nature medicine

Article

https://doi.org/10.1038/s41591-023-02268-w

Genomics of perivascular space burden unravels early mechanisms of cerebral small vessel disease

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SUPPLEMENTARY DATA

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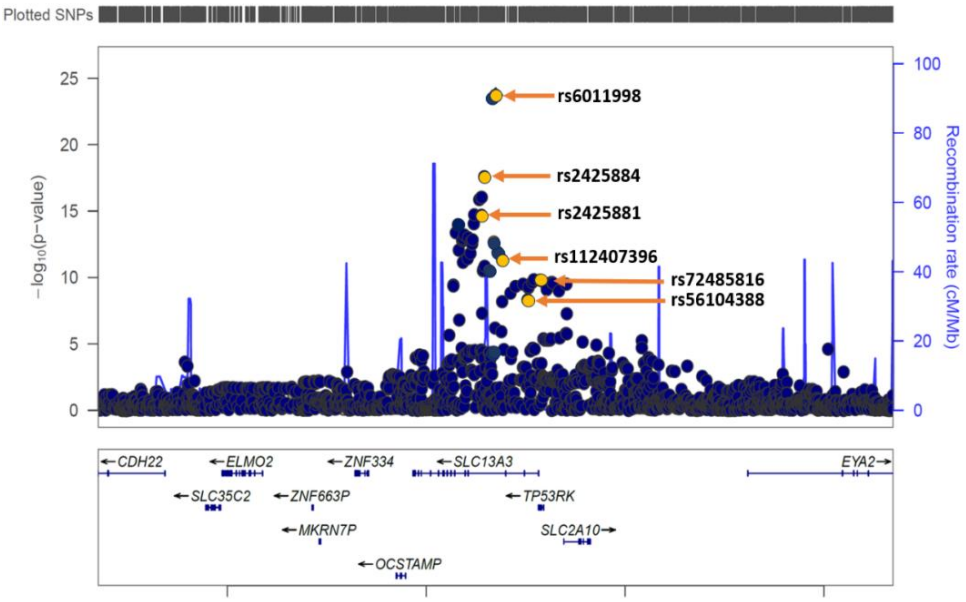
SUPPLEMENTARY FIGURES

1) Supplementary Fig. 1 : Regional association plots

Each circle indicates a single-nucleotide polymorphism (SNPs) with a color scale corresponding to the r^2 value for that SNP and the top SNP from 1000 Genomes. Purple diamonds indicate the SNPs with the strongest association. Estimated recombination from 1000 Genomes are indicated with blue lines. The bottom panels show the relative position of genes within each locus.

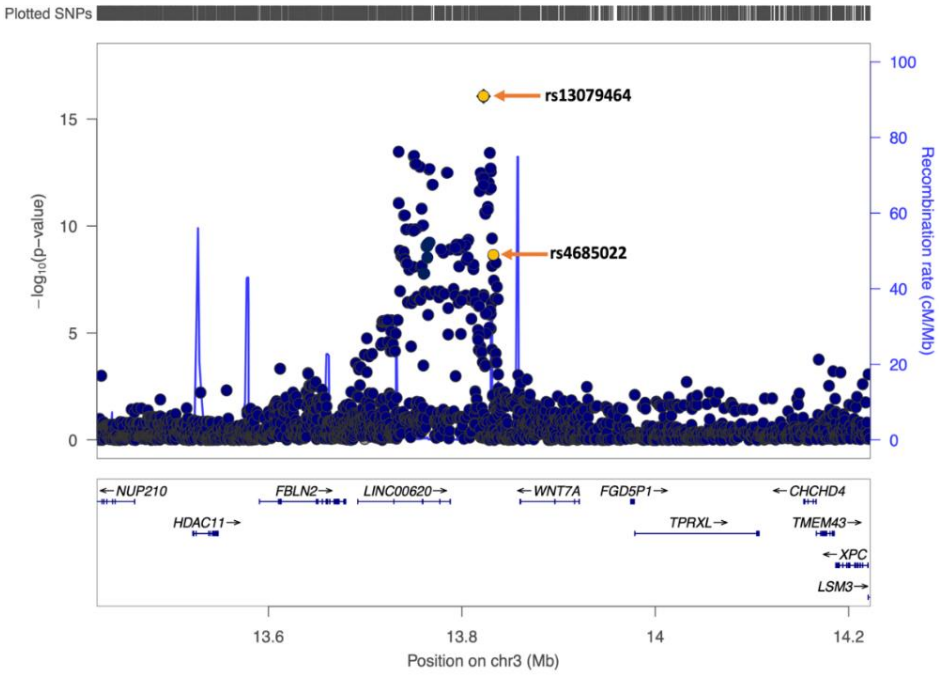
1.1. Perivascular spaces in white matter

Chr20q13.12

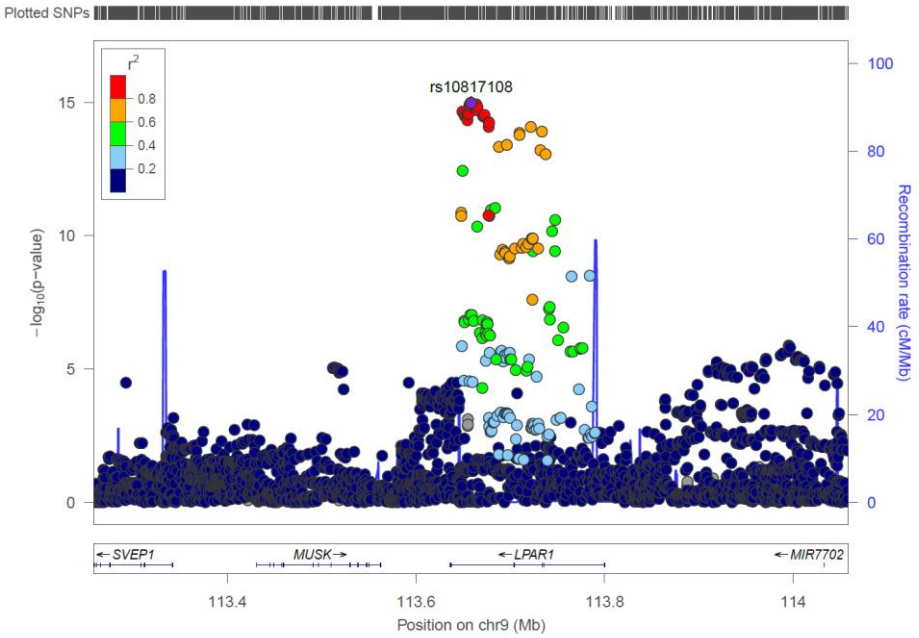


Regional plot of the chr20q13.13 locus with 6 independent signals identified by GCTA-COJO (orange).

Chr3p25.1



Chr 9q31.3



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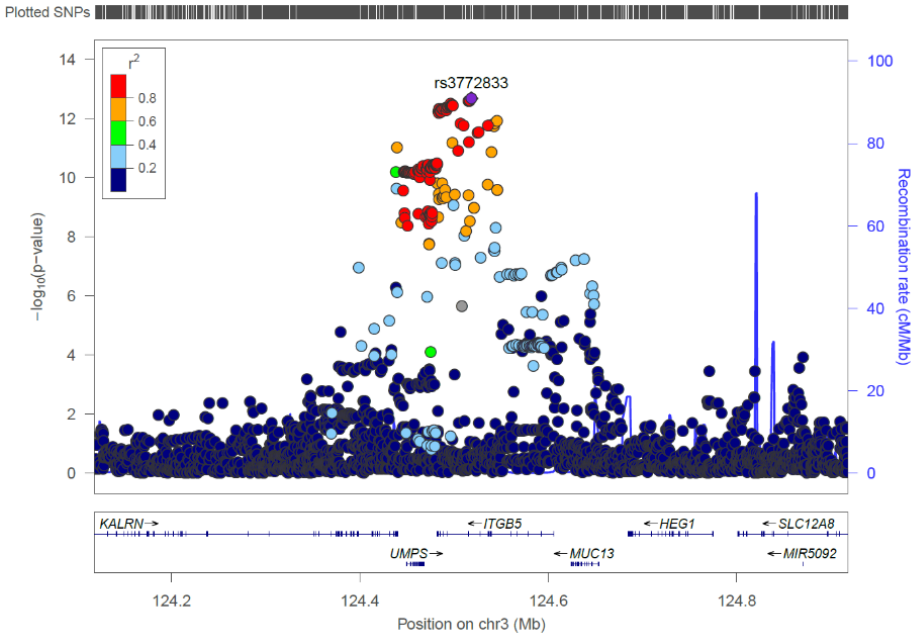
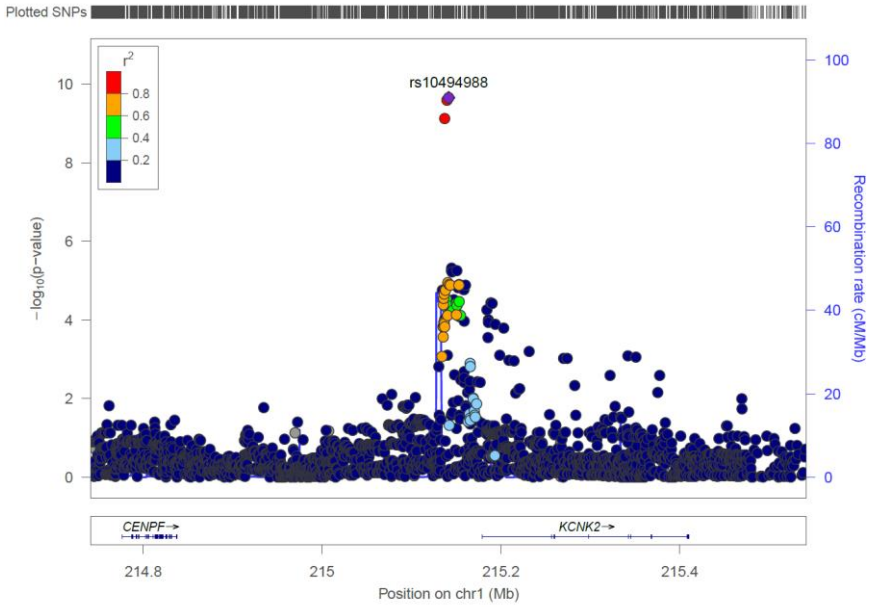


Chr 1q41



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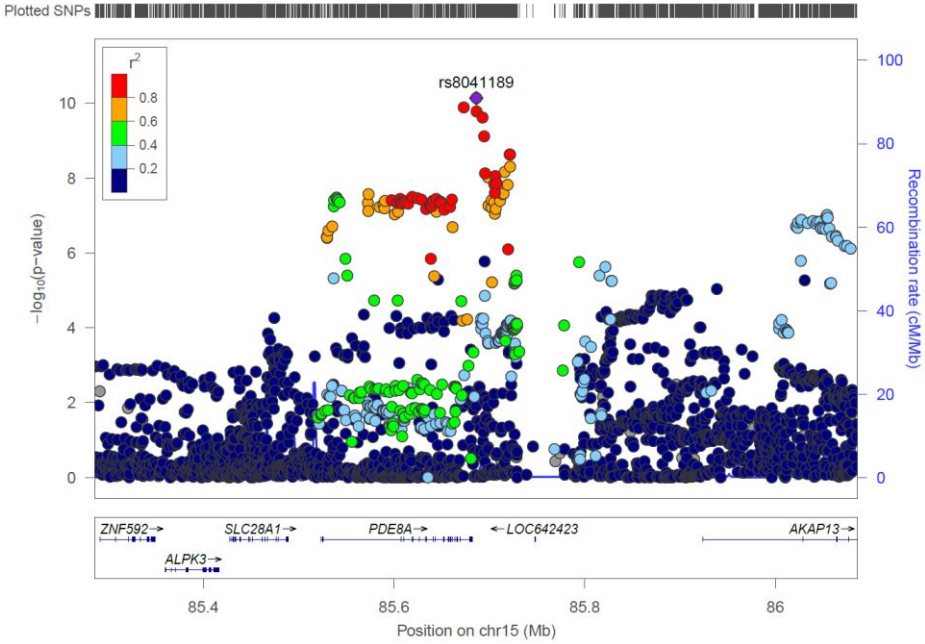
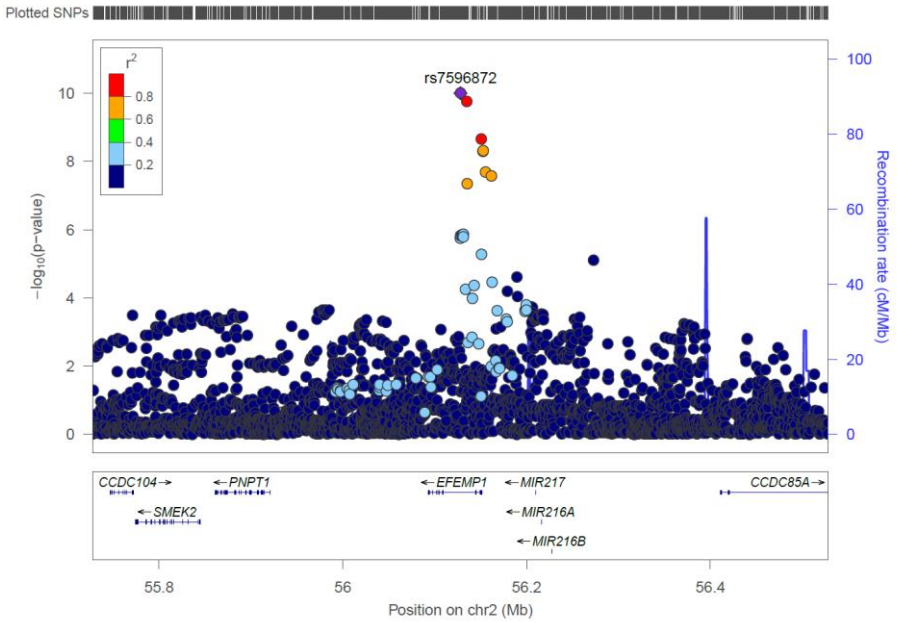
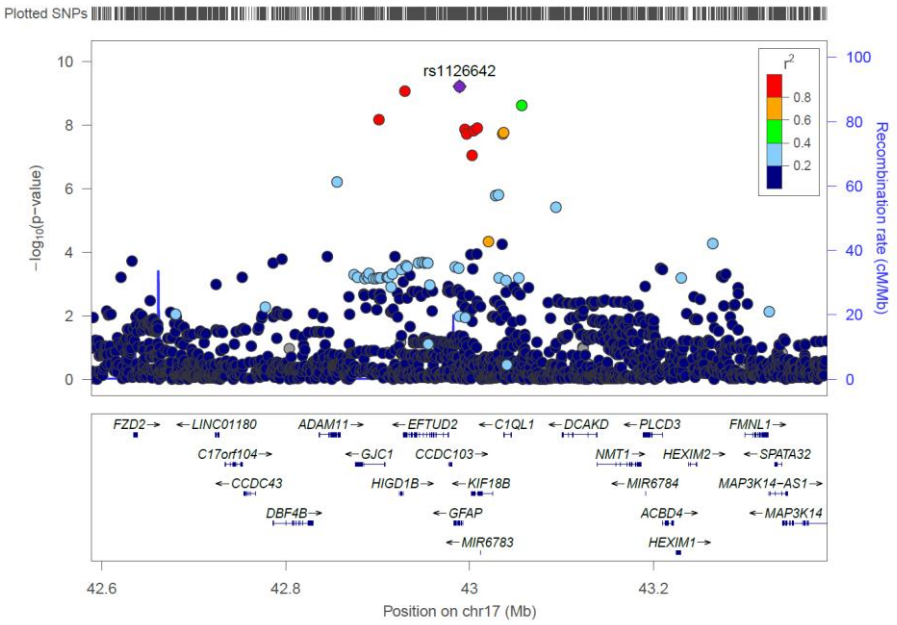


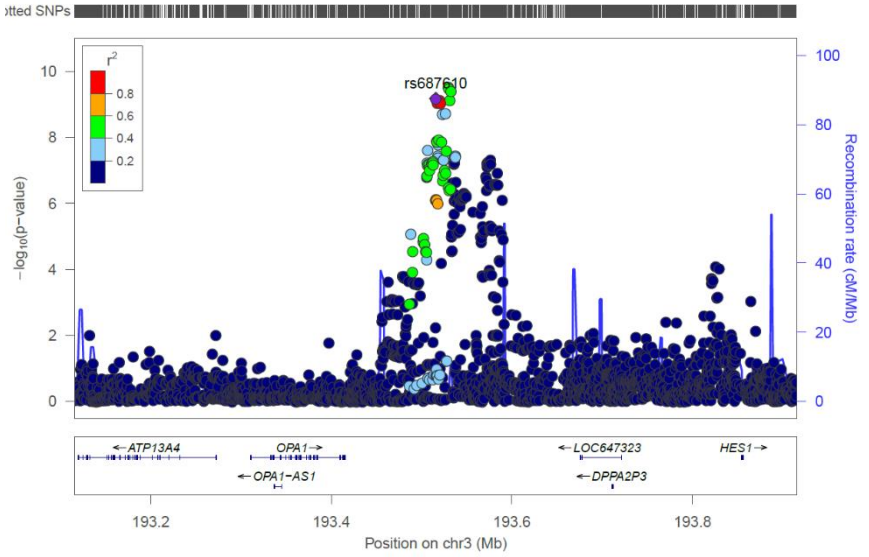
Chr 2p16.1



Chr 17q21.31



Chr 3q29



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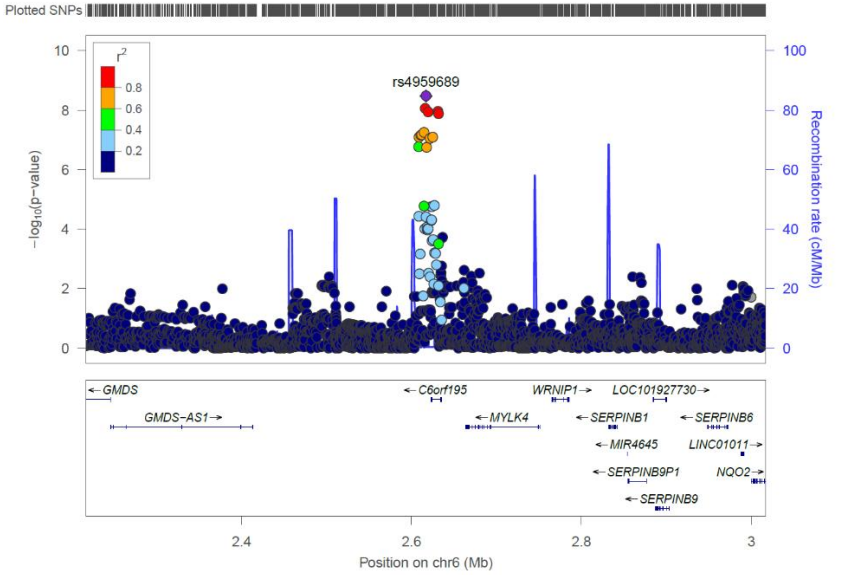
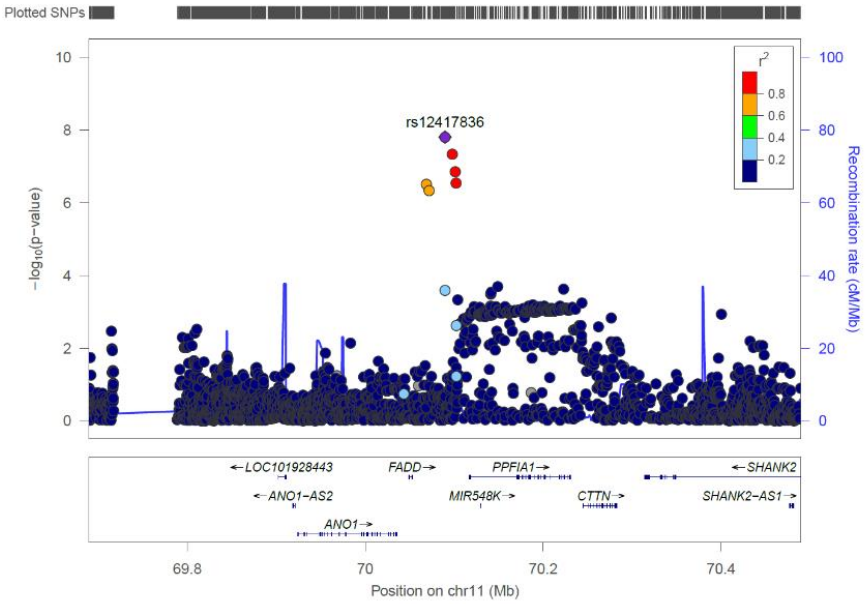
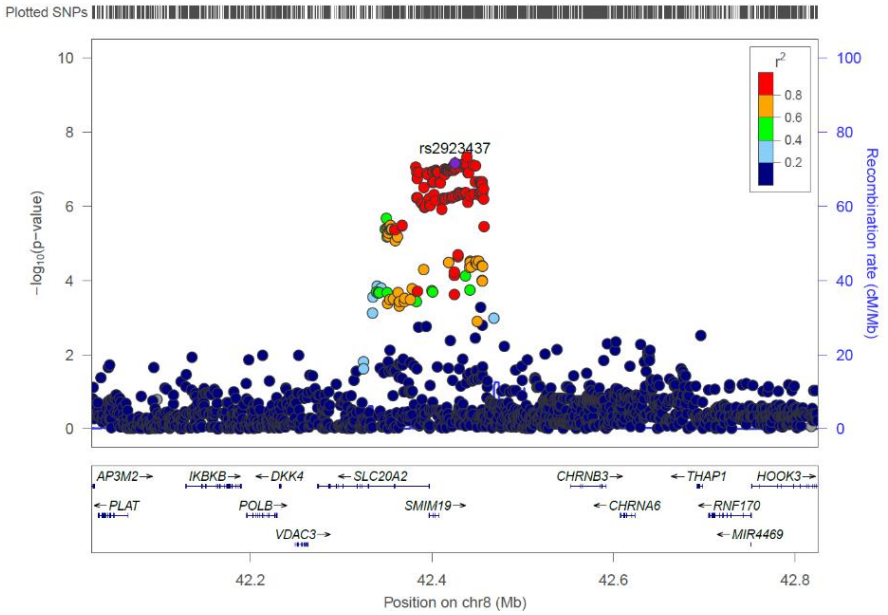


Chr 11q13.3



Chr 8p11.21



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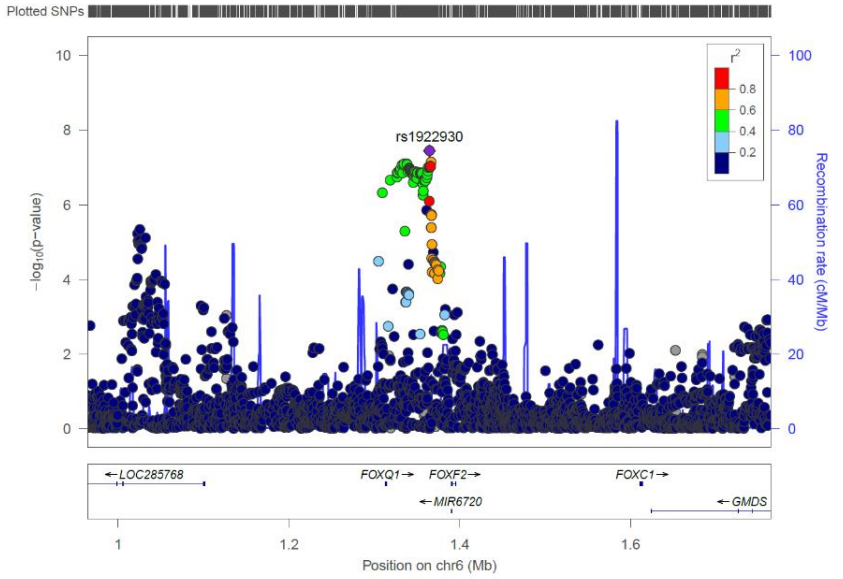
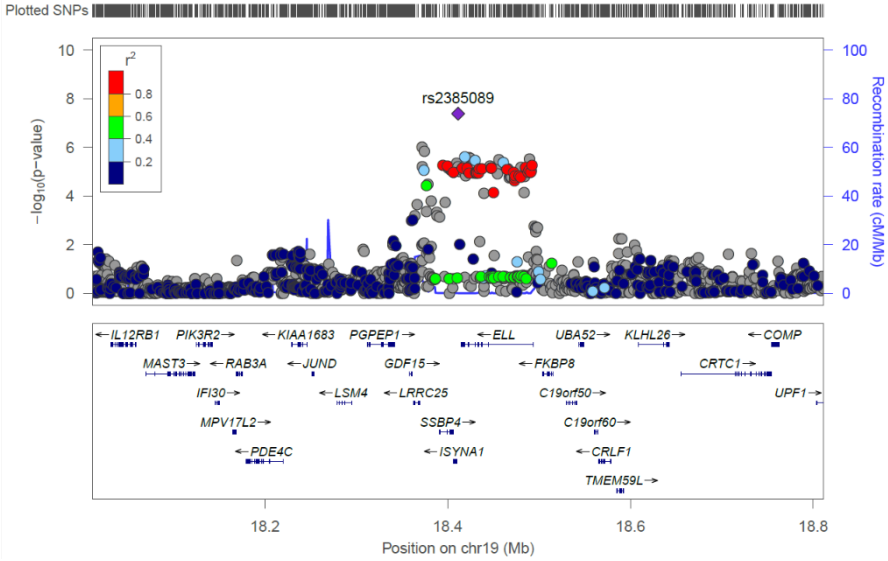
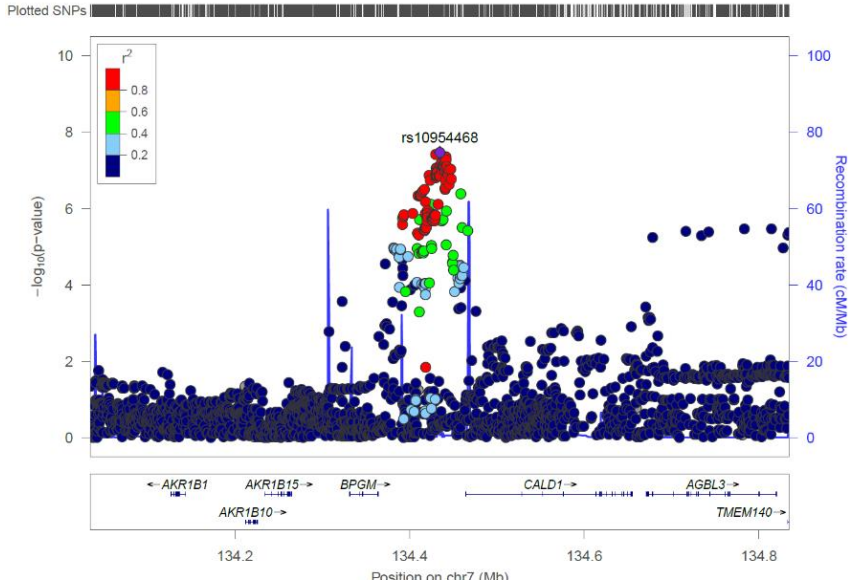


Chr 19p13.11

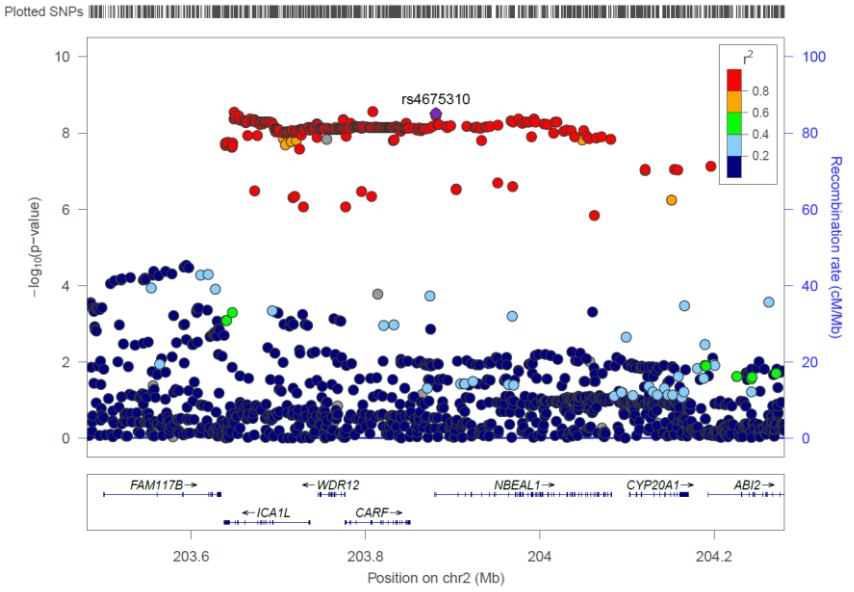


Chr 7q33 (European locus)

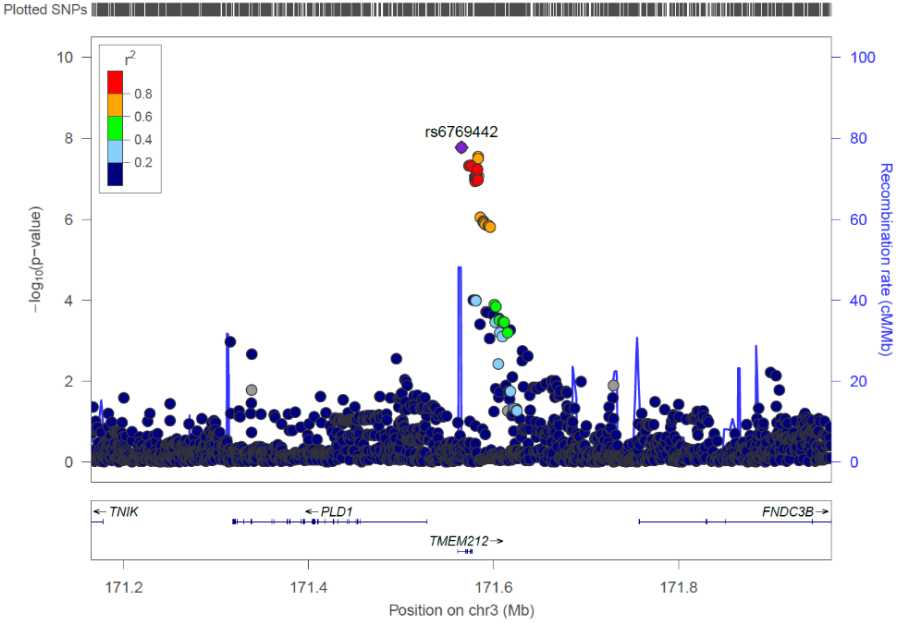


1.2. Perivascular spaces in basal ganglia

Chr2q33.2

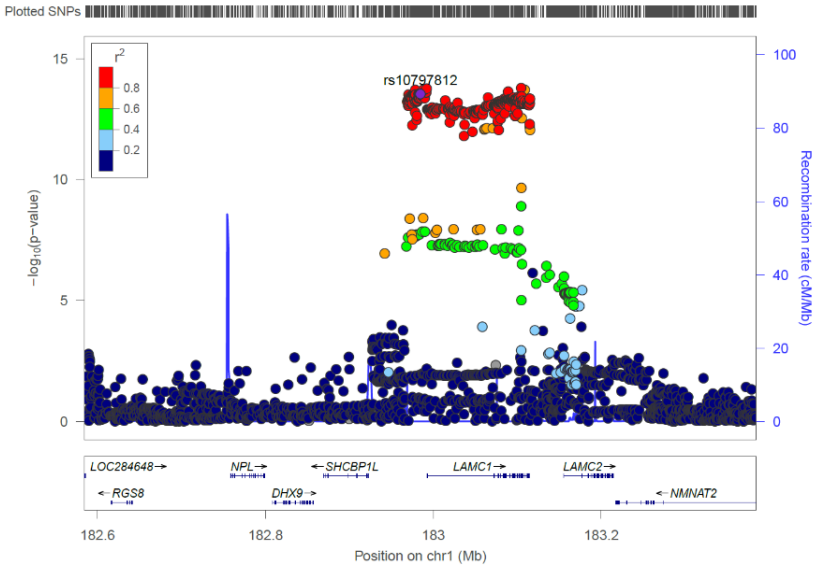


Chr3q26.31

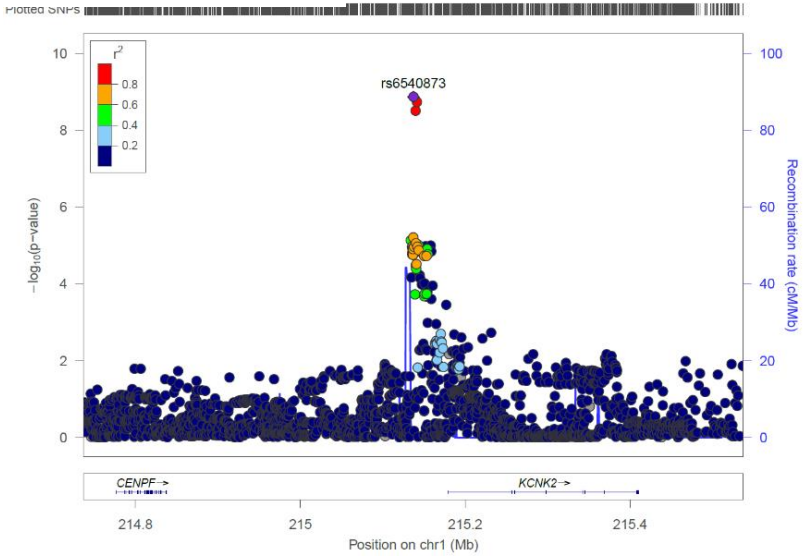


1.3. Perivascular spaces in hippocampus

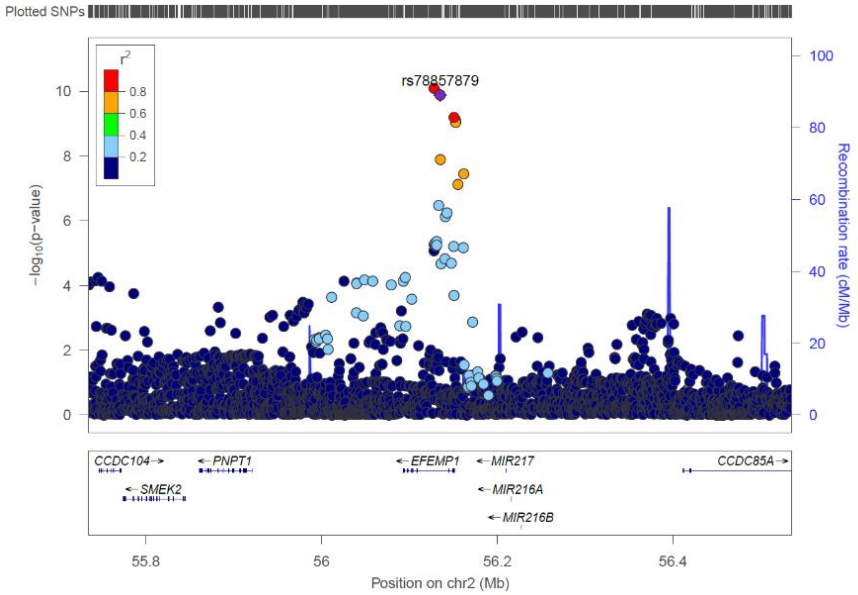
Chr1q25.3



Chr1q41

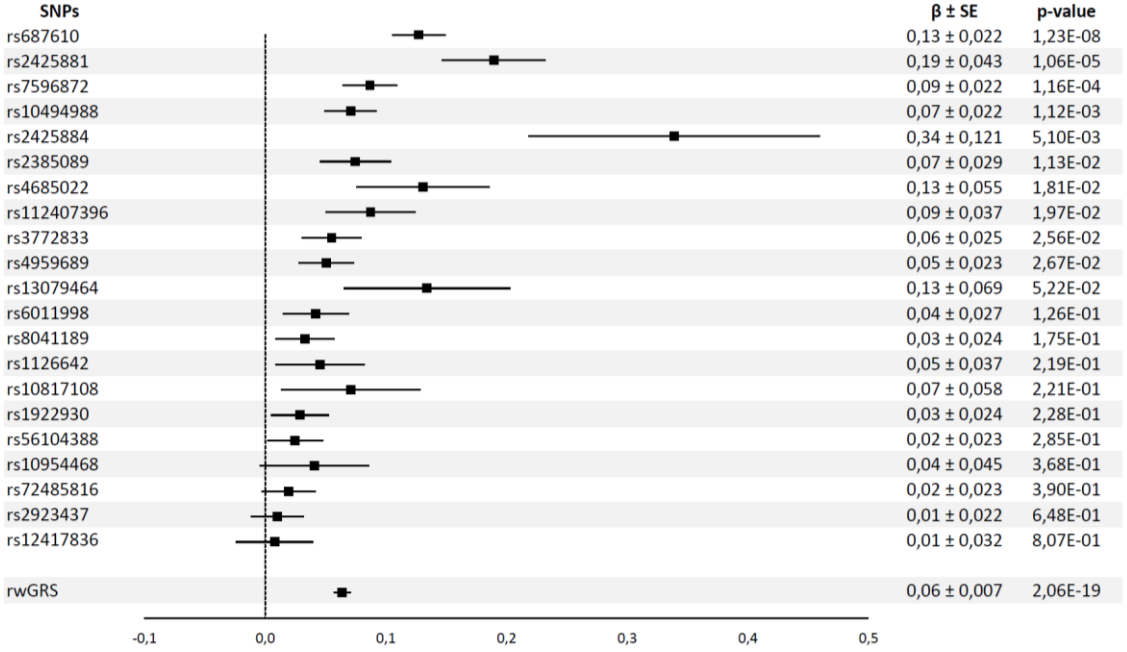


Chr2p16.1

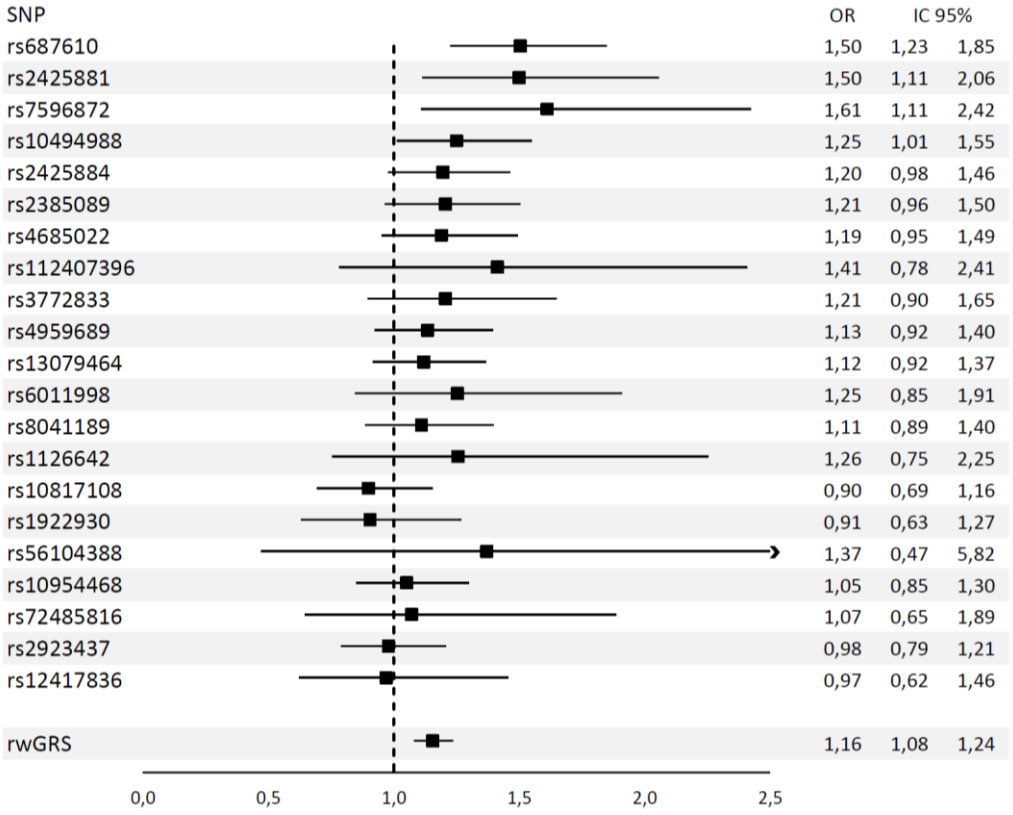


2) Supplementary Fig. 2 : Association of WM-PVS SNPs with WM-PVS burden in the i-Share cohort (N=1,748)

A. Continuous PVS measures in i-Share



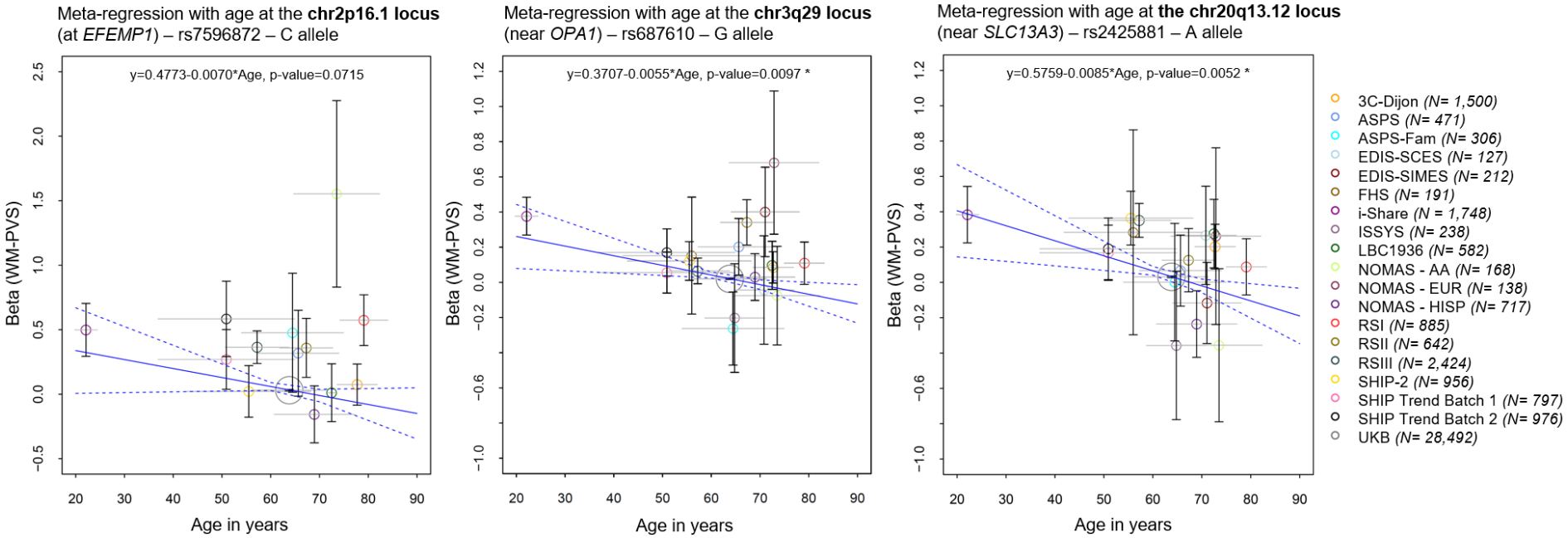
B. Dichotomous PVS measures in i-Share



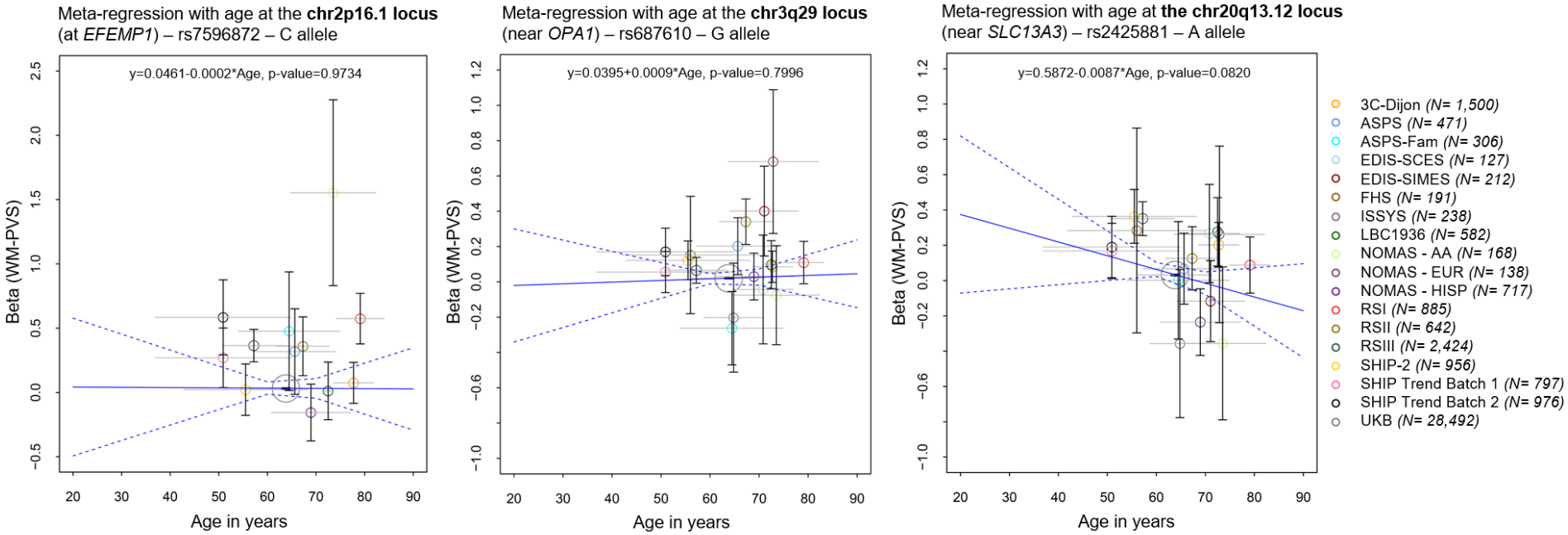
rwGRS indicates rescaled weighted genetic risk score. Data are presented as effect estimates (beta) +/- SE (A) and as odds Ratio and 95% confidence interval (B). The model is a logistic regression adjusted for age, sex, intracranial volume and the first four principal components of population stratification.

3) Supplementary Fig. 3 : Meta-regression with age of the three genome-wide significant WM-PVS loci that also showed significant associations with WM-PVS in young adults

A. Meta-regression including all the cohorts



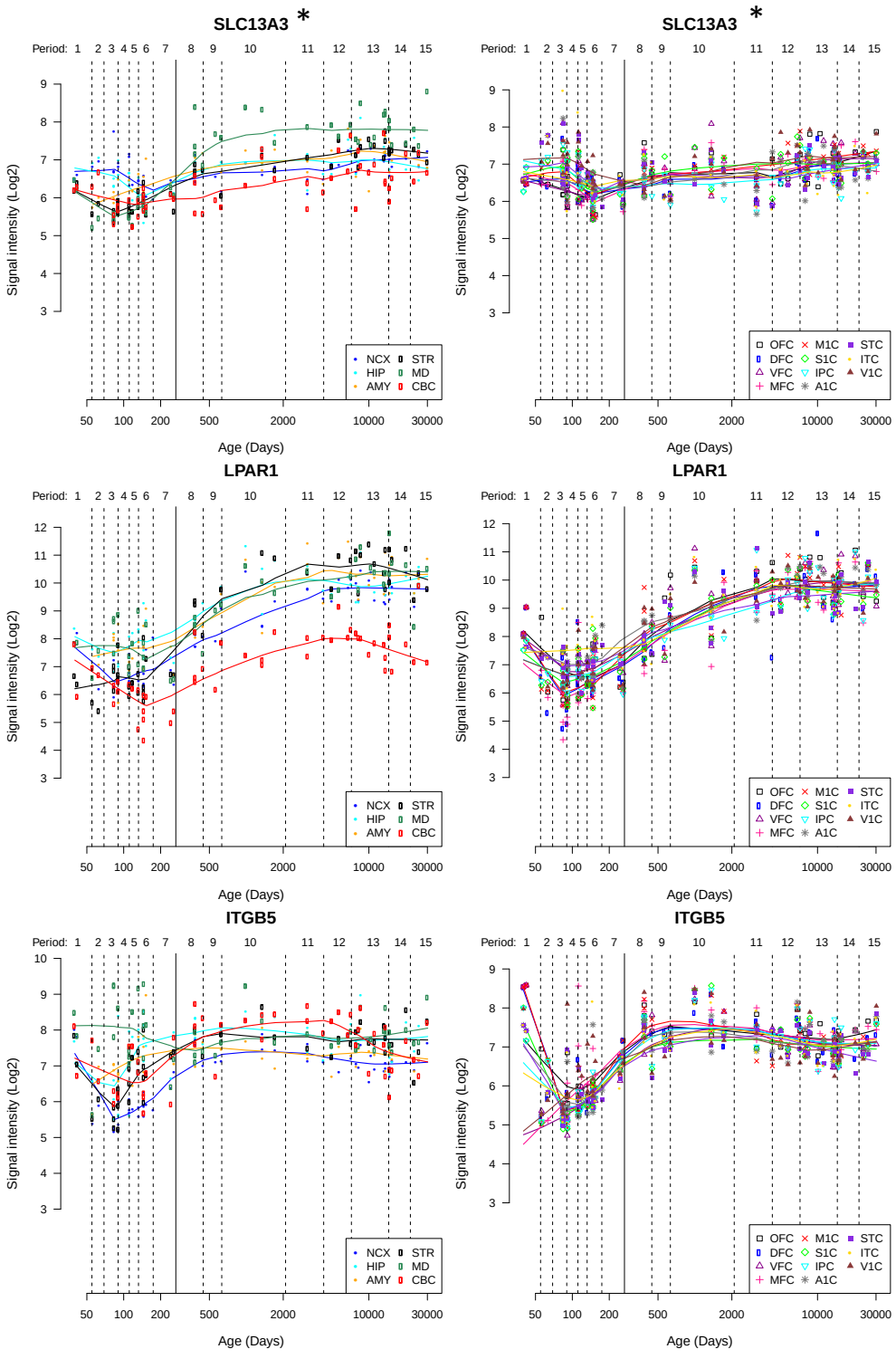
B. Meta-regression without the i-Share Study

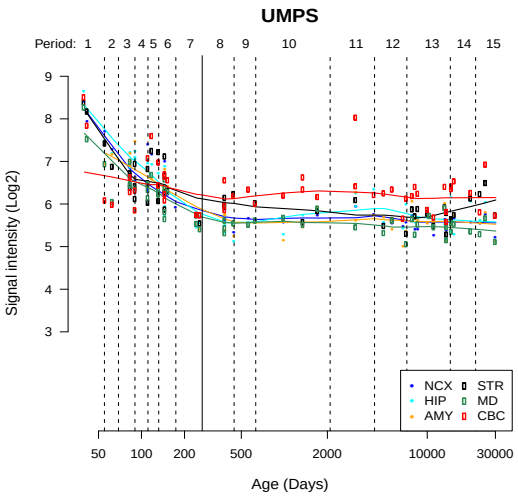


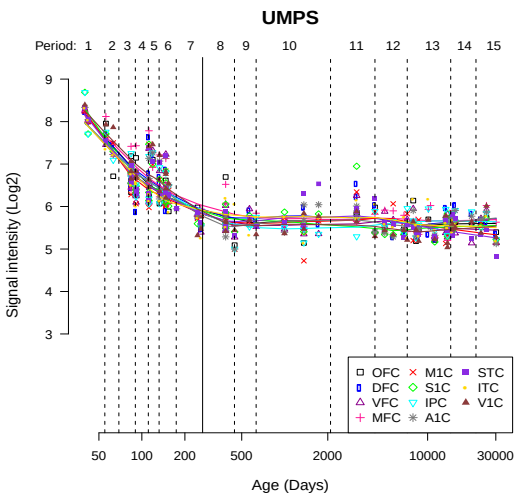
We tested for a significant modifying effect of age on associations with WM-PVS for the three genome-wide significant WM-PVS loci that also showed significant associations with WM-PVS in young adults (Methods). Data are presented as effect estimates (beta) +/- SE for the lead SNPs at these three loci in each individual cohort: A: all cohorts included in the GWAS meta-analysis and the follow-up cohort in young adults (i-Share); B: all cohorts included in the GWAS meta-analysis. *Significant associations ($p<0.05/3=0.017$, two-sided, correcting for multiple testing).

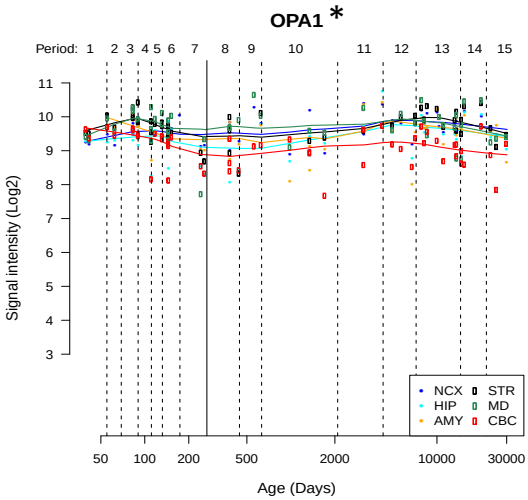
4) Supplementary Figure 4. Brain expression pattern across the lifespan of genes near genome-wide significant PVS loci that are also identified in the TWAS or that are the nearest genes of variants showing an association with PVS already in young adults

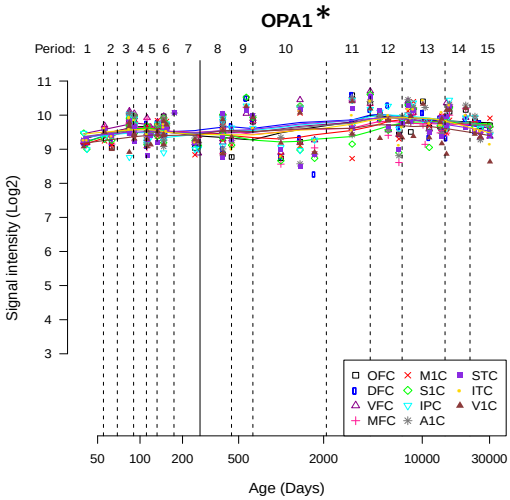
4.1. Genes in WM-PVS loci




UMPS
Period: 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Signal intensity (Log2)
Age (Days)
50 100 200 500 2000 10000 30000
NCX STR
HIP MD
AMY CBC


UMPS
Period: 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Signal intensity (Log2)
Age (Days)
50 100 200 500 2000 10000 30000
OFC M1C STC
DFC S1C ITC
VFC IPC V1C
MFC A1C


OPA1 *
Period: 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Signal intensity (Log2)
Age (Days)
50 100 200 500 2000 10000 30000
NCX STR
HIP MD
AMY CBC


OPA1 *
Period: 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Signal intensity (Log2)
Age (Days)
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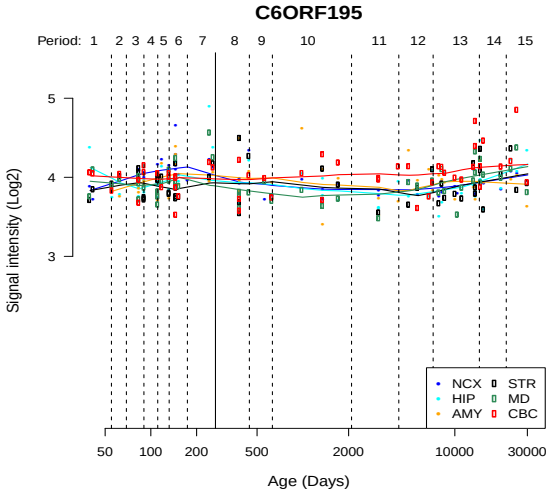
DFC S1C ITC
VFC IPC V1C
MFC A1C


C6ORF195
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Age (Days)
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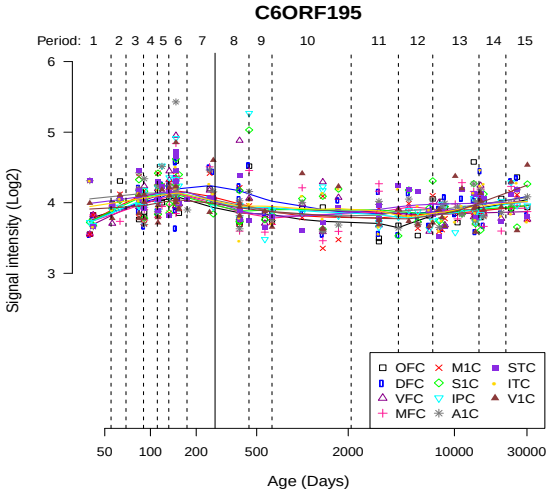
NCX STR
HIP MD
AMY CBC


C6ORF195
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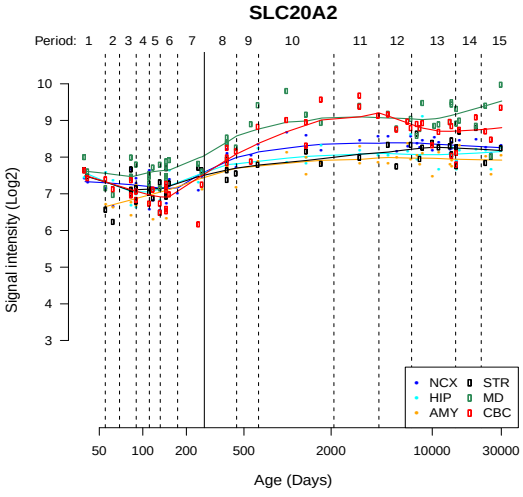
DFC S1C ITC
VFC IPC V1C
MFC A1C


SLC20A2
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Signal intensity (Log2)
Age (Days)
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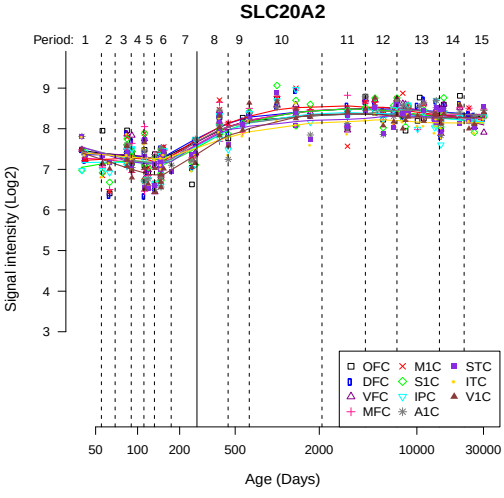
NCX STR
HIP MD
AMY CBC


SLC20A2
Period: 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Signal intensity (Log2)
Age (Days)
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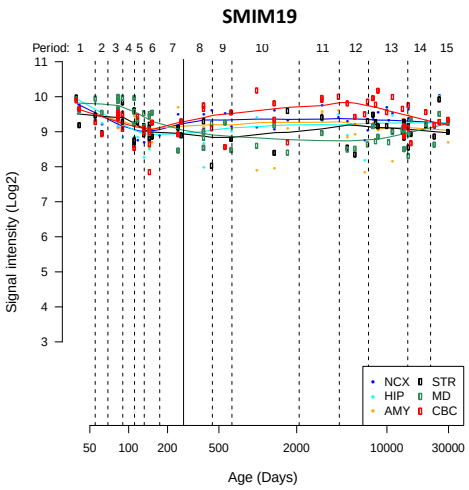
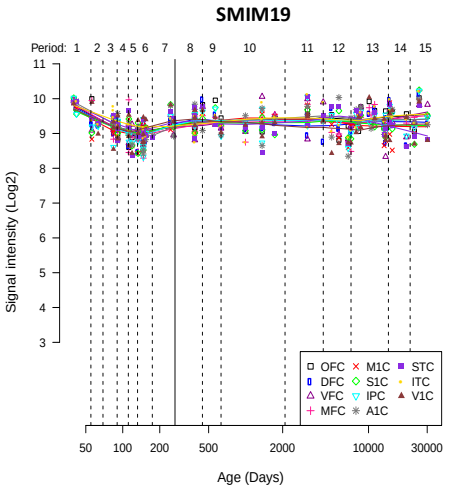
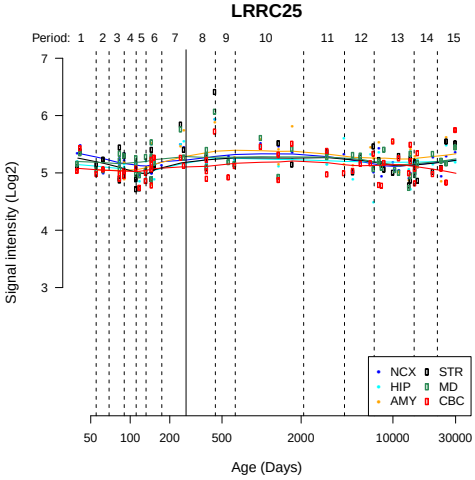
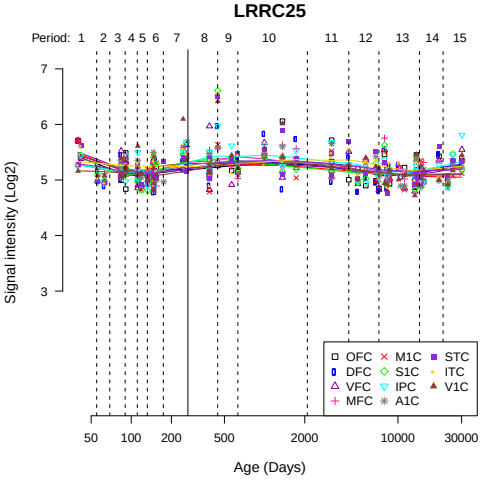
OFC M1C STC
DFC S1C ITC
VFC IPC V1C
MFC A1C

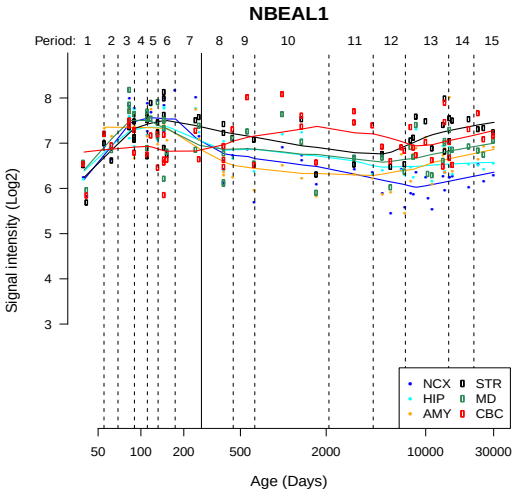


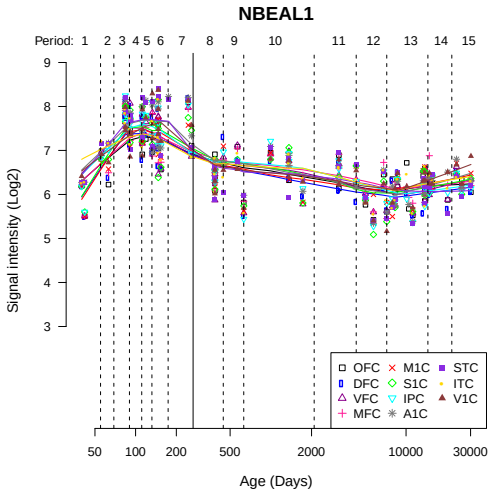


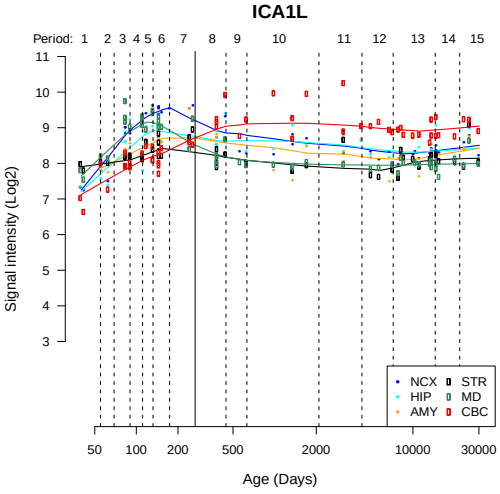


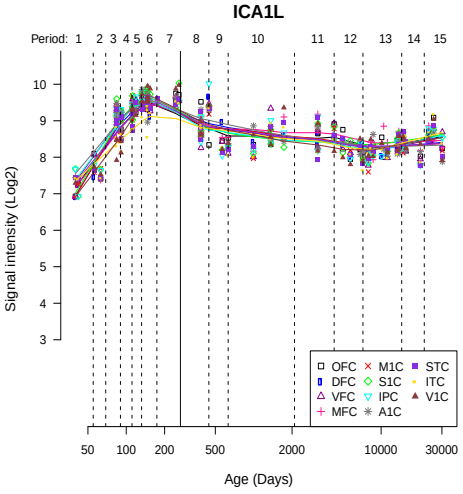


4.2. Genes in BG-PVS loci

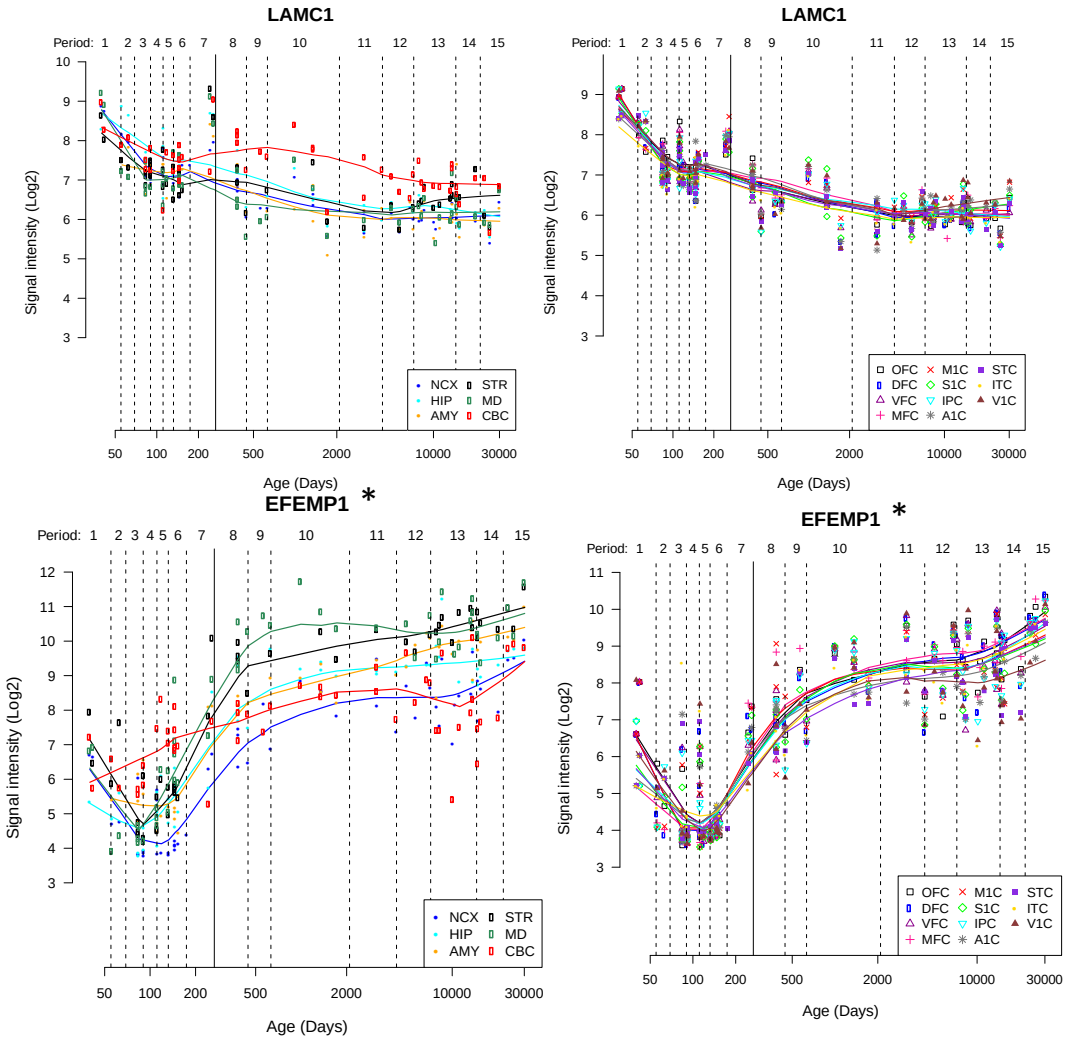








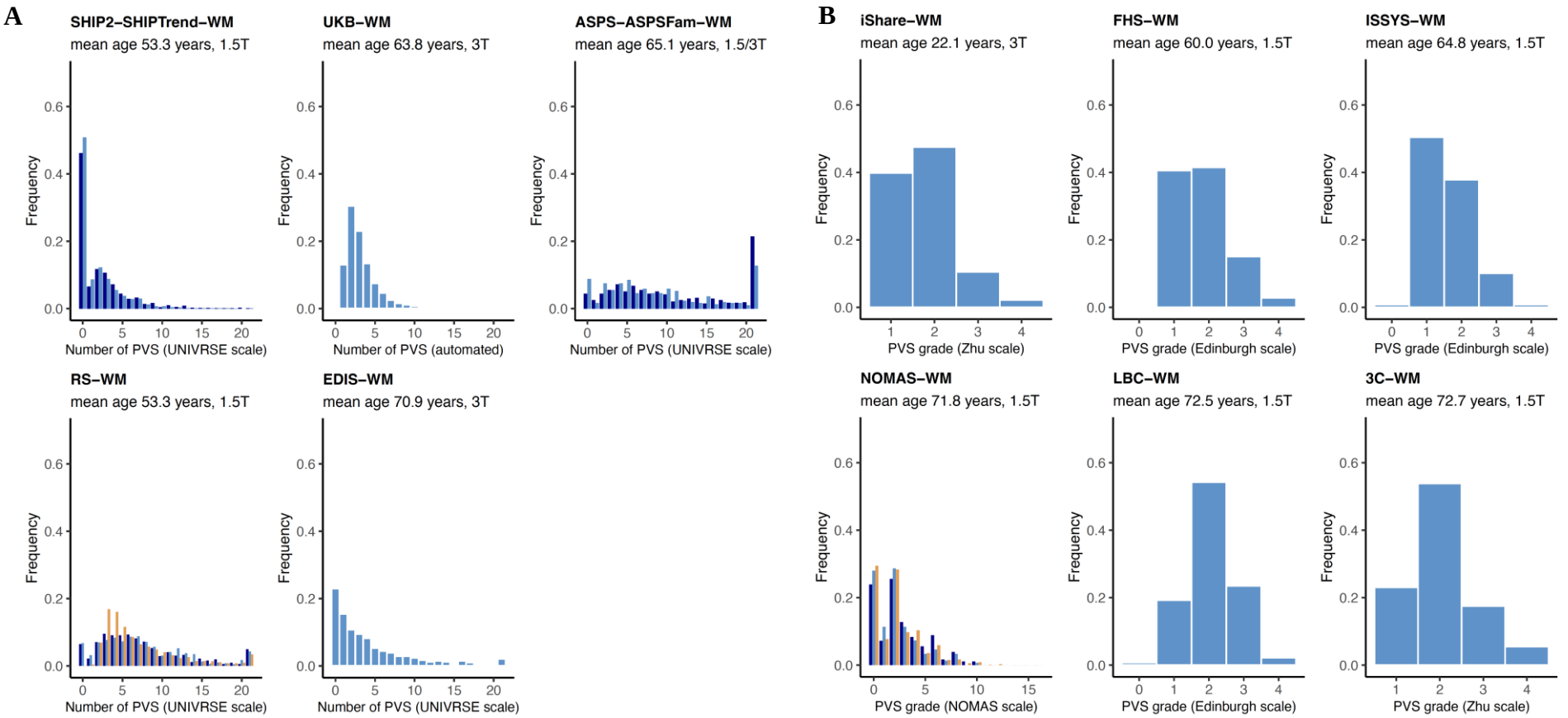
4.3. Genes in HIP-PVS loci



The figure displays brain expression pattern across the lifespan of the 11 significant PVS TWAS-COLOC genes from genome-wide significant PVS GWAS loci and the genes closest to the 3 loci associated with PVS burden across the adult lifespan. The spatio-temporal gene expression level is plotted as log2-transformed exon array signal intensity (y-axis) against the post conception days (x-axis) as provided by the Human Brain Transcriptom project database. Periods of human development and adulthood are indicated by vertical dashed lines: 4-8 post conception weeks [PCW] (period 1), 8-10 PCW (period 2), 10-13 PCW (period 3), 13-16 PCW (period 4), 16-19 PCW (period 5), 19-24 PCW (period 6), 24-38 PCW (period 7), birth- 6 postnatal months (period 8), 6-12 postnatal months (period 9), 1- 6 years (period 10), 6-12 years (period 11), 12-20 years (period 12), 20-40 years (period 13), 40-60 years (period 14), and 60 years+ (period 15). The boundary between pre- and postnatal periods is indicated by the solid vertical line. Each colored point represents the expression level of each gene across 16 anatomical brain regions and ages. Brain structure includes 11 neocortical areas (NCX, blue), and 5 subcortical regions: hippocampus (HIP, cyan), amygdala (AMY, orange), striatum (STR, black), mediodorsal nucleus of thalamus (MD, dark green), and cerebellar cortex (CBC, red).
Neocortical areas include orbital prefrontal cortex (OFC), dorsolateral prefrontal cortex (DFC), ventrolateral prefrontal cortex (VFC), medial prefrontal cortex (MFC), primary motor cortex (M1C), primary somatosensory cortex (S1C), posterior inferior parietal cortex (IPC), primary auditory cortex (A1C), posterior superior temporal cortex (STC), inferior temporal cortex (ITC), and primary visual cortex (V1C). *Genes associated with extensive PVS burden in the GWAS meta-analysis and in the young adult cohort (i-Share study)

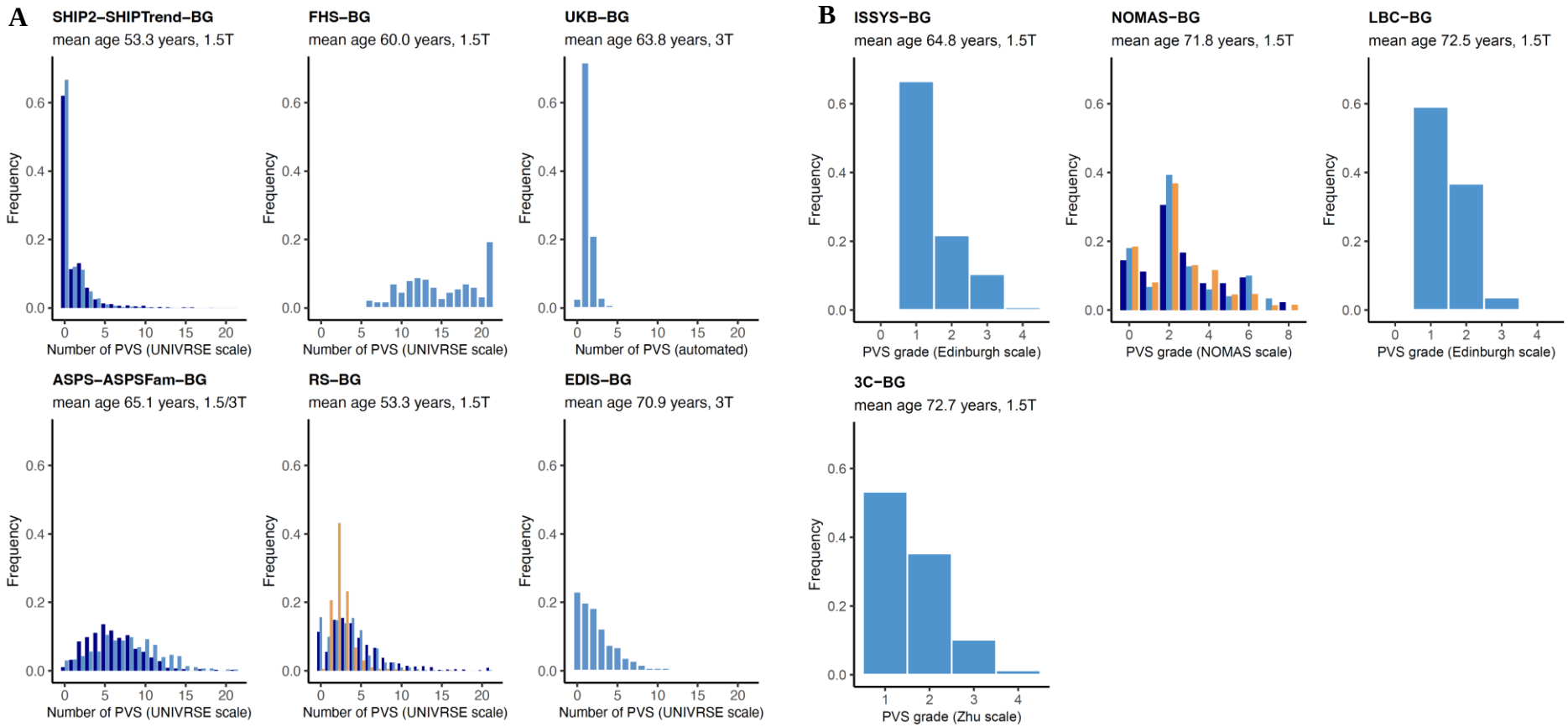
5) Supplementary Figure 5. PVS distribution

White matter PVS distribution in the GWAS meta-analysis and the i-Share cohorts



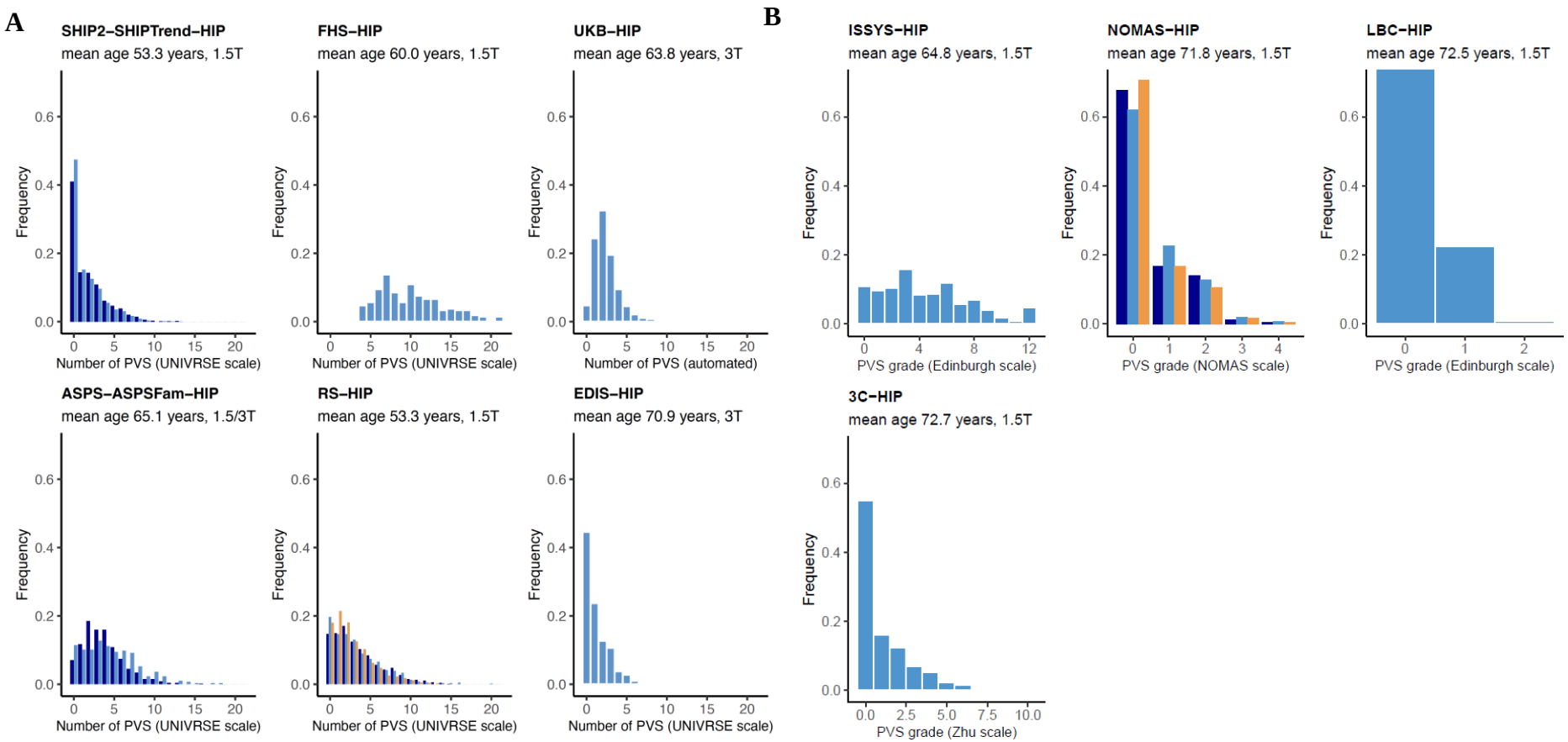
Distribution of PVS burden using the UNIVRSE scale or an automated method (A) and grade-based scales (B). (A) SHIP2 is represented in dark blue, SHIPTrend in light blue; ASPS in dark blue, ASPS-fam in light blue; RSI in dark blue, RS2 in light blue, RS3 in orange. (B) NOMAS-AA (American African ancestry) is represented in dark blue; NOMAS-EUR (European ancestry) in light blue and NOMAS-HISP (Hispanic ancestry) in orange.

Basal ganglia PVS distribution in the GWAS meta-analysis cohorts



Distribution of PVS burden using the UNIVRSE scale or an automated method (A) and grade-based scales (B). (A) SHIP2 is represented in dark blue, SHIPTrend in light blue; ASPS in dark blue, ASPS-fam in light blue; RSI in dark blue, RS2 in light blue, RS3 in orange. (B) NOMAS-AA (American African ancestry) is represented in dark blue; NOMAS-EUR (European ancestry) in light blue and NOMAS-HISP (Hispanic ancestry) in orange.

Hippocampus PVS distribution in the GWAS meta-analysis cohorts



Distribution of PVS burden using the UNIVRSE scale or an automated method (A) and grade-based scales (B). (A) SHIP2 is represented in dark blue, SHIPTrend in light blue; ASPS in dark blue, ASPS-fam in light blue; RSI in dark blue, RS2 in light blue, RS3 in orange. (B) NOMAS-AA (American African ancestry) is represented in dark blue; NOMAS-EUR (European ancestry) in light blue and NOMAS-HISP (Hispanic ancestry) in orange.