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PODIUM PRESENTATION

EPIDEMIOLOGY

Epigenome-wide association study and integrative cross-omics analyses of cerebral white matter hyperintensities implicate novel gene networks related to Alzheimer's disease

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Abstract

Background: Cerebral white matter hyperintensities (WMH) on magnetic resonance imaging are markers of cerebral small vessel disease (cSVD), a major risk factor for Alzheimer's disease and related dementia (ADRD). Despite the successful identification of multiple genetic variants associated with this highly heritable condition, its genetic architecture remains incompletely understood. More specifically, the role of DNA methylation (DNAm) has received little attention.

Method: We investigated the association of blood DNAm at approximately 450,000 CpG sites with WMH burden in 9,732 middle to late age adults from 14 cohorts. Integrative cross-omics analyses followed to elucidate the role of identified DNAm in cSVD.

Result: We identified 12 single-CpG and 46 region-based DNAm associations with WMH burden. Our top discovery single CpG, cg24202936 ($P = 7.6\times10^{-8}$), was associated with *F2* expression in blood ($P = 6.4\times10^{-5}$), and colocalized with *FOLH1* expression in brain (posterior probability = 0.75). Some single-CpG loci (cg17417856 and cg06809326) with suggestive evidence ($P<1\times10^{-5}$) were also identified as differentially methylated regions (DMRs) in *PRMT1* and in *CCDC144NL-AS1*. Mendelian randomization analyses showed that cg06809326 is causally associated with WMH burden (OR [95% CI]: 1.39 [1.03-1.87], $P = 0.03$) and that expression of *CCDC144NL-AS1* mediates this association. DMR analysis, joint epigenetic association analysis, and multi-omics colocalization analysis consistently identified a role of DNAm near *SH3PXD2A*, a locus previously identified in genome-wide association studies of WMH. Gene set enrichment analyses revealed functions of the WMH-associated DNAm loci in the blood-brain barrier (BBB) and in the immune response. Integrative cross-omics analysis identified 19 key regulatory genes in two WMH-associated networks related

to extracellular matrix (ECM) organization, and lipid and lipoprotein metabolism. A drug repositioning analysis indicated peroxisome proliferator-activated receptor alpha (PPAR-α) agonist as a target drug for WMH, which was also proposed as a promising target for ADRD.

Conclusion: Our epigenome-wide association study and integrative cross-omics analyses implicate novel genes influencing WMH burden, which converged on pathways related to the immune response and to a compromised BBB possibly due to disrupted cell-cell and cell-ECM interactions. The results also suggest that PPAR-α may contribute to lowering risk for WMH possibly through protection against BBB disruption, which may potentially modify the ADRD risk.

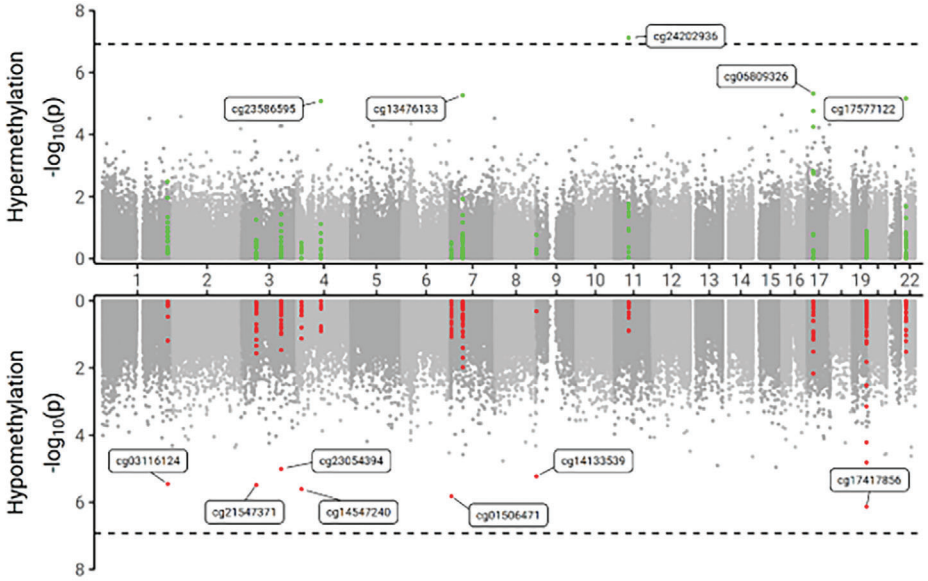

Figure 1 Miami plot of epigenome-wide associations in WMH burden Associations (-log10(*P* value), y-axis) between increased DNAm level (hypermethylation) and WMH burden (top); and between decreased DNAm level (hypomethylation) and WMH burden (bottom) are plotted against DNAm locations (x-axis). The dashed line indicates the Bonferroni threshold (1.2×10^{-7}) for epigenome-wide significance. Target CpGs with a *P* value smaller than the suggestive significance threshold (1.0×10^{-5}) are labelled with probe names. Single-CpGs within ±50 kb are highlighted in green (top) and red (bottom).

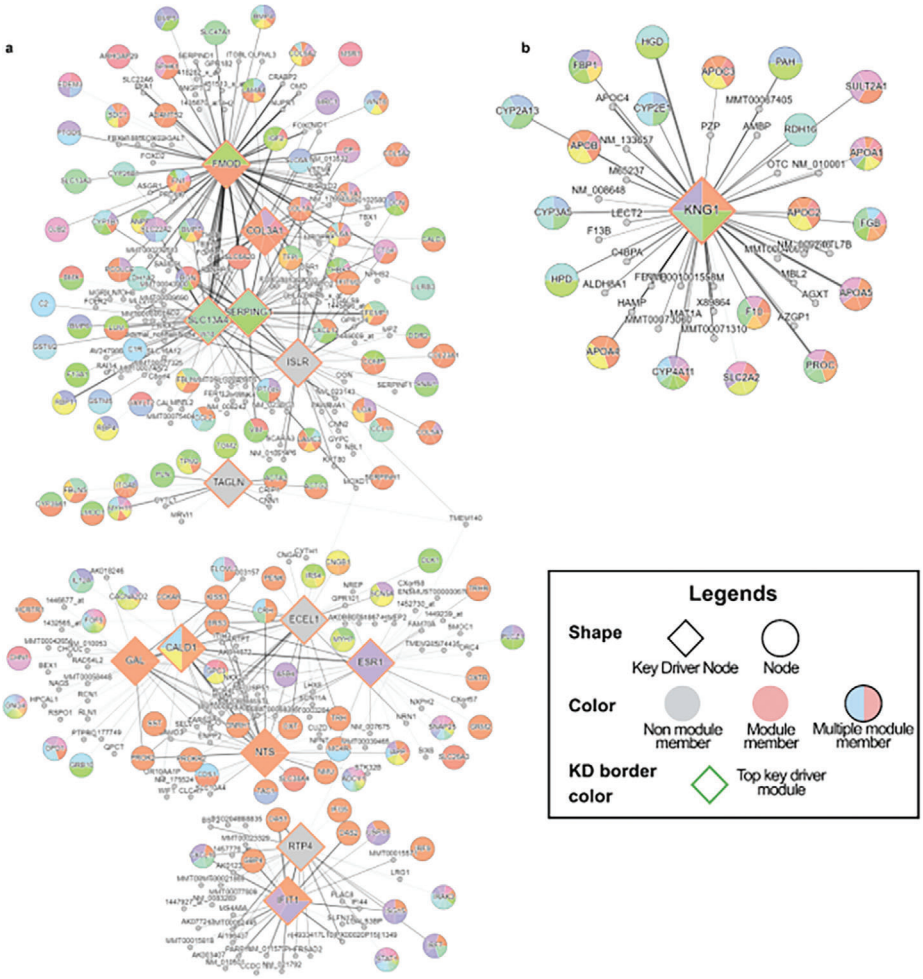

Figure 2 WMH-associated Gene Networks. WMH-associated genes based on multi-molecular evidence are organized around the 19 key driver genes. a. WMH-associated network consisting of four sub-networks - extracellular matrix (ECM) organization (*FMOD, COL3A1, SEPING1, SLC13A4,* and *ISLR*); smooth muscle contraction (*TAGLN*); G-protein-coupled receptor (GPCR) ligand binding (*GAL, ECEL1, ESR1,* and *NTS*) and cytokine signaling in immune system (*IFIT1* and *RTP4*) b. WMH-associated network of lipid and lipoprotein metabolism (*KNG1*).