that both retinal imaging biomarkers²⁵⁻³³ and brain MRI traits³⁴⁻⁴¹ are
3 heritable, with the genetic influences of common genetic variants being identified in
4 hundreds of genomic regions. As expected, genetic overlaps were identified between
5 retinal imaging traits and eye disorders (such as the cupping of the optic nerve head and
6 glaucoma³⁰) as well as between brain MRI traits and brain disorders (such as functional
7 connectivity of the visual network and Alzheimer's disease³⁹). However, few studies have
8 used imaging genetics to study brain health from a retinal perspective. A large-scale
9 cross-organ analysis of retinal and brain imaging traits may provide an opportunity to
10 identify retinal imaging biomarkers for brain disorders and to uncover the genetic basis
11 for eye-brain connections.

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13 Using multimodal retinal and brain imaging traits from the UK Biobank (UKB) study⁴², we
14 investigated the cross-organ genetic architecture of the eye and brain. A total of 156
15 retinal imaging traits were examined, of which 46 were derived from OCT images and 110
16 from fundus photographs. The 46 OCT derived measurements were already available in
17 the UKB database, such as retinal thickness across layers^{43,44} and vertical cup-to-disc
18 ratio²⁹. For the fundus images, we used 11 different pre-trained transfer learning³¹
19 models built from the ImageNet⁴⁵ database to extract imaging features of the retinal
20 structure. In each deep transfer learning model, the top 10 principal components (PCs)
21 were considered, explaining an average of 70.71% variance (range = [50.58%, 95.84%]) in
22 the last layer, resulting in 110 fundus image features (11 x 10). These deep-learning-based
23 image embeddings and low-dimensional representations contain eye-specific biological
24 information, which may not be present in standard eye measurements³¹. We conducted
25 GWAS for these 156 (46 + 110) retinal imaging traits and then evaluated their genetic
26 connections with 458 imaging traits from three primary brain MRI modalities, including 1)
27 101 regional brain volumes³⁵ and 63 cortical thickness traits⁴⁶ from structural MRI; 2) 110
28 diffusion tensor imaging (DTI) parameters from diffusion MRI³⁷; and 3) 92 functional
29 connectivity and activity (or amplitude) traits from resting state and task-based functional
30 MRI (fMRI)³⁹, respectively. The **Methods** section and **Table S1** provide more information
31 on these retinal and brain imaging data. An overview of the study design and data analysis
32 is provided in **Figure 1**. GWAS summary statistics for retinal imaging traits and our data

1 analysis results will be made available through the eye imaging genetics knowledge portal
2 (Eye-KP) at <https://www.eyekp.org/>.

3

4 **RESULTS**

5 **Phenotypic multimodal eye-brain connections**

6 We examined phenotypic associations between 156 retinal imaging traits and 458 brain
7 MRI traits after adjusting for a wide variety of vascular risk factors³ and imaging
8 confounders³⁴, as well as body size, age, and sex effects (see the **Methods** section for the
9 complete list of adjusted covariates). For discovery, we analyzed data of UKB white British
10 individuals (average $n = 6,454$ across different modalities). At the false discovery rate (FDR)
11 level of 5% (by the Benjamini-Hochberg procedure, $P < 4.37 \times 10^{-4}$, 156×458 tests), we
12 identified 625 associations (**Figs. 2A** and **S1**), 135 of which were replicated in a hold-out
13 independent validation dataset (average $n = 959$) with concordant association signs (**Fig.**
14 **S2**). Among the 625 associations, 121 further survived the conservative Bonferroni
15 significance level ($P < 6.99 \times 10^{-7}$), and 66 can be replicated in the same hold-out
16 independent dataset. These significant results were mainly related to multiple brain
17 structural modalities, including regional brain volumes, cortical thickness, and DTI
18 parameters. They were broadly related to both OCT measures and fundus image features
19 (**Table S2**). Below we summarized the patterns of associations that have been replicated.

20

21 Thicknesses of the macula⁴⁴, the retinal nerve fiber layer (RNFL)⁴³, and the ganglion cell
22 and inner plexiform layer (GCIPL)⁴³ consistently had positive associations with the
23 fractional anisotropy (FA) of multiple white matter tracts, including those related to the
24 visual pathway (**Figs. 2B-C** and **S3**). Various eye diseases are associated with retinal
25 thinning⁴⁷. Moreover, previous studies have consistently demonstrated the thinning of
26 the RNFL and GCIPL to be associated with cerebrovascular diseases⁴⁸ and early-stage
27 Alzheimer's disease⁴⁹. These results suggest a parallel relationship between retinal and
28 brain health, as well as changes in brain white matter that may be related to both. The
29 strongest associations were observed between the GCIPL thickness of the left eye and the
30 mean FA of the posterior thalamic radiation, sagittal stratum, and fornix-stria terminalis
31 tracts ($\beta > 0.142$, $P < 1.91 \times 10^{-23}$). The posterior thalamic radiation overlaps with the optic
32 radiation in the visual pathway, which links the lateral geniculate nucleus to the primary

1 visual cortex, transmitting visual input from the eye. There were also similar associations
2 between fundus image features and DTI parameters, although the associations were
3 weaker than those for retinal thickness traits (**Fig. S3**). Moreover, thickness measures of
4 the RNFL, GCIPL, macula, and inner nuclear layer (INL)⁴³ were positively associated with
5 volumes of multiple brain cortical and subcortical structures, including the pericalcarine,
6 thalamus, pallidum, and putamen (**Figs. 2D-E and S4**). The pericalcarine is the location
7 where the primary visual cortex (V1) concentrates, and we found that the regional brain
8 volumes of the pericalcarine had consistent positive associations with the RNFL, GCIPL,
9 and macular thickness ($\beta > 0.052$, $P < 5.90 \times 10^{-5}$). We also found positive associations
10 with brain structures in the dorsal and ventral visual pathways that extended from the
11 primary visual cortex, such as the cuneus ($\beta > 0.057$, $P < 1.08 \times 10^{-4}$). The thalamus and
12 macular are both derived from the diencephalon. Positive associations between regional
13 brain volumes of the thalamus and macular thickness were found ($\beta > 0.120$, $P < 1.24 \times$
14 10^{-8}), emphasizing their developmental origins. Negative associations between retinal
15 layer thickness and enlargement of the lateral ventricles were also detected. The left and
16 right hemispheres of the brain demonstrated consistent associations with retinal imaging
17 traits. For example, the left and right brain thalamus volumes were significantly
18 correlated with the thicknesses of the macular and GCIPL in both eyes ($\beta > 0.120$, $P < 1.24$
19 $\times 10^{-8}$). The GCIPL thickness was also positively associated with global and regional brain
20 cortical thickness measures, including the primary visual cortex (the pericalcarine, $\beta =$
21 0.048 , $P = 7.74 \times 10^{-5}$). The top two regions with the strongest links were the precuneus,
22 which is in the dorsal visual pathway ($\beta = 0.073$, $P = 2.33 \times 10^{-8}$), and the fusiform, which
23 is in the ventral visual pathway ($\beta = 0.064$, $P = 4.22 \times 10^{-7}$, **Figs. 2F and S4**),

24

25 We repeated the above analyses separately for females and males to examine the sex-
26 specific patterns (average $n = 3,338$ and $3,150$, respectively). At the FDR 5% level ($P < 4.37$
27 $\times 10^{-4}$), 53 associations were identified in both females and males, the female sample
28 identified 191 additional associations, and 62 more were only found in males. The
29 additional associations found in analyses that included only females or males were
30 primarily related to fundus image traits. Specifically, the female analysis showed more
31 significant associations with DTI parameters, while the male analysis revealed more
32 significant associations with cortical thickness measures (**Figs. S5-S7**). For OCT measures,

1 males and females demonstrated similar eye-brain association patterns, although the
2 number of significant pairs that survived multiple testing adjustments varied between the
3 two samples. For example, the mean FA of the fornix-stria terminalis, posterior thalamic
4 radiation, and sagittal stratum tracts was associated with the thickness of RNFL, GCIPL,
5 and macula in both males and females, with more significant pairs being identified in
6 females (**Fig. S8**). These retinal thickness traits were also consistently associated with
7 volumes of the pericalcarine, thalamus, and accumbens regions in sex-specific analysis
8 (**Fig. S9**). In summary, although only a relatively small percentage of subjects had both
9 brain and retinal imaging data in the UKB study, we uncovered that the retinal imaging
10 biomarkers, such as the thickness of different retinal layers, were associated with smaller
11 brain volumes, reduced cortical thickness, and weaker white matter structural
12 connections in the brain. Many retina-related brain structural variations were observed
13 in the primary visual cortex and other structures in the visual pathways. Our results are
14 consistent with previous studies that have found parallel changes in eye-brain structures
15 during pathological progression^{1,3}, as well as providing further information on the most
16 relevant brain MRI modalities and biomarkers for clinical applications and future research.
17

18 **GWAS for 156 retinal imaging traits**

19 Based on UKB individuals of white British ancestry⁵⁰, we estimated the proportion of
20 phenotypic variance explained by single nucleotide polymorphisms (SNPs) for the 156
21 retinal imaging traits (average $n = 60,748$). The average SNP-based heritability (h^2) was
22 42.21% for the 46 OCT measures (h^2 range = (19.28%, 68.28%)), all of which were
23 significant at FDR 5% level (**Fig. S10** and **Table S3**). Of the 110 fundus image traits, 90 were
24 significant at FDR 5% level, with the mean h^2 being 19.27% (h^2 range = (4.06%, 42.75%)).
25 In each of the 11 transfer learning models, at least seven of the 10 PCs had significant h^2 .
26 Additionally, we estimated h^2 separately for females and males, and the results were
27 highly consistent between the two sexes (mean $h^2 = 24.83%$ among females vs. 23.33%
28 among males, correlation = 0.972, $P = 0.457$, **Fig. S11**).

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30 We conducted GWAS based on the same white British cohort to uncover the genetic
31 architecture of the 156 retinal imaging traits (average $n = 60,748$). QQ and Manhattan
32 plots can be viewed on our server (<http://165.227.78.169:443/>) developed via PheWeb⁵¹.

1 Linkage disequilibrium score regression (LDSC) intercepts⁵² were all near one, indicating
2 that no confounding factor resulted in the genomic inflation of test statistics (average =
3 1.004, range = (0.974, 1.031)). At a stringent GWAS significance level 3.20×10^{-10} (5×10^{-8} /
4 156, that is, the standard GWAS significance level after further considering Bonferroni-
5 type adjustment for 156 retinal imaging traits), we identified independent (linkage
6 disequilibrium [LD] $r^2 < 0.1$) significant genetic associations in 258 genomic regions
7 (cytogenetic bands). Significant associations were found for all 46 OCT measures and 91
8 of the 110 fundus image traits (**Fig. S12** and **Table S4**). We also estimated these significant
9 genetic effects separately for males and females in a sex-specific analysis. We found that
10 the genetic effects were highly consistent in both sexes (correlation = 0.975, $P = 0.76$, **Fig.**
11 **S13**).

12

13 We replicated our GWAS results using independent European and non-European datasets
14 (**Methods**). First, we performed GWAS of the 156 retinal imaging traits using the UKB
15 European ancestry but non-British subjects (average $n = 5,320$). For the 4,329 identified
16 independent (LD $r^2 < 0.1$) image-variant associations in 258 genomic regions, 1,630
17 (37.65%, in 162 genomic regions) passed the FDR 5% significance level in this European
18 validation GWAS, and 2,210 (51.05%, in 189 regions) were significant at the nominal
19 significance level (0.05) (**Fig. S14** and **Table S5**). Most of the significant genetic effects
20 (2,207/2,210, in 188 regions) had concordant directions in the two independent GWAS,
21 with the correlation of their genetic effects being 0.958 (**Fig. S15**). Among the 188
22 replicated genomic regions, 146 were associated with OCT measures, and 103 were
23 associated with fundus image traits. These results suggest the high generalizability of our
24 GWAS findings in European samples. Next, we repeated the validation GWAS on the non-
25 European UKB subjects (average $n = 6,490$) and found that 25.18% (1,090/4,329, in 142
26 regions) associations were significant at the nominal significance level, most of which
27 (1,068/1,090, in 140 regions) had the same genetic effect directions as the discovery
28 GWAS (**Fig. S16**). Overall, 107 replicated regions were observed for OCT measures and 51
29 for fundus image traits in non-European validation analysis.

30

31 We have also developed polygenic risk scores (PRS) via PRS-CS⁵³ to evaluate the out-of-
32 sample prediction performance of our discovery GWAS results (**Methods**). The PRS for

1 133 of the 156 retinal imaging traits were significant at FDR 5% level (P range = $(6.90 \times 10^{-98}, 3.82 \times 10^{-2})$, **Table S6** and **Fig. S17**), with the mean incremental R-squared being 2.51% (S.E. = 2.29%). A total of 22 traits had R-squared greater than 5%. The highest prediction accuracy was observed on a set of traits related to the INL⁴³, such as the thickness from the INL to the retinal pigment epithelium (RPE) (R-squared = 9.46% and 8.43% for right and left eyes, respectively) and the thickness between the INL to the external limiting membrane (ELM) (R-squared = 7.68% and 7.20% for right and left eyes, respectively). To evaluate the transferability of GWAS findings, we also examined the PRS performance on non-European UKB subjects. We found that 101 retinal imaging PRS had significant prediction performance in the non-European UKB dataset at FDR 5% level (P range = $(2.77 \times 10^{-65}, 2.88 \times 10^{-2})$). The average incremental R-squared of these significant PRS was 1.39% (S.E. = 1.45%), which was significantly lower than their corresponding performance in European dataset ($P = 7.89 \times 10^{-9}$). These results demonstrate the capability of our GWAS summary statistics in out-of-sample analyses and also illustrate the challenge of cross-population genetic prediction.

16

17 **Genetic underpinnings of eye-brain connections in 65 genomic loci**

18 We examined eye-brain genetic pleiotropy in 188 replicated genomic regions of retinal imaging traits that had concordant genetic effect directions in the discovery and validation GWAS. First, for the retinal imaging-significant genetic variants and those in LD with them ($r^2 \geq 0.6$), we symmetrically searched for GWAS signals that have been identified to be associated with brain MRI traits^{35,37,39,46}. Second, we performed association lookups in the NHGRI-EBI GWAS catalog⁵⁴ to identify shared genetic influences between retinal imaging traits and brain-related complex traits and diseases (**Methods**). In 65 of these 188 genomic regions, we found genetic overlaps between the retinal imaging traits and brain phenotypes, 47 of which had also been linked to various eye traits and conditions, such as glaucoma⁵⁵, refractive error⁵⁶, advanced age-related macular degeneration⁵⁷, and cataracts⁵⁸. Specifically, we found genetic pleiotropy for a wide range of brain traits and disorders, including stroke, Parkinson's disease, Alzheimer's Disease, glioma/glioblastoma, neuropsychiatric disorders, migraine, mental health, and cognitive traits (**Fig. 3** and **Table S7**). Shared genetic influences were also identified in 18 regions with different brain MRI modalities, including 10 regions with regional brain

1 volumes³⁵, 9 regions with DTI parameters³⁷, 3 regions with cortical thickness traits⁴⁶, and
2 2 regions with resting fMRI traits³⁹ (**Fig. S18**). Using Bayesian colocalization analysis⁵⁹, we
3 examined whether there were common causal genetic variants underlying the
4 overlapping genetic signals between retinal structures and brain phenotypes (posterior
5 probability of the shared causal variant hypothesis [PPH4] > 0.8^{59,60}). In addition, we found
6 that many retinal imaging-significant genetic variants were expression quantitative trait
7 loci (eQTLs) reported in large-scale eQTL studies of brain tissues⁶¹. Our results are
8 summarized in **Table S8**, with selected eye-brain trait pairs being displayed in **Figures 4-5**
9 and **S19-S79**. Below we have provided more details for each brain MRI modality and major
10 brain phenotype category.

11
12 Brain volumetric measures had genetic overlaps with retinal structures in 10 genomic loci
13 (LD $r^2 \geq 0.6$, **Figs. 4A** and **S19-27**). For example, shared genetic components between
14 cerebrospinal fluid (CSF) volume and vertical cup-to-disc ratio⁶² were found in 11q24.3
15 (**Fig. 4A**). The retinal index variant rs4937515 was an eQTL of *ADAMTS8* in brain tissues⁶¹,
16 and there was strong evidence of shared causal genetic variants between the two traits
17 (PPH4 = 0.997). The rs4937515 was also in LD ($r^2 \geq 0.6$)⁶³ with known genetic risk variants
18 of glaucoma (index variant rs2875238)⁵⁵. The CSF is the primary fluid within the central
19 nervous system, and the biological role of CSF pressure has been well-established in
20 glaucoma and other ophthalmic diseases^{64,65}. Our results provide further evidence of
21 genetic links underlying the connections between CSF and eye disorders. Colocalizations
22 between retinal imaging traits and brain volumes were also observed in 8q23.1 (e.g., right
23 thalamus), 22q13.1 (e.g., left lateral ventricle), 17q24.2 (e.g., left caudal anterior
24 cingulate), 6q25.1 (e.g., right hippocampus), and 7q22.1 (e.g., right accumbens area). In
25 these regions, retinal imaging traits also tagged (LD $r^2 \geq 0.6$) schizophrenia, major
26 depressive disorder, neuroticism, and cognitive traits. In addition, genetic overlaps
27 between retinal structures and cortical thickness traits were found in 3 loci (17q21.31,
28 8p23.1, and 1q21.3), where several brain structures in the visual pathways were involved,
29 including the precentral, supramarginal, fusiform, and precuneus (**Fig. 4B**). In summary,
30 we identify locus-specific genetic overlaps between the thickness of different retinal
31 layers and the morphometry of multiple brain regions, which play essential roles in
32 cognitive functions and are affected in various brain disorders.

1

2 Retinal structures also had widespread genetic pleiotropy with brain structural and
3 functional connectivity. Retinal imaging traits and DTI parameters had shared genetic
4 influences in 9 genomic regions, 7 of which had strong evidence of colocalization (**Figs. 4C**
5 **and S28-35**). For example, the overall macular thickness⁴⁴ and the mode of anisotropy
6 (MO)⁶⁶ of the inferior fronto-occipital fasciculus tract had common causal genetic variants
7 in 17q24.2 (PPH4 = 0.816, **Fig. 4C**). The inferior fronto-occipital fasciculus is the longest
8 associative white matter tract that connects various brain areas and involves multiple
9 functions. Thinner retinal layers had close relationships with the reduced volume and
10 worse microstructural integrity of the brain's white matter⁶⁷. These results provide
11 genetic insights into retina-white matter connections. Both retinal imaging traits and DTI
12 parameters also overlapped genetically with cognitive traits (such as intelligence in
13 22q13.1), psychiatric disorders (such as in 14q24.3), and eye disorders (such as advanced
14 age-related macular degeneration in 17q25.3). We also found shared genetic influences
15 between functional connectivity of resting fMRI and retinal imaging traits in 11q13.3 and
16 17q21.31 (**Figs. 4D and S36**).

17

18 In addition, many genomic regions associated with retinal imaging traits have been linked
19 to brain-related complex traits and diseases in previous GWAS. In 6q14.2, 6q21, 13q14.2,
20 15q26.1, and 16q22.1 regions, the thickness of different retinal layers was in LD ($r^2 \geq 0.6$)
21 with schizophrenia⁶⁸⁻⁷⁰ (**Figs. 5A and S37-S40**). For example, the INL thickness had shared
22 causal genetic variants with schizophrenia (PPH4 = 0.952). The retinal index variant
23 (rs7752421) was an eQTL of *SNAP91* in human brain tissues⁶¹, affecting gene expression
24 levels in the brain. In excitatory neurons, synaptic defects are increasingly associated with
25 schizophrenia, and altered expression of *SNAP91* has been observed to impact synaptic
26 development⁷¹. As schizophrenia patients often report visual perception changes, OCT
27 measures of the retinal structure have received increasing attention in schizophrenia
28 research⁷². The identified genetic links in our analysis support the use of retinal layer
29 assessments as potential biomarkers for schizophrenia. Retinal structures were also in LD
30 ($r^2 \geq 0.6$) with other neuropsychiatric disorders and mental health traits, such as bipolar
31 disorder⁷³, anxiety⁷⁴, depressive symptoms⁷⁵, neuroticism⁷⁶, subjective well-being⁷⁷, and

1 risk-taking tendency⁷⁸ (**Figs. S41-S49**). For example, the thickness of various retinal layers
2 had shared genetic influences with neuroticism in multiple regions (**Figs. S41-S47**).

3

4 There were 23 genomic regions associated with cognitive traits (such as intelligence⁷⁹,
5 cognitive performance⁸⁰, general cognitive ability⁸¹, and reaction time⁸², **Figs. S50-S57**)
6 and/or educational attainment⁸³ (**Figs. 5B and S58-S72**). Several studies have reported
7 that retinal layer thickness may be a prognostic biomarker of cognitive impairment and
8 long-term cognitive decline in older individuals^{84,85}. Retinal imaging traits were in LD ($r^2 \geq$
9 0.6) with multiple neurodegenerative disorders, such as in 2q24.3, 17q21.31, 8p23.1, and
10 15q12 with Parkinson's disease⁸⁶ (**Fig. S73**); in 17q21.31 with corticobasal degeneration⁸⁷;
11 in 7p21.3 with frontotemporal dementia⁸⁸; in 5q14.3, 17q21.31, 6p12.1 with Alzheimer's
12 disease⁸⁹, and several more loci (such as 1q32.1, 2p25.3, and 11q14.2) with biomarkers
13 of Alzheimer's disease⁹⁰ (**Figs. S74-76**). Genetic overlaps with other brain diseases were
14 also observed. For example, vertical cup-to-disc ratio²⁹ was in LD ($r^2 \geq 0.6$) with glioma/
15 glioblastoma⁹¹ and white matter microstructure in 9p21.3 (**Fig. 5C**). Glioma may affect the
16 optic nerve (optic nerve glioma), which is the most common primary neoplasm of the
17 optic nerve⁹². Retinal imaging traits also had shared genetic effects with
18 migraine/headache⁹³ in 5 regions and cerebrovascular diseases in 9 regions, including
19 stroke⁹⁴, Moyamoya disease⁹⁵, intracranial aneurysm⁹⁶, and cerebral aneurysm⁹⁷ (**Figs. 5D**
20 **and S77-79**). In summary, our findings indicate close genetic connections between the
21 eye and the brain. Abnormalities in retinal structure may provide insight into the genetic
22 risk of neurodegenerative diseases and neuropsychiatric disorders.

23

24 **Genetic correlation and heritability enrichment patterns**

25 We examined genetic correlations (GC) between 156 retinal imaging traits and 39 sets of
26 publicly available GWAS summary statistics of brain-related complex traits and diseases
27 using cross-trait LDSC⁹⁸ (**Table S9**). At FDR 5% level ($P < 2.06 \times 10^{-3}$), we observed 246
28 significant genetic correlation pairs between 69 retinal imaging traits and 21 brain
29 phenotypes, including brain disorders, cognitive traits, and mental health traits (**Fig. S80**).

30

31 For example, multiple cognitive traits (such as cognitive function, numerical reasoning,
32 intelligence, and cognitive performance) and education had consistent positive genetic

1 correlations with the thickness of RNFL⁴³ and the overall thickness between the ELM to
2 the inner and outer photoreceptor segments (ISOS)⁴³ as well as their subfields (**Fig. 6A**).
3 Consistent with our results, previous clinical studies have identified RNFL thickness to be
4 phenotypically related to global cognitive score, executive function, and verbal function⁹⁹⁻
5 ¹⁰¹. These studies examined RNFL thickness as a possible early biomarker of cognitive
6 decline, whose thinning suggests axonal loss during the neurodegenerative process of the
7 brain^{101,102}. On the other hand, negative genetic correlations with cognitive traits were
8 observed for the thickness of GCIPL, INL, and RPE⁴³, as well as disc diameter²⁹. The
9 negative correlations between GCIPL thickness and cognitive traits were also in line with
10 one recent study on patients with Alzheimer's disease, where GCIPL thickening correlated
11 with poor cognition in Alzheimer's disease¹⁰³. One hypothesis on the intrinsic mechanism
12 for its thickening suggested that pathological amyloid β ($A\beta$) accumulation and
13 neuroinflammation of retinal ganglion cells (RGCs) contributed to the thickening of
14 GCIPL¹⁰³, which was supported by a parallel study on RGCs in mouse model¹⁰⁴. The
15 thickness between the ISOS and RPE and their subfields were negatively associated with
16 depression and neuroticism. There were also negative associations between depression
17 symptoms and vertical cup-to-disc ratio²⁹ ($GC < -0.166$, $P < 7.72 \times 10^{-4}$), between cross
18 disorder (five major psychiatric disorders¹⁰⁵) and disc diameter ($GC = -0.116$, $P = 1.33 \times$
19 10^{-3}), and between the RNFL thickness and cannabis use disorder ($GC = -0.174$, $P = 1.29 \times$
20 10^{-3}). In addition, we found positive genetic correlations between RPE thickness and
21 attention-deficit/hyperactivity disorder (ADHD) as well as between the INL thickness and
22 stroke ($GC > 0.149$, $P < 1.88 \times 10^{-3}$). For fundus imaging traits, there were also widespread
23 genetic correlations with the above brain phenotypes identified by OCT measures, such
24 as ADHD, cannabis use disorder, cognitive traits, and cross disorder. In addition, fundus
25 imaging traits had higher correlations with schizophrenia ($|GC| = 0.133$, $P = 1.10 \times 10^{-3}$),
26 major depressive disorder ($|GC| = 0.316$, $P = 1.92 \times 10^{-3}$), and risk tolerance ($|GC| = 0.097$,
27 $P = 1.92 \times 10^{-3}$). These results demonstrated the genome-wide genetic similarity between
28 retinal structures and brain disorders and traits.

29

30 We also performed partitioned heritability analysis¹⁰⁶ via LDSC to identify the tissues and
31 cell types where genetic variation led to changes in retinal imaging traits. First, we
32 examined a wide variety of tissue and cell type-specific regulatory elements from the

1 Roadmap Epigenomics Consortium¹⁰⁷. Among all tissue and cell types, the strongest
2 heritability enrichments were observed in active gene regulatory regions of multiple brain
3 tissues (**Fig. S81** and **Table S10**). Next, we repeated the partitioned heritability analysis
4 using chromatin accessibility data from neurons (NeuN+) and glia (NeuN-) sampled from
5 14 cortical and subcortical brain regions¹⁰⁸. We observed that the heritability of retinal
6 structures had consistently stronger enrichment in brain glial regulatory elements than
7 neuronal regulatory elements (**Fig. S82**). These heritability enrichments suggest that
8 genetic variants associated with retinal structures may also alter the function of
9 regulatory elements in brain tissues, especially glial cells, indicating the genomic links
10 between the eye and the brain.

11

12 **Genetic causal links with brain disorders**

13 We applied Mendelian randomization (MR) with GWAS summary statistics from the
14 FinnGen database¹⁰⁹ to examine the directional relationships between retinal structure
15 and brain disorders. We used eight different MR methods¹¹⁰⁻¹¹⁷, and prioritized significant
16 results that passed the Bonferroni adjustment of multiple testing in at least two methods
17 (**Methods**). The results presented below have also passed several robustness tests, such
18 as the MR-Egger intercept test for pleiotropy¹¹⁸.

19

20 Causal genetic effects were found between retinal imaging traits and brain disorders in
21 both directions, and these results suggested close relationships between retinal
22 structures and Alzheimer's disease (**Table S11**). For example, causal genetic effects from
23 Alzheimer's disease to retinal structures were identified in multiple OCT measures and
24 fundus imaging traits, including the thickness of INL ($\beta > 0.025$, $P < 4.74 \times 10^{-5}$) and the
25 central subfield between the ISOS and RPE ($\beta > 0.027$, $P < 1.12 \times 10^{-5}$). We also observed
26 causal effects from psychiatric diseases and other degenerative diseases of the nervous
27 system to retinal structures, such as the INL thickness ($\beta > 0.040$, $P < 3.56 \times 10^{-7}$). These
28 newly established positive causal effects between psychiatric diseases and INL thickness
29 can be linked to the identified negative genetic correlations between INL thickness and
30 cognitive traits in our previous section. There was a similar conclusion reached in previous
31 studies regarding the thickness of the RNFL, whose thinning was indicative of cognitive
32 decline^{119,120}. On the contrary, other recent studies have also noted correlations between

1 INL thickening and brain-related diseases, such as Alzheimer's disease and multiple
2 sclerosis^{121,122}. These studies suggested that INL thickness was a response marker for
3 inflammation during the early stages of diseases, which was further confirmed by another
4 study, where effective disease treatment was associated with a reduction in INL
5 thickness¹²³. In addition, when we used retinal imaging traits as exposures and brain
6 disorders as outcomes, we observed causal effects from retinal structural changes to
7 dementia and Alzheimer's disease. These causal links were all observed on fundus
8 imaging traits generated from pre-trained transfer learning models. For OCT measures,
9 causal links were identified between anxiety disorders and the thickness of the central
10 subfield between the INL and RPE ($\beta = 0.278$, $P = 7.92 \times 10^{-6}$). Overall, MR analysis
11 indicates that retinal imaging traits have genetic interactions with brain
12 neurodegenerative and neuropsychiatric diseases, especially dementia and Alzheimer's
13 disease.

14

15 **Joint prediction of brain phenotypes using retinal and brain imaging**

16 Using retinal and brain imaging traits, we examined whether they could be combined to
17 better predict brain-related complex traits and diseases than using only one type of
18 imaging data. We used a training, validation, and testing design, in which both retinal and
19 brain images were available for the subjects in the validation and testing datasets. Model
20 parameters were tuned based on the validation data, and prediction performance was
21 evaluated in the independent testing dataset (**Methods**).

22

23 First, retinal imaging traits had significant prediction power on 16 brain phenotypes,
24 including cognitive traits (such as fluid intelligence and prospective memory), neuroticism,
25 family history of stroke, mental and behavioral disorders (ICD-10 Chapter F, such as
26 depressive episode), and diseases of the nervous system (ICD-10 Chapter G, such as
27 multiple sclerosis and carpal tunnel syndrome) (prediction correlation β range = [0.068,
28 0.179], $P = [8.11 \times 10^{-19}, 7.88 \times 10^{-4}]$, **Fig. S83** and **Table S12**). The strongest prediction
29 accuracy was observed on fluid intelligence ($\beta = 0.179$, $P = 8.11 \times 10^{-19}$). The top-ranking
30 features for fluid intelligence prediction were from both OCT measures and fundus
31 imaging traits, such as the thickness of RNFL, INL, and GCIPL (**Table S12**). Moreover, the
32 prediction accuracy was improved by adding more retinal imaging traits, suggesting that

1 various retinal structural variations captured by different retinal imaging modalities and
2 pre-trained models can contribute to cognitive performance prediction (**Fig. S84** and
3 **Table S12**). Multiple clinical studies have suggested that retinal imaging traits like retinal
4 layer thickness show promising prediction power for pathological cognitive decline and
5 dementia diagnoses^{8,102}. Similar additive effects were observed on other brain
6 phenotypes, such as the family history of stroke (**Fig. S85**).

7

8 Next, we included brain MRI traits in the prediction model of these brain phenotypes.
9 **Figure 6B** shows that multimodal brain imaging data can significantly predict all these
10 brain phenotypes (β range = [0.091, 0.314], P range = [7.61×10^{-6} , 3.25×10^{-56}]), and using
11 both retinal and brain imaging traits can further improve the performance (β range =
12 [0.120, 0.344], P range = [3.72×10^{-9} , 7.54×10^{-68}]). For example, multiple categories of
13 brain MRI traits can predict fluid intelligence, including DTI parameters ($\beta = 0.118$, $P =$
14 7.05×10^{-9}), regional brain volumes ($\beta = 0.132$, $P = 8.17 \times 10^{-11}$), cortical thickness traits
15 ($\beta = 0.100$, $P = 9.01 \times 10^{-7}$), resting fMRI ($\beta = 0.216$, $P = 7.01 \times 10^{-27}$), and task fMRI ($\beta =$
16 0.197 , $P = 2.11 \times 10^{-22}$). Adding retinal imaging traits to each of these brain modalities
17 improved the prediction performance over only using this single brain modality. The
18 largest improvement was observed when we added all imaging data types together ($\beta =$
19 0.344 , $P = 7.54 \times 10^{-68}$). The prediction accuracy further moved up to 0.391 ($P = 9.56 \times 10^{-$
20 $89}$) by adding the genetic PRS of fluid intelligence (**Fig. 6C**). These results demonstrate that
21 integrating retinal and brain imaging modalities may lead to better predictions of brain-
22 related complex traits and diseases than using only one type of imaging data alone.

23

24 **DISCUSSION**

25 Imaging of the eye is inexpensive and noninvasive, and it can provide rich information
26 about the retina's structure and function. Many brain diseases, such as neuropsychiatric
27 and neurodegenerative disorders, are diagnosed and monitored primarily based on
28 subjective reports of clinical symptoms¹²⁴. The accuracy of these subjective reports is
29 often complicated by the fact that patients with impaired mental capacity report
30 inconsistent symptoms in varying degrees, which can bias the downstream data analysis
31 and clinical prediction¹²⁵. Also, patients presenting with acute mental symptomatology
32 may have hard-to-define underlying ailments, which leads to imprecise medical

1 management. Retinal imaging traits may serve as objective biomarkers for brain
2 abnormalities and to assess the progression of neurological conditions¹²⁶. In this paper,
3 we identified novel eye-brain connections using multimodal imaging data from the two
4 organs. The pericalcarine (primary visual cortex) and other structures within the visual
5 pathway were associated with retinal features. Furthermore, we observed correlations
6 between retinal features and thalamic volume, both of which are derived from the
7 diencephalon. We then described the genetic co-architecture of the eye and the brain in
8 65 genomic regions, suggesting genetic associations that overlap among retinal features,
9 brain MRI traits, and eye disorders (such as macular degeneration). We found genetic
10 correlations and causal links between retinal imaging traits and various cognitive and
11 mental health traits, as well as brain disorders. Additionally, we demonstrated that multi-
12 organ images could be combined to improve the prediction of brain phenotypes. As
13 neuroprotective treatments become more widely available, this ability to predict brain
14 diseases could have major clinical benefits. Compared with previous clinical studies, our
15 findings support hypotheses regarding underlying mechanisms of eye-brain connections
16 from a novel cross-organ genetic perspective.

17

18 This study has a few limitations. Our analyses were based on the ongoing UKB brain
19 imaging study, which currently covered only a small proportion of all UKB participants
20 (about 10% by 2022) and consisted primarily of European ancestry individuals. We
21 conducted phenotypic analyses on an even smaller sample of UKB subjects with both eye
22 and brain imaging data. It is anticipated that more brain-related retinal imaging
23 biomarkers can be discovered and replicated as the UKB brain imaging study collects data
24 from more subjects¹²⁷. Furthermore, it is challenging to infer phenotypic causality from
25 our current cross-sectional analysis. Repeated UKB imaging scans in the future will allow
26 us to study the causal relationships between eye and brain changes in a longitudinal study
27 design. In addition, the eye-brain genetic links identified were European or UKB specific,
28 and it will be important to examine whether these cross-organ genetic overlaps can be
29 generalized to other populations or studies when more data are collected¹²⁸. In summary,
30 the massive genetic connections between the brain and the eye found in our UKB-based
31 study support the use of retinal imaging to study and manage the risk of brain disorders.

1 The utility of these retinal imaging biomarkers needs to be verified in future clinical and
2 research settings.

3

4 **METHODS**

5 Methods are available in the *Methods* section.

6 *Note: One supplementary information pdf file and one supplementary table zip file are*
7 *available.*

8

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22

23 **AUTHOR CONTRIBUTIONS**

24 B.Z. designed the study. Y.J.L. and B.Z. processed the raw retinal imaging data. B.Z., Z.F.,
25 Z.W., J.S., X.Y., X.F.W., B.L., X.Y.W, and C.C. analyzed the data. Z.F., B.Z., Y.Y., and J.L.
26 designed the website and developed online resources. Y.L.Y, Y.L., J.L.S., J.M.O., T.L., and
27 H.Z. provided comments and helped interpret the results. B.Z. wrote the manuscript with
28 feedback from all authors.

29

30 **CORRESPONDENCE AND REQUESTS FOR MATERIALS** should be addressed to B.Z and H.Z.

31

32 **COMPETING FINANCIAL INTERESTS**

1 The authors declare no competing financial interests.

2

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29

30 **METHODS**

31 **Eye and brain imaging data**

1 Our study was based on data obtained from the UK Biobank (UKB) study, which recruited
2 approximately half a million individuals between the ages of 40 and 69 between 2006 and
3 2010⁴² (<https://www.ukbiobank.ac.uk/>). The ethics approval of the UKB study was from
4 the North West Multicentre Research Ethics Committee (approval number: 11/NW/0382).
5 The optical coherence tomography (OCT) and retinal imaging scans were part of the eye
6 measurements conducted during the participant's visit to the UKB assessment center. We
7 considered two sets of retinal imaging traits. First, we used the derived OCT measures in
8 Category 100079 (<https://biobank.ndph.ox.ac.uk/showcase/label.cgi?id=100079>), which
9 were generated and returned by previous studies^{29,43,44}. These measures mainly provide
10 the thickness of different retinal layers and their subfields, as well as the vertical cup-to-
11 disc ratio and disc diameter. As suggested, we used the data in Data-Fields 28552 &
12 28553⁴³ to perform quality control for these OCT measures by keeping images with an
13 image quality score > 45. We further only keep the OCT measures with a sample size >
14 30,000, resulting in 46 measures with an average sample size of 62,425.

15

16 Second, we downloaded the raw fundus retinal eye images from Category 100016
17 (<https://biobank.ndph.ox.ac.uk/showcase/label.cgi?id=100016>) and performed GWAS on
18 these whole images by extracting imaging biomarkers using transfer learning models.
19 Briefly, we used multiple pre-trained deep convolutional neural networks (CNNs) trained
20 from the ImageNet⁴⁵ database. The ImageNet database contains more than 14 million
21 images classified into more than 20,000 classes, which can be used to train models that
22 extract various features from retinal fundus images. Many CNNs models have been
23 trained on ImageNet and were widely used in the image processing field to learn complex
24 patterns from images. In addition to the ResNet50¹²⁹ model used by the transferGWAS³¹,
25 we implemented 10 more pre-trained CNN models, including the AlexNet¹³⁰, Vgg16¹³¹,
26 Vgg19¹³¹, GoogLeNet (Inception V1)¹³², Inception (V3)¹³², ResNet18¹²⁹, ResNet34¹²⁹,
27 SqueezeNet¹³³, MobileNet¹³⁴, and ShuffleNet¹³⁵. These pre-trained models are available
28 on Pytorch¹³⁶ and represent different designs and architectures, such as layer depth, size
29 of kernels, and hyperparameters. For example, the ResNet50 has 50 layers with kernel
30 size 1×1 , 3×3 , and 7×7 , while AlexNet has 8 layers with kernel size 3×3 , 5×5 , and 11
31 $\times 11$. All pre-trained models use the rectified linear unit (ReLU) as the activation function.
32 We began by combining the original left and right retinal fundus images and the rotated

1 images with 90°, 180°, and 270°, each with and without horizontal mirroring. Next, we
2 input these eight retinal fundus images into each pre-trained model and averaged the
3 outputs from the last layer of convolutional networks. Then we generated the top-10
4 ranked principal components (PCs) from each of the 11 models as retinal imaging
5 biomarkers in downstream GWAS analyses. The average sample size across all these 110
6 (10 × 11) fundus imaging traits is 78,513. In all the OCT measures and fundus image traits,
7 the values greater than five times the median absolute deviation from the median were
8 treated as outliers and removed.

9

10 The UKB brain MRI data were generated from raw images downloaded from Category
11 100003 (<https://biobank.ndph.ox.ac.uk/showcase/label.cgi?id=100003>). The multimodal
12 brain imaging traits used in the present paper have been extracted in previous papers by
13 our research group^{35,37,39,46}. First, we had 101 regional brain volumes³⁵ and 63 cortical
14 thickness traits⁴⁶ generated from T1-weighted structural MRI images. These structural
15 MRI traits were produced by the advanced normalization tools¹³⁷ (ANTs). For the 101
16 volumetric traits, we had brain volumes for 98 pre-defined cortical and subcortical areas
17 and three global brain volume measures (total gray matter volume, total white matter
18 volume, and total brain volume). We also examined the thickness of 62 cortical areas and
19 the global thickness. Second, the ENIGMA-DTI pipeline^{138,139} was used to generate 110
20 tract-averaged DTI parameters based on diffusion MRI, including fractional anisotropy,
21 mean diffusivity, axial diffusivity, radial diffusivity, and mode of anisotropy, for 21
22 predefined major white matter tracts and the whole brain (5 × 22). For resting fMRI, we
23 applied the Glasser360 atlas¹⁴⁰ to partition the cerebral cortex into 360 regions for 12
24 functional networks¹⁴¹, including the primary visual, secondary visual, auditory,
25 somatomotor, cingulo-opercular, default mode, dorsal attention, frontoparietal,
26 language, posterior multimodal, ventral multimodal, and orbito-affective networks. We
27 generated 92 functional activity (amplitude) and functional connectivity traits, including
28 the average activity for each network and the average connectivity for each pair of
29 networks (including within the same network), as well as the global activity and
30 connectivity of the whole cortex. Similarly, 92 functional activity and connectivity traits
31 were generated from task fMRI³⁹. In summary, we considered 458 brain MRI traits of brain

1 structure and function. See **Table S1** for the complete ID list of both retinal imaging and
2 brain imaging traits.

3

4 **Phenotypic eye-brain imaging analyses**

5 In our phenotypic analysis, we examined pairwise associations between 156 retinal
6 imaging traits and 458 brain MRI traits. We used the UKB subjects with both two imaging
7 types and adjusted a wide range of covariates, including age, sex, standing height,
8 assessment center, body mass index, weight, waist-to-hip ratio, smoking status, mean
9 arterial blood pressure, age-squared, age-sex-interaction, age-squared-sex-interaction,
10 top 40 genetic PCs¹⁴², volumetric scaling, head motion, head motion-squared, brain
11 position, brain position-squared^{34,36}, diabetes, ICD-10 disease code starting with R73
12 (“elevated blood glucose level”, such as hyperglycemia), I70 (“atherosclerosis”, such as
13 atherosclerosis of aorta), I10 (Essential (primary) hypertension), and E78 (“disorders of
14 lipoprotein metabolism and other lipidaemias”, such as hyperlipidemia). For regional
15 brain volumes, we additionally corrected for total brain volume to remove global effects.
16 We fitted linear models for each pair of imaging traits (R version 3.6.0) and used a
17 discovery-validation design, in which the UKB individuals of white British ancestry
18 (average $n = 6,454$ across different modalities) were used to discover eye-brain imaging
19 associations, which were verified by a hold-out independent validation dataset (average
20 $n = 959$, relatives¹⁴² of the discovery sample were removed). The Benjamini-Hochberg
21 procedure was used to adjust for multiple testing, and we reported significant
22 associations at the false discovery rate (FDR) of 5%. Validation criteria included a P value
23 less than 0.05 in the hold-out independent dataset with concordant association signs
24 between the discovery and validation datasets. We also considered the conservative
25 Bonferroni multiple testing correction and highlighted these top-ranking significant
26 findings in the paper. In addition, we repeated the above analysis separately for females
27 and males (average $n = 3,338$ and $3,150$, respectively) and reported the sex-specific
28 association patterns.

29

30 **Genetic analysis of 156 retinal imaging traits**

31 We performed GWAS for the 156 retinal imaging traits using the imputed genotyping data
32 from the UKB study. For the set of subjects with both retinal imaging traits and genetic

1 data, we performed the following quality controls³⁹: 1) removed individuals with missing
2 genotype rate > 0.1; 2) removed variants with missing genotype rate > 0.1; 3) removed
3 variants with minor allele frequency (MAF) < 0.01; 4) removed variants that failed the
4 Hardy-Weinberg equilibrium test at 1×10^{-7} level; and 5) removed variants with
5 imputation INFO score < 0.8. The SNP-based heritability of white British samples was
6 estimated based on all autosomal SNPs using GCTA⁵⁰ (average $n = 60,748$). We adjusted
7 for the effects of age, sex, assessment center, age-squared, age-sex interaction, age-
8 squared-sex interaction, and top 40 genetic PCs¹⁴².

9

10 Using the same set of subjects and covariates data, we performed GWAS using linear
11 mixed effect models via fastGWA¹⁴³. SNP heritability and GWAS were also conducted
12 separately for males and females. We defined the independent ($LD\ r^2 < 0.1$) significant
13 genetic associations and loci using FUMA¹⁴⁴ (version v1.3.8). The details of FUMA
14 annotations can be found at <https://fuma.ctglab.nl/tutorial>. Briefly, FUMA identified
15 variants whose P values passed our stringent GWAS significance level 3.20×10^{-10} (the
16 standard GWAS significance level after further Bonferroni-adjusted for the 156 retinal
17 imaging traits) and were independent of other significant variants ($LD\ r^2 < 0.1$). Based on
18 these independently significant variants, FUMA constructed LD blocks by considering all
19 variants ($MAF \geq 0.0005$, including variants from the 1000 Genomes reference panel) in LD
20 ($r^2 \geq 0.6$) with at least one independent significant variant. For independently significant
21 associations defined by FUMA, we performed validations using 1) the UKB European but
22 non-British subjects (average $n = 5,320$) and 2) UKB non-European subjects (average $n =$
23 6,490). Relatives of the discovery GWAS sample were removed, and we adjusted for the
24 top 10 genetic PCs instead of the top 40. Other adjusted covariates remained the same.
25 We also developed polygenic risk scores (PRS) using summary statistics from discovery
26 GWAS and examined their prediction accuracy on the two validation datasets. We
27 constructed PRS based on PRS-CS⁵³ with all default parameters. The validation genotype
28 data were randomly selected from 1,500 UKB European subjects without retinal imaging
29 data.

30

31 **Genetic eye-brain imaging analyses**

1 For the independently significant variants and all variants in their LD blocks, we used
2 FUMA to look them up on the NHGRI-EBI GWAS catalog (version e104_2021-09-15) to
3 search for any previously GWAS results reported on these variants ($P < 9 \times 10^{-6}$). We
4 focused on the existing GWAS results of brain and eye-related complex traits and diseases
5 and manually categorized them into 14 groups, including stroke (and other
6 cerebrovascular disorders, such as Moyamoya disease, intracranial aneurysm, and
7 cerebral aneurysm), Parkinson's disease, Alzheimer's disease, glioma/glioblastoma (GBM),
8 other neurological disorders (such as amyotrophic lateral sclerosis, progressive
9 supranuclear palsy, corticobasal degeneration, and frontotemporal dementia),
10 schizophrenia, other psychiatric disorders (such as bipolar disorder, depression, major
11 depressive disorder, and autism spectrum disorder), psychological traits (such as
12 neuroticism, anxiety, subjective well-being, and risk tolerance), cognitive traits (such as
13 general cognitive ability, the highest math class taken, intelligence, and reaction time),
14 education, brain structure/function, migraine, Alzheimer's disease biomarkers (such as
15 cerebrospinal fluid biomarker levels, rate of cognitive decline in Alzheimer's disease, and
16 plasma t-tau levels), and eye traits/diseases (such as macular thickness, refractive error,
17 spherical equivalent, and glaucoma). In addition, we systematically examined genetic
18 overlaps with the GWAS results of brain MRI traits reported in previous studies, including
19 101 regional brain volumes³⁵, 215 DTI parameters³⁷ (including the 110 tract-average
20 values used in our phenotypic analysis and 105 additional PCs of fractional anisotropy),
21 63 cortical thickness traits⁴⁶, 92 resting fMRI traits, and 92 task fMRI traits³⁹. For the index
22 variants of retinal imaging traits defined by FUMA, we looked up the MetaBrain
23 database⁶¹ (<https://www.metabrain.nl/>) to see if they were reported eQTLs in large-scale
24 gene expression meta-analysis of brain tissues. For each locus with shared genetic
25 influences, we tested for common causal genetic variants between the retinal imaging
26 trait and the brain phenotype using Bayesian colocalization analysis⁵⁹. The colocalization
27 was established if the posterior probability of the shared causal variant hypothesis (PPH4)
28 was greater than 0.8^{59,60}.

29

30 Cross-trait LDSC⁹⁸ (<https://github.com/bulik/ldsc/>, version 1.0.1) was used to examine the
31 pairwise genetic correlation between 156 retinal imaging traits and 39 sets of publicly
32 available GWAS summary statistics of brain phenotypes. The default European LD scores

1 provided by the LDSC software were used, which were based on the 1000 Genomes
2 European data. We used the HapMap3 variants, and variants in the major
3 histocompatibility complex region were excluded. For the 46 OCT measures, we also used
4 LDSC to perform the heritability enrichment analysis¹⁰⁶ with genetic variant annotations
5 of tissue type and cell type-specific regulatory elements. The heritability explained by the
6 annotated genome regions was estimated and tested with percentages and enrichment
7 scores. Baseline annotation models were included in the analysis when we analyzed
8 additional annotations. We tested for the annotations of regulatory elements from
9 multiple adult and fetal tissues from the Roadmap Epigenomics Consortium¹⁰⁷ and two
10 major brain cell types (neurons and glia) sampled from various brain cortical and
11 subcortical brain regions¹⁰⁸.

12

13 Bi-directional Mendelian randomization (MR) analysis was used to discover the causal
14 effect between 156 retinal imaging traits and 25 brain-related clinical endpoints. Eight
15 MR methods¹¹⁰⁻¹¹⁷ were implemented, including MR Egger, simple median, simple mode,
16 fixed effect inverse variance weighted (IVW), multiplicative random effect IVW, DIVW,
17 MR-RAPS, and GRAPPLE. The 25 brain-related clinical endpoints were all from the latest
18 release (R7) of FinnGen database (https://www.finnngen.fi/en/access_results), where
19 of them were mental and behavior disorders, and the remaining 13 phenotypes were
20 diseases of the nervous system. Most of the diseases we selected have a number of cases
21 greater than 10,000, except for a few important brain diseases, including Alzheimer's
22 disease ($n > 6,000$), other neurological diseases ($n = 7288$), and epilepsy ($n = 8523$). **Table**
23 **S11** provides more information on the MR methods and FinnGen data. Exposure GWAS
24 summary statistics were first clumped with Plink¹⁴⁵ to guarantee that the instrumental
25 variables used in MR models are independent. The P value significance threshold (p_1) and
26 the secondary significance threshold (p_2) in clumping were set to 5×10^{-8} , and the 1000
27 Genomes European reference panel was applied. Besides, the threshold over the squared
28 correlation between two genetic variants was set to be $r^2 = 0.01$ and window size = 1Mb.
29 After clumping, the selected SNPs from exposure GWAS data were extracted from
30 outcome GWAS summary statistics with function *extract_outcome_data()* in the two-
31 sample MR package (<https://mrcieu.github.io/TwoSampleMR/>). To ensure that the effect
32 of a genetic variant on the exposure and outcome corresponded to the same allele, data

1 harmonization was performed using the *harmonise_data function()* with the default
2 settings. The estimated causal pairs of retinal imaging trait and brain disease were further
3 screened with several rules. The first step was to discard pairs with fewer than six genetic
4 variants. Second, we dropped the pairs whose estimated MR Egger intercept differed
5 significantly from zero¹¹⁸. Bonferroni correction was then performed on the MR results of
6 each method separately. Finally, we reported the causal pairs that were significant for
7 either of the IVW methods and at least one of the robust MR methods (DIVW, simple
8 mode, simple median, MR-RAPS, and GRAPPLE).

9

10 **Prediction of brain phenotypes using retinal and brain imaging data**

11 We examined the prediction power of 156 retinal imaging traits on 32 brain-related
12 complex traits and diseases, including cognitive traits, neuroticism sum score, family
13 history of brain disorders, mental and behavioral disorders (ICD-10 Chapter F), and
14 diseases of the nervous system (ICD-10 Chapter G). We focused on unrelated white British
15 subjects and randomly selected 50,944 subjects as the training dataset, 2,464 subjects as
16 the validation dataset, and 2,464 subjects as our testing dataset. The subjects in the
17 validation and testing datasets also had brain MRI data, enabling testing the prediction
18 performance with both two imaging types in later steps. For each of the 32 traits, we used
19 ridge regression for prediction and the effect sizes of retinal imaging traits were estimated
20 on the training dataset via the *glmnet*¹⁴⁶ package (R version 3.6.0). All model parameters
21 were tuned based on validation data, and prediction performance was examined based
22 on the correlation between the predicted values and the observed ones in the
23 independent testing data. In all the training, validation, and testing datasets, we removed
24 the effects of age, sex, age-sex interaction, age-squared, age-squared-sex interaction,
25 assessment center, and top 40 genetic PCs. For brain phenotypes where retinal imaging
26 traits had significant predictive power after Bonferroni correction for multiple testing, we
27 further examined the predictive power of multiple brain MRI modalities and the joint
28 performance of using retinal and brain imaging traits. In brain imaging prediction, we used
29 the same validation and testing datasets as the retinal imaging analysis and all other
30 unrelated white British subjects (average $n = 37,239$) as training data. Finally, we
31 examined the prediction accuracy of genetic PRS for fluid intelligence. We used the
32 unrelated white British subjects without retinal or brain imaging data as training GWAS

1 ($n = 71,406$) and developed the PRS with PRS-CS⁵³. The same set of covariates as the
2 imaging prediction analysis was removed.

3

4 **Code availability**

5 We made use of publicly available software and tools. The original codes to apply pre-
6 trained transfer learning models to extract features from raw retinal fundus images are
7 available at <https://github.com/mkirchler/transferGWAS>. Our code with more
8 implemented pre-trained CNN models will be shared on Zenodo <https://zenodo.org/>.

9

10 **Data availability**

11 GWAS summary statistics of brain MRI traits can be freely downloaded at BIG-KP
12 (<https://bigkp.org/>). GWAS summary statistics of retinal imaging traits will be made
13 publicly available at Eye-KP (<https://www.eyekp.org/>). The individual-level data used in
14 this study can be obtained from <https://www.ukbiobank.ac.uk/>.

15

16 **Figure legends**

17 **Fig. 1 Study overview and workflow.**

18 **(A)** An overview of the study design. We used multimodal retinal and brain imaging data
19 to understand the phenotypic and genetic connections between the brain and the eye.
20 We considered multiple brain magnetic resonance imaging (MRI) modalities, including
21 structural MRI, diffusion MRI, resting-state functional MRI (fMRI), and task-based fMRI.
22 For the eye, we used traits derived from retinal optical coherence tomography (OCT) and
23 extracted from fundus retinal images using pre-trained transfer learning models. **(B)** A
24 brief description of the overall workflow and major analyses in each part.

25

26 **Fig. 2 Phenotypic eye-brain imaging associations.**

27 **(A)** This figure shows the $-\log_{10}(\text{p-value})$ of testing the associations between 156 retinal
28 imaging traits (46 derived OCT measures and 110 fundus image traits) and 458 brain MRI
29 traits, including 101 regional brain volumes, 63 cortical thickness traits, 110 diffusion
30 tensor imaging (DTI) parameters, 92 resting fMRI traits, and 92 task fMRI traits. Table S1
31 provides more information on these imaging traits. The red dashed horizontal line

1 indicates the Benjamini-Hochberg FDR 5% significance level ($\text{raw } P < 4.37 \times 10^{-4}$). Each
2 brain imaging modality is labeled with a different color. We have also labeled the brain
3 structures that had the strongest associations in each modality. **(B-C)** Location of the
4 white matter tracts whose DTI parameters were significantly associated with **(B)** the
5 thickness of the ganglion cell and inner plexiform layer (GCIPL, left eye) and **(C)** the overall
6 thickness of the macula (left eye). AD, axial diffusivity; RD, radial diffusivity; MO, mode
7 of anisotropy; and FA, fractional anisotropy. **(D-E)** Location of the brain regions whose
8 volumes were significantly associated with **(D)** the thickness of GCIPL (right eye) and **(E)**
9 the overall thickness of the macula (right eye). **(F)** Location of the cortical brain regions
10 whose thickness was significantly associated with the thickness of GCIPL (left eye).

11

12 **Fig. 3 Genomic loci associated with both eye imaging traits and brain-related complex**
13 **traits and diseases.**

14 **(A)** Ideogram of genomic regions (names are in black) influencing both retinal imaging
15 traits and brain-related complex traits and diseases, including the phenotypes reported
16 on the NHGRI-EBI GWAS catalog (<https://www.ebi.ac.uk/gwas/>) and the brain MRI traits
17 available on BIG-KP (<https://bigkp.org/>). Each category of brain phenotypes is labeled
18 with a different color, and we use different shapes for OCT measures and fundus image
19 traits. **(B)** Table summary, where the x -axis represents the genomic regions and y -axis
20 displays the category of brain phenotypes. Derived OCT measures and fundus image traits
21 are labeled with different colors, and a third color is used when both are observed in the
22 locus.

23

24 **Fig. 4 Selected genetic loci that were associated with both eye and brain imaging traits.**

25 **(A)** In 11q24.3, we observed shared genetic influences between the vertical cup-to-disc
26 ratio (regressed on disc diameter, left eye, VCDR_regressed_left, index variant rs4937515)
27 and the cerebrospinal fluid volume (CSF volume, index variant rs4936099). Bayesian
28 colocalization analysis suggested the shared causal variant between the two traits
29 (posterior probability PPH4 = 0.997). **(B)** In 1q21.2, we observed shared genetic influences
30 between the inner nuclear layer (INL) thickness (left eye, INL_thickness_left) and the

1 cortical thickness of the right precentral brain region (Right_precentral_thickness, shared
2 index variant rs71578488, PPH4 = 0.562). In this region, the INL_thickness_left was also
3 in LD ($r^2 \geq 0.6$) with cerebrospinal fluid biomarker levels. **(C)** In 17q24.2, we observed
4 shared genetic influences between the overall macular thickness (right eye,
5 overall_macular_thickness_right, index variant rs4791212) and the mean MO of the
6 inferior fronto-occipital fasciculus (IFO_MO, index variant rs12451721, PPH4 = 0.963). We
7 also observed genetic overlaps (LD $r^2 \geq 0.6$) with self-reported math ability, risk-taking
8 tendency, and loneliness. **(D)** In 11q13.3, we observed shared genetic influences between
9 the ninth PC of the Vgg19 model on fundus image (Vgg19_PC9) and the functional
10 connectivity within the auditory network (Auditory<=>Auditory, shared index variant
11 rs12807936, PPH4 = 0.994).

12

13 **Fig. 5 Selected genetic loci that were associated with both eye and brain-related**
14 **complex traits and disorders.**

15 **(A)** In 6q14.2, we observed shared genetic influences between the inner nuclear layer (INL)
16 thickness (right eye, INL_thickness_right, index variant rs7752421) and schizophrenia
17 (index variant rs3798869). Bayesian colocalization analysis suggested the shared causal
18 variant between the two traits (posterior probability PPH4 = 0.952). In this region, the
19 thickness of INL was also in LD ($r^2 \geq 0.6$) with bipolar disorder and cognitive ability. **(B)** In
20 14q11.2, we observed shared genetic influences between the overall macular thickness
21 (right eye, overall_macular_thickness_right, index variant rs200581586) and educational
22 attainment (index variant rs4982712, PPH4 = 0.764). In this region, the overall macular
23 thickness was also in LD ($r^2 \geq 0.6$) with intelligence and cognitive ability. **(C)** In 9p21.3, we
24 observed shared genetic influences between the vertical cup-to-disc ratio (regressed on
25 disc diameter, left eye, VCDR_regressed_left, index variant 9:22053956_TA_T) and
26 Glioma (index variant rs4977756). We also observed genetic overlaps (LD $r^2 \geq 0.6$) with
27 self-reported math ability, risk-taking tendency, and loneliness. **(D)** In 13q14.13, we
28 observed shared genetic influences between the fifth PC of the Vgg16 model on fundus
29 image (Vgg16_PC5, index variant rs866376) and ischemic stroke (index variant rs9526212,
30 PPH4 = 0.994).

31

1 **Fig. 6 Genetic correlations and prediction analysis.**

2 **(A)** We show the selected genetic correlations between brain-related complex traits and
3 diseases (x -axis) and retinal imaging traits (y -axis). The asterisks highlight significant
4 genetic correlations after adjusting for multiple testing using the Benjamini-Hochberg
5 procedure to control the FDR at 5% level. The colors represent genetic correlations. **Table**
6 **S1** provides more information on these retinal imaging traits. ADHD, attention-
7 deficit/hyperactivity disorder. **(B)** Predicting brain phenotypes using both retinal and
8 brain imaging traits. **(C)** The accuracy of fluid intelligence prediction using multiple data
9 types. Retinal image, including all retinal imaging traits. DTI parameters, diffusion tensor
10 imaging parameters; Brain image, including all brain imaging modalities.

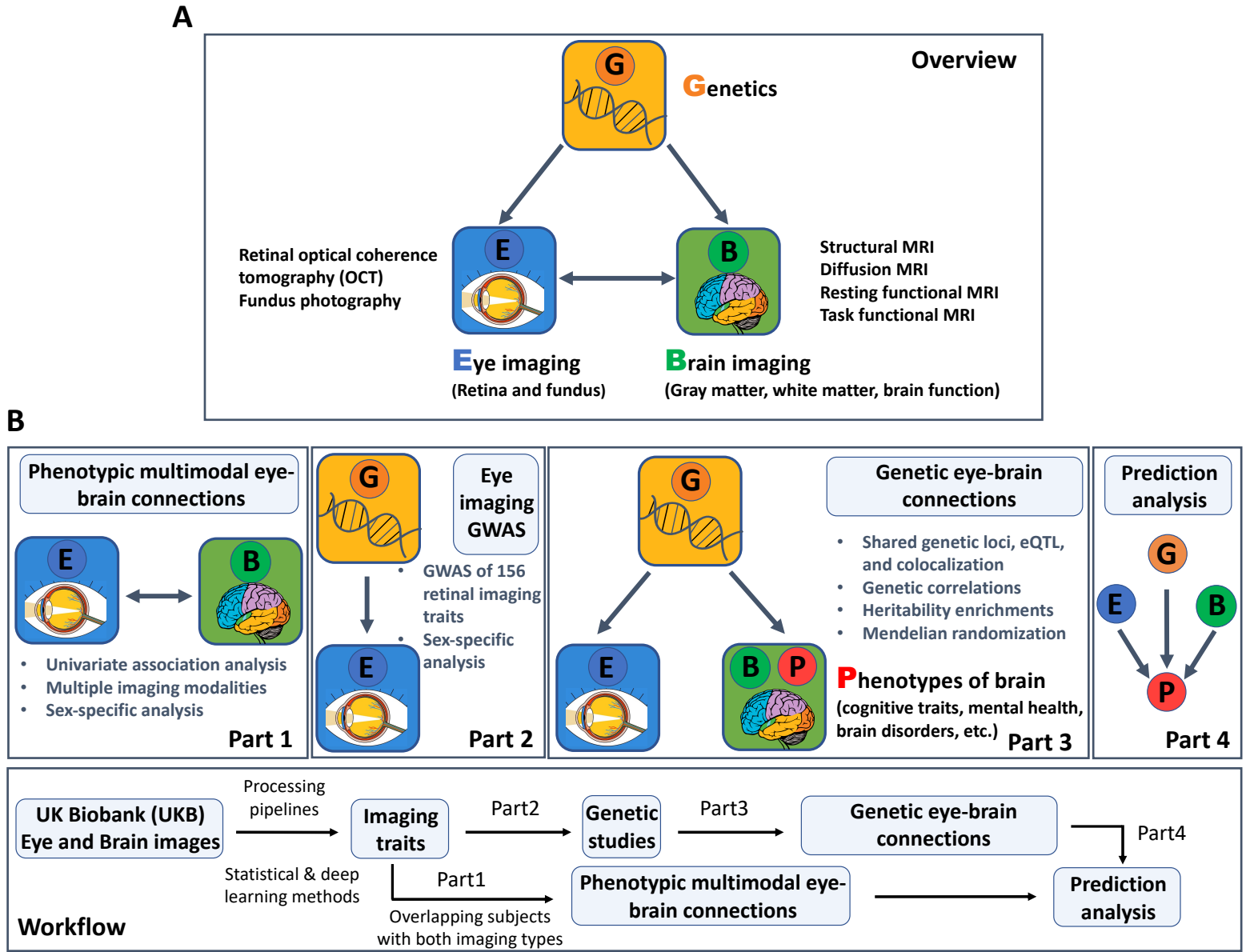


Figure 1

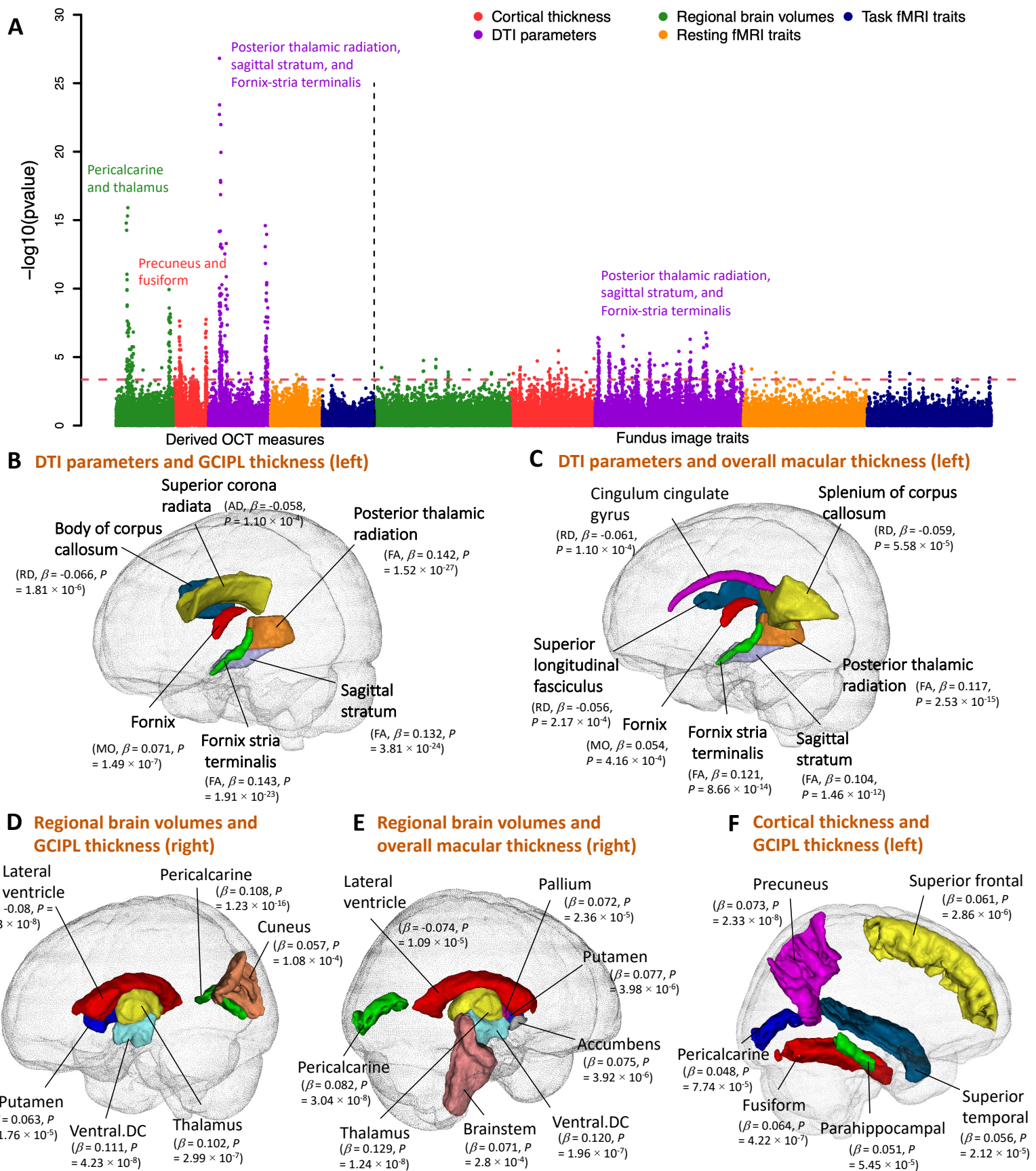


Figure 2

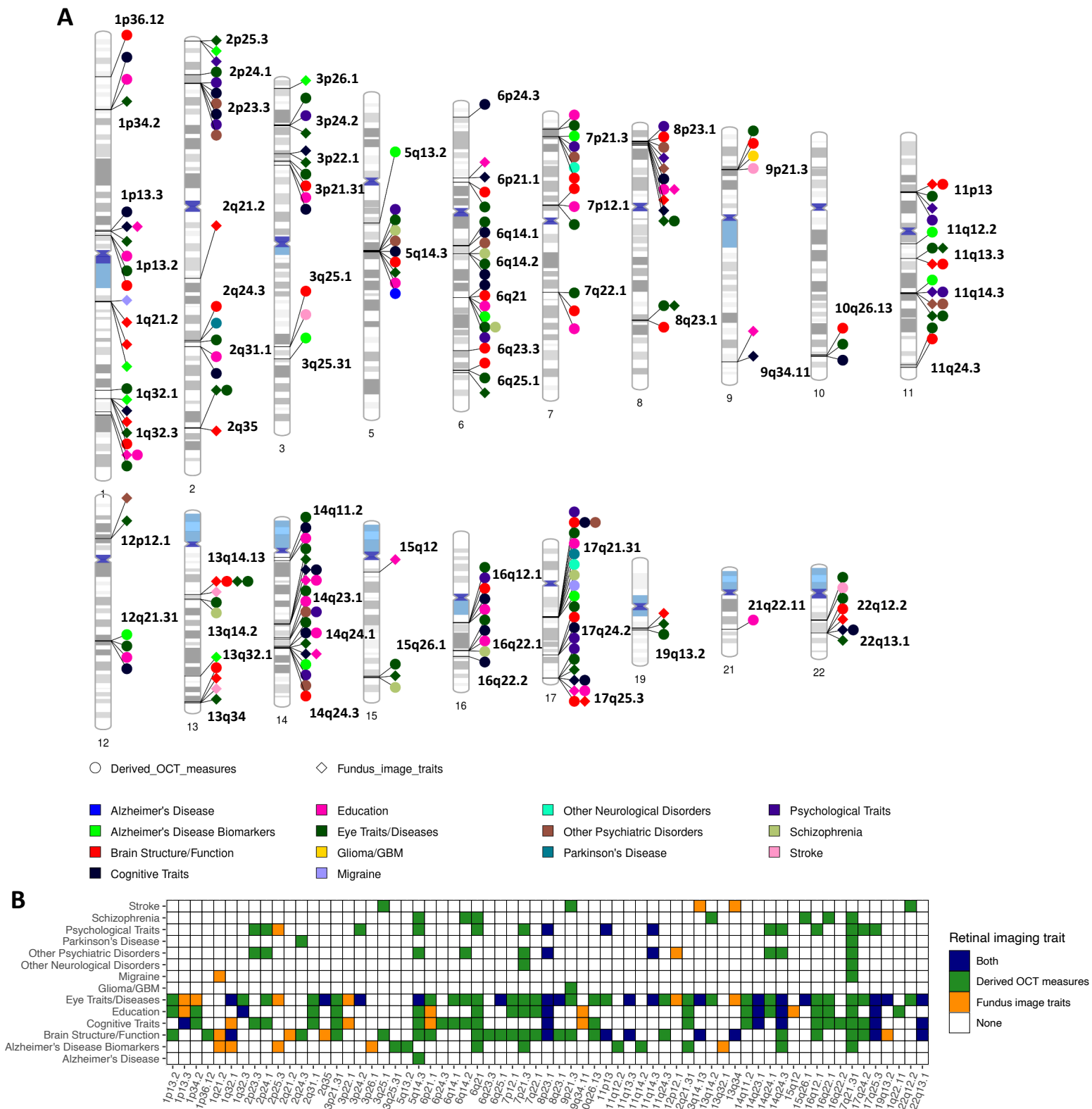


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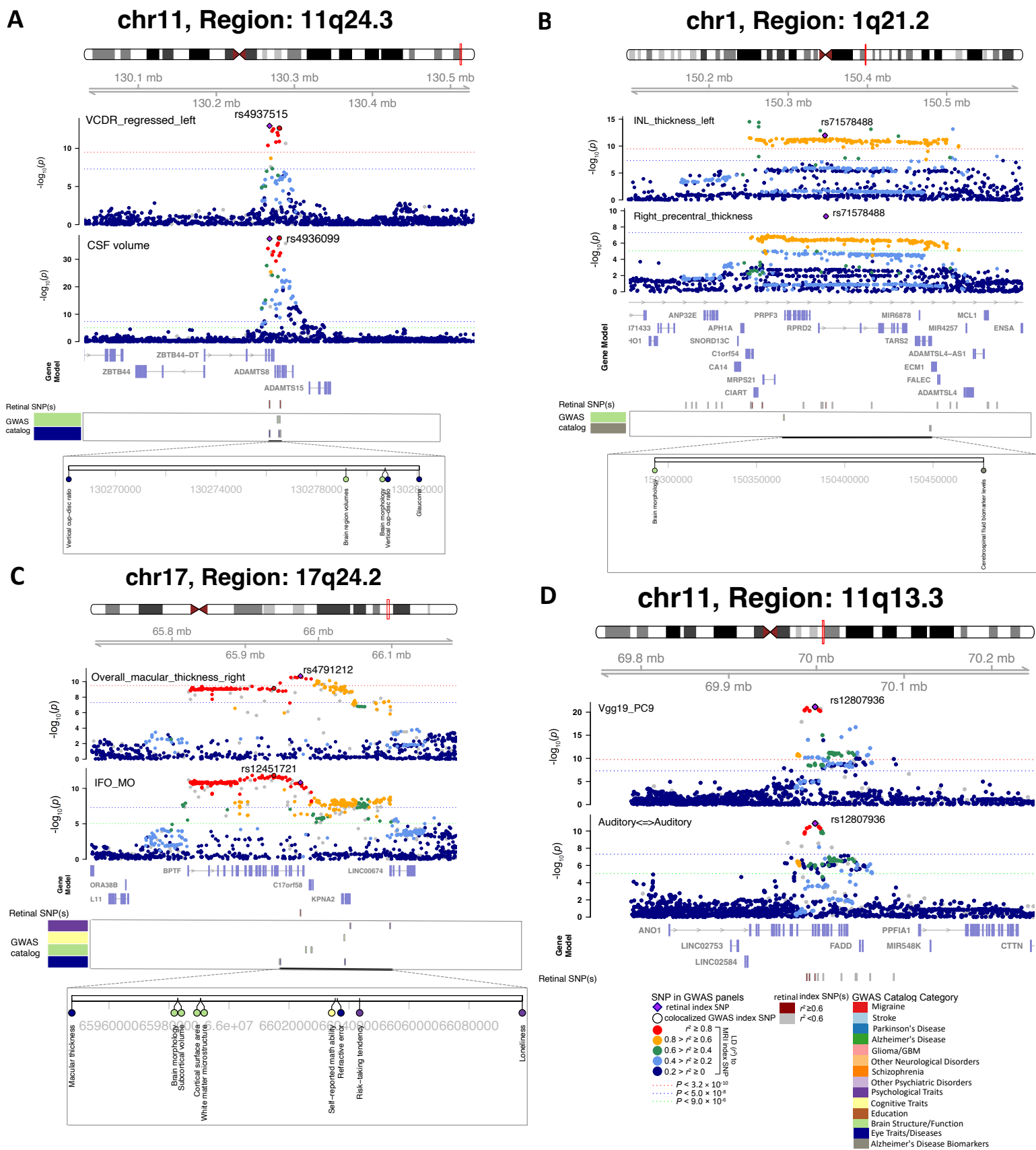


Figure 4

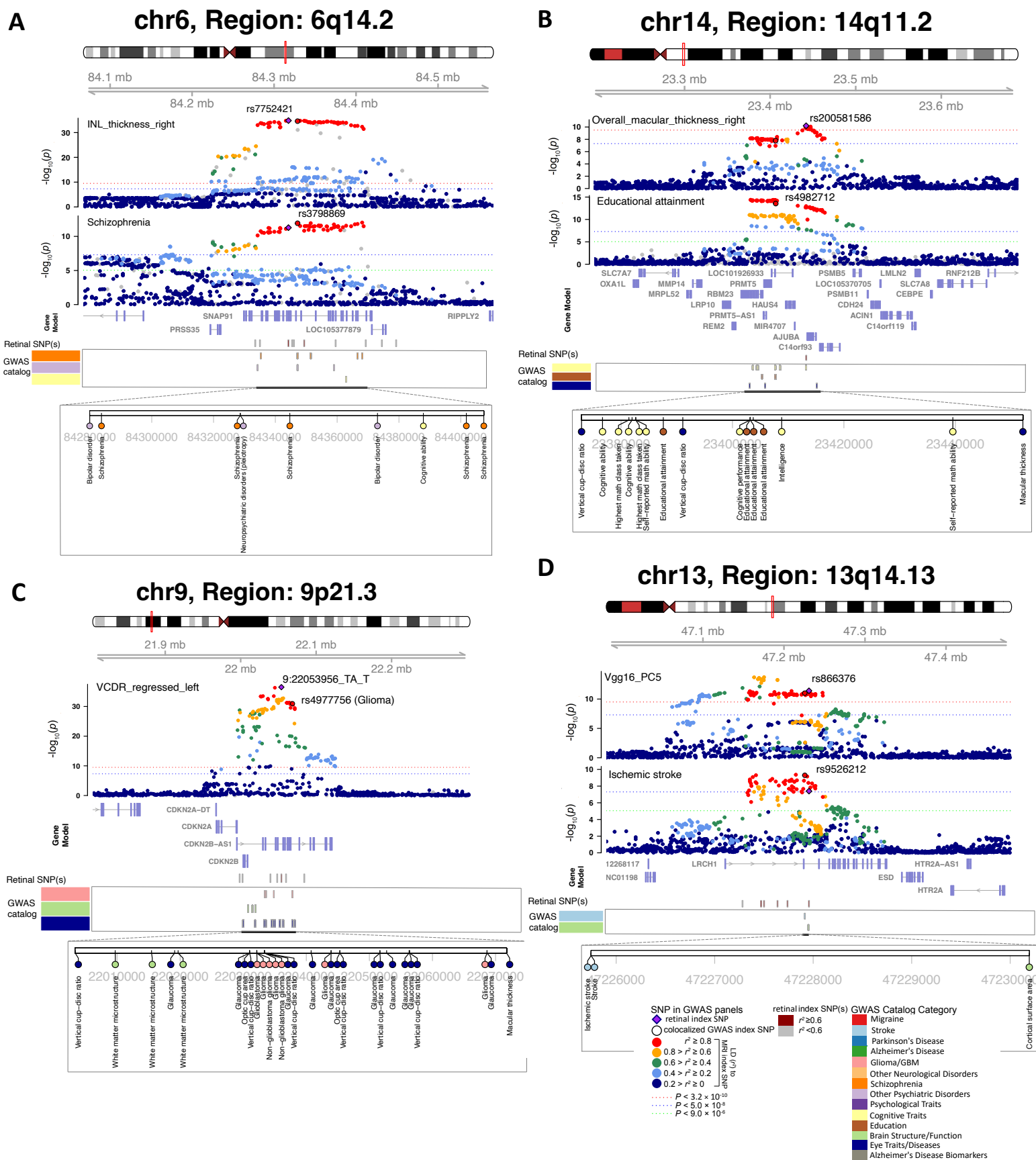


Figure 5

