Identifying tissue specific transcriptomic effects on brain volume measures from GWAS summary data

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Introduction:

Genome-wide association studies (GWAS) of brain imaging phenotypes have successfully identified numerous associations between genetic variants such as single nucleotide polymorphisms (SNPs) and structural and functional traits in the brain [1-5]. However, it is unclear how these genetic variations influence the regional gene expression levels which may subsequently lead to phenotypic changes in the brain. S-PrediXcan [6] is a tissue-specific transcriptomic data analysis method that can be applied to bridge this gap. The method can be used to integrate the GWAS summary statistics of an imaging trait with the PrediXcan models [10] linking SNPs to gene expressions in a specific brain tissue, and to detect genes whose expression levels have mediating effects on the imaging trait. In this work, we perform an S-PrediXcan analysis on GWAS summary data from two large imaging genetics biobanks, UK Biobank (UKB) [4,5,7] and Enhancing Neuroimaging Genetics through Meta Analysis (ENIGMA) [1,2,8], to identify tissue-specific transcriptomic effects on two closely related brain volume measures: total brain volume (TBV) and intracranial volume (ICV).

Methods:

S-PrediXcan [6] is a method that estimates the mediating effects of gene expression levels on phenotypes using only GWAS summary data. We applied S-PrediXcan to thirteen GTEx brain tissues [9] and two brain volume phenotypes (TBV and ICV). Input materials for our S-PrediXcan analysis included the TBV GWAS summary statistics from the UKB cohort (n=19,629) [5] and the ICV GWAS summary statistics from the ENIGMA2 cohort (n=30,717) [2]. Another required input was trained PrediXcan models [10] using elastic-net from the GTEx transcriptomes of thirteen brain tissues [6], where each tissue-specific model predicts gene expression level in the corresponding brain tissue using relevant SNPs. The PrediXcan models and SNP covariances were downloaded from http://predictdb.org/. S-PrediXcan was performed to integrate GTEx PrediXcan models with UKB and ENIGMA2 summary statistics to identify tissue-specific transcriptomic variations associated with TBV and ICV. Significant gene-TBV and gene-ICV associations were reported using FDR < 0.05.

Results:

We first performed the analysis by using GWAS summary data from the UKB cohort and identified 208 significant gene-TBV associations, which involved 52 genes and 13 brain tissues (Fig. 1). To determine whether these 52 genes would also be associated with ICV (a relevant brain volume measure), the analysis was repeated by using GWAS summary data from the independent ENIGMA2 cohort. We observed that 10 out of 52 genes associated with TBV were also associated with ICV (Fig. 2). Among these 10 genes, 9 of them (except FAM215B) were significantly associated with TBV in the gene-based association analysis of the original UKB GWAS [5]. While the original UKB analysis revealed the significant collective effect of SNPs within each of these genes, our analysis identified the mediating effects of the expression levels of these genes on not only TBV (in UKB) but also ICV (in the independent ENIGMA2 cohort). In addition, our S-PrediXcan analysis also yielded valuable tissue specificity information, revealing varying mediating effects of these genes across different brain tissues (Fig. 2).

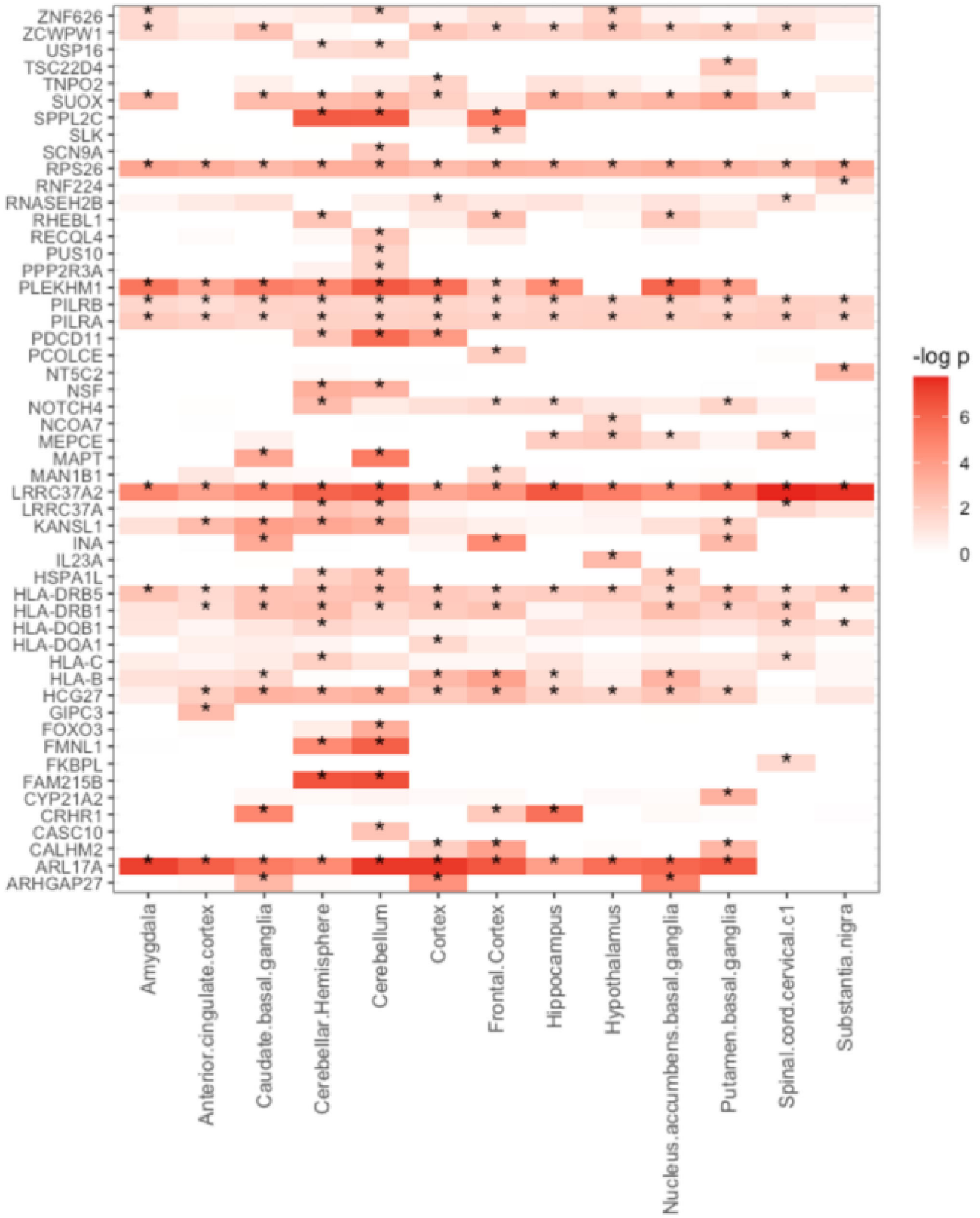

Fig. 1. Genes that are highly associated with total brain volume (TBV) based on UKB GWAS summary statistics. * indicates significant tissue specific gene-TBV association (FDR < 0.05), where 13 GTEx brain tissues are plotted on x axis.

(https://files.aievolution.com/prd/hbm2101/abstracts/abs_1731/Figure01.png)

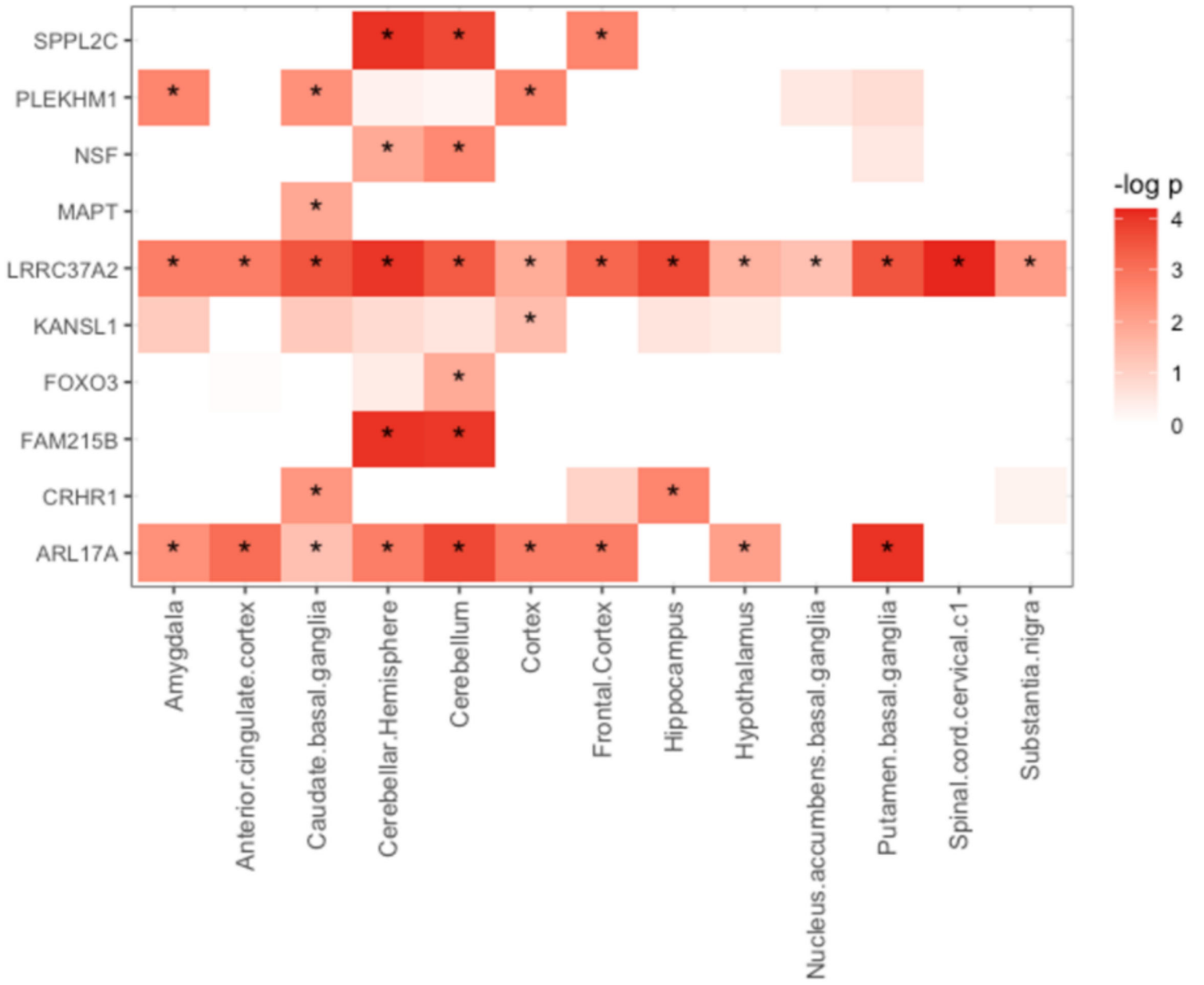

Fig. 2. Common genes that are associated both with TBV using UKB GWAS summary statistics and with intracranial volume (ICV) using ENIGMA GWAS summary statistics. * indicates significant tissue specific gene-ICV association (FDR < 0.05), where 13 GTEx brain tissues are plotted on x axis. See **Fig. 1** for the gene-TBV map.

(https://files.aievolution.com/prd/hbm2101/abstracts/abs_1731/Figure02.png)

Conclusions:

Tissue-specific transcriptomic association analysis using S-PrediXcan was performed on UKB and ENIGMA2 GWAS summary data and identified genes with varying mediating effects on both total brain volume (TBV) and intracranial volume (ICV) across thirteen GTEx brain tissues. These identified genes, coupled with their tissue specificity findings, warrant further investigation in independent cohorts and/or molecular validation to better understand molecular mechanisms of the brain.

Genetics:

Genetic Association Studies
Genetic Modeling and Analysis Methods [1]
Transcriptomics [2]

Neuroanatomy, Physiology, Metabolism and Neurotransmission:

Anatomy and Functional Systems
Neuroanatomy Other

Keywords:

Data analysis
Informatics
Morphometrics
MRI
Phenotype-Genotype
Statistical Methods
STRUCTURAL MRI
Structures

[1|2]Indicates the priority used for review

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No

Please indicate below if your study was a "resting state" or "task-activation" study.

Other

Healthy subjects only or patients (note that patient studies may also involve healthy subjects):

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Not applicable

Please indicate which methods were used in your research:

Structural MRI
Computational modeling
Other, Please specify - Genotyping

For human MRI, what field strength scanner do you use?

3.0T

Which processing packages did you use for your study?

Free Surfer

Provide references using author date format

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