

Multi-trait Genome-wide analysis of Vascular Dementia and Cerebrovascular Disease Markers Reveals Shared Etiology and Novel Genetic Loci

Jingxian Huang, Fotios Koskeridis, Devendra Meena, Abbas Dehghan, Ioanna Tzoulaki

¹ Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, UK

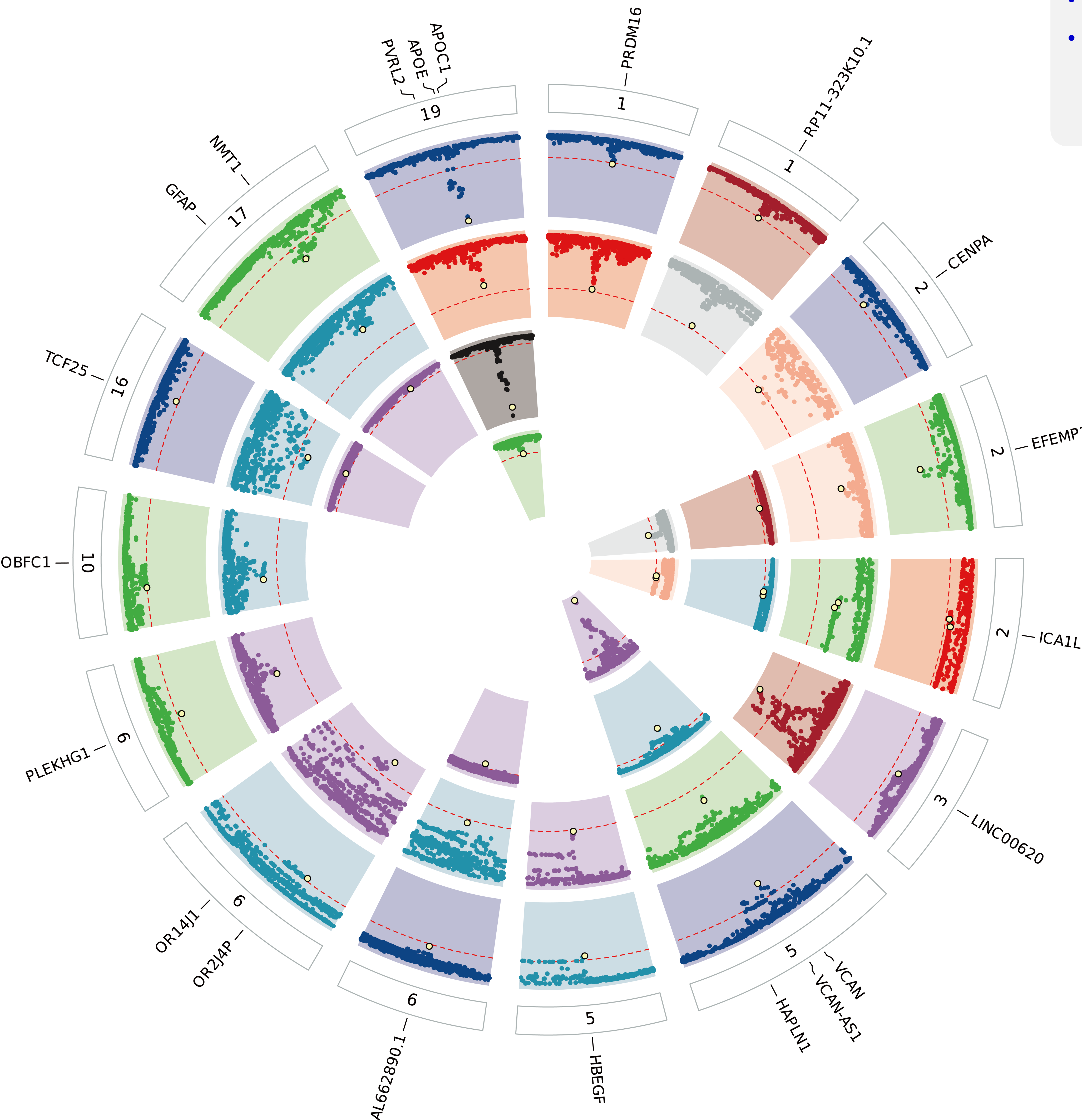
² UK Dementia Research Institute at Imperial College London, London, UK

Background & Aims

Vascular dementia (VaD), the second most common form of dementia after Alzheimer's disease, arises from a complex interplay between genetic predisposition and vascular risk factors. Genome-wide association studies (GWAS) have so far identified only a small number of genetic variants linked to VaD, mainly due to insufficient power and the heterogeneity in disease pathology which cannot be fully captured by single-trait GWAS.

- I. Map shared genetic architecture between VaD and cerebrovascular disease (CBVD) markers.
- II. Investigate novel and pleiotropic loci between VaD and CBVD markers.
- III. Pinpoint putative target genes underlying genetic loci.

Results - HyPrColoc



Methods

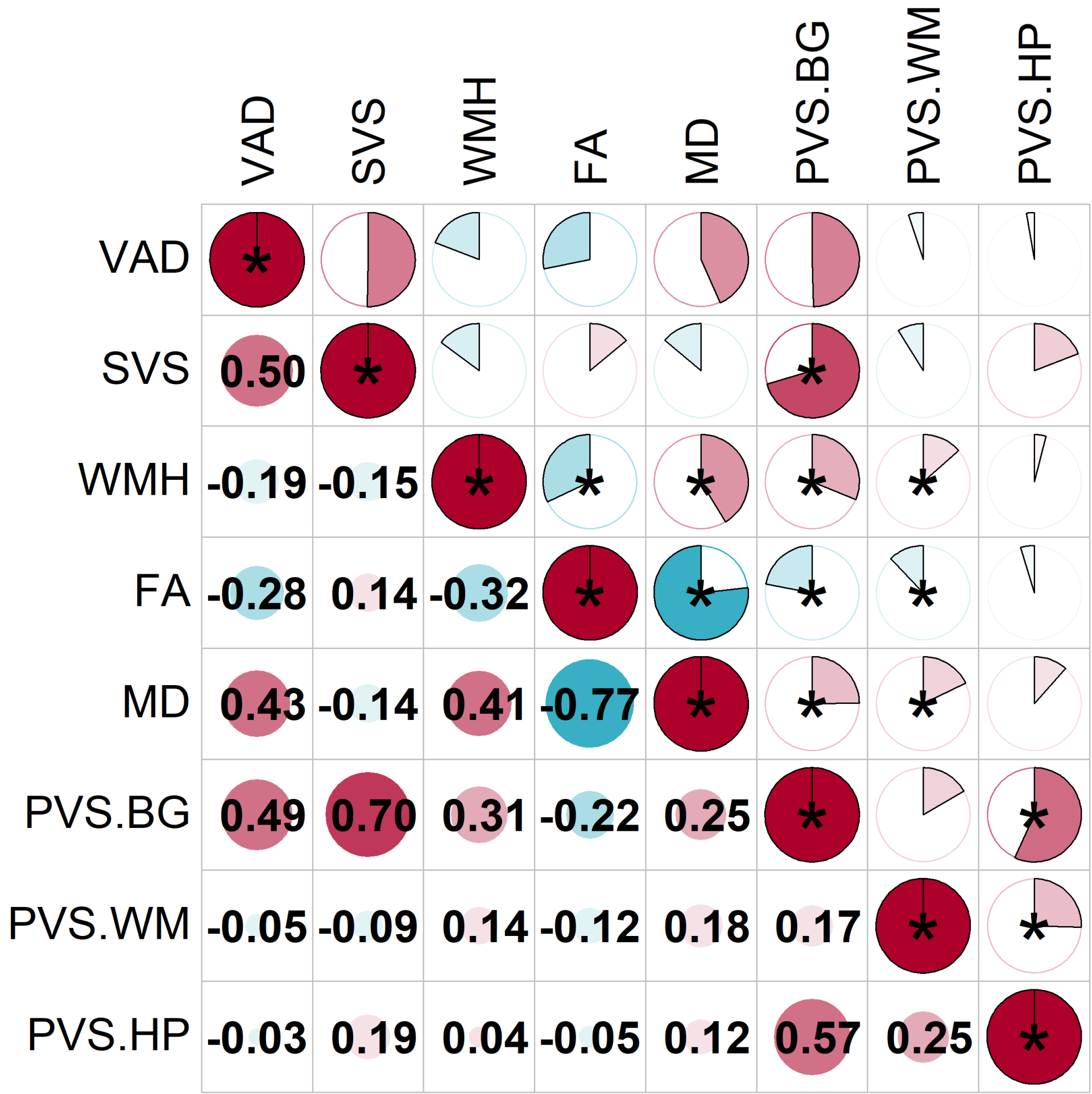
- I. Linkage disequilibrium score regression (LDSC) to measure genetic correlation.
- II. Multi-trait analysis of GWAS (MTAG) for joint analysis of summary statistics from GWAS.
- III. Multi-trait colocalization (HyPrColoc) to investigate shared genetic loci across phenotypes and nearby genes.
- IV. Transcriptome-wide association study (TWAS) and summary-data-based Mendelian randomization (SMR) to validate putative target genes.

Included CBVD markers:

- Small vessel stroke (SVS)
- Brain microbleeds
- Brain infarction
- MRI measures-WMH, fractional anisotropy (FA), and mean diffusivity (MD)
- Extensive PVS burden at white matter (WM), basal ganglia (BG), and hippocampal (HP)



Results – genetic correlation

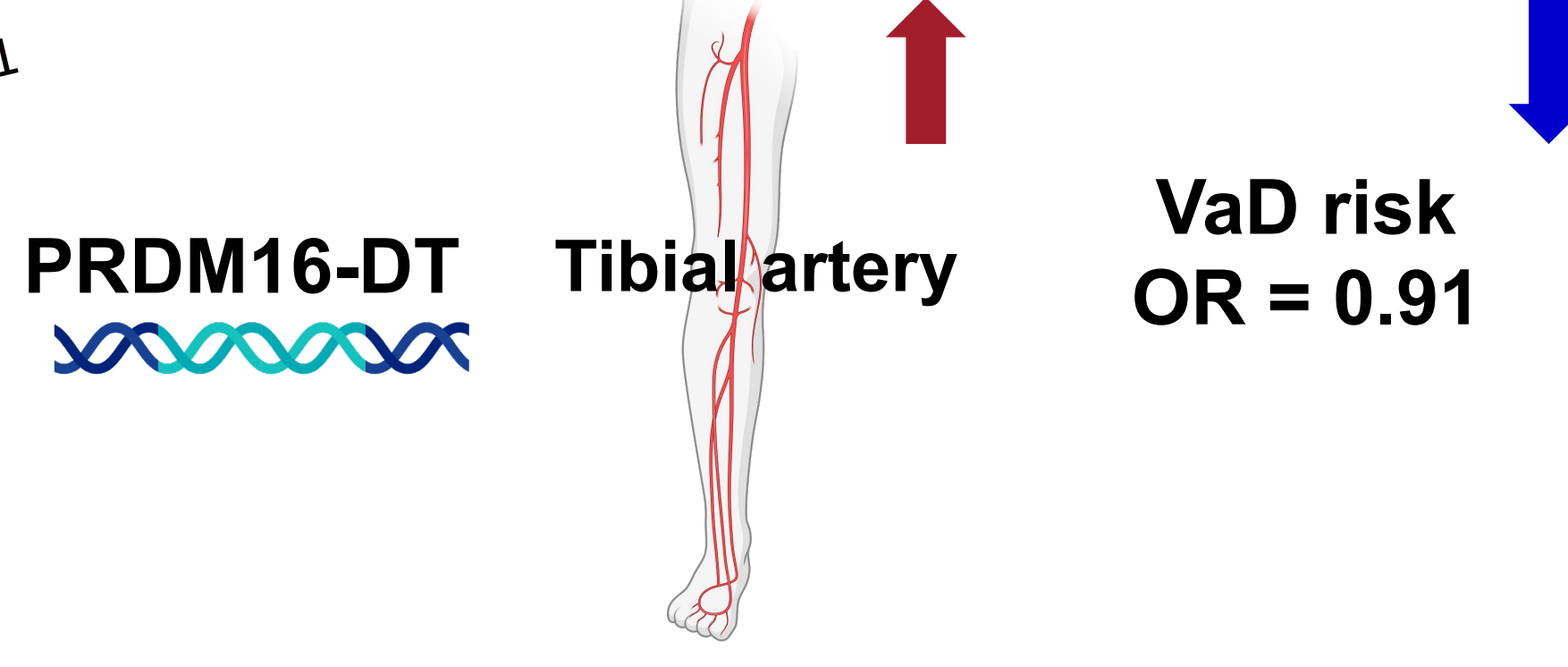


- One novel locus for VaD:
PRDM16 (rs2455132, $P_{\text{MTAG}} = 4.64 \times 10^{-8}$, odds ratio (OR) = 0.98)
- 15 region with shared genetic loci
- 5 with VaD and gene expression:
PRDM16, CENPA, AL662890.1, TCF25, and APOC1-APOE-PVRL2

TWAS:



SMR:



- Vascular dementia
- Small vessel stroke
- Brain infarction
- White matter hyperintensities
- Fractional anisotropy
- Mean diffusivity
- Extensive perivascular space burden - basal ganglia
- Extensive perivascular space burden - white matter
- Extensive perivascular space burden - hippocampal