

Association of common genetic variants with brain microbleeds

A genome-wide association study

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Study question

Do common genetic variants contribute to individual variation in the presence of brain microbleeds (BMB)?

What is known and what this paper adds

BMB represent one of a spectrum of MRI markers of cerebral small vessel disease, with others including white matter hyperintensities (WMH) and lacunar infarcts. Genome-wide association studies (GWAS) of these other markers, particularly WMH, have provided novel insights into the underlying disease mechanisms. This investigation identified one genomic signal in the *APOE* region associated with BMB and its results further suggest that genetic predisposition to small vessel disease confers risk of BMB, indicating genetic overlap with other cerebral small vessel disease markers.

Methods

For these GWAS analyses, the investigators used data from 25,862 people who participated in 11 population-based cohort studies and 3 case-control or case-only stroke cohorts. The data sources included the Cohorts of Heart and Aging Research in Genomic Epidemiology consortium, the UK Biobank study, and the Alzheimer's Disease Neuroimaging Initiative. These individuals underwent brain pathology assessments with susceptibility-weighted or T2*-weighted gradient-echo MRI scans, and the investigators classified any observed BMB as lobar or mixed. The investigators imputed genotype data to the Haplotype Reference Consortium or 1,000 Genomes reference panel. They used logistic regression models for cohort-specific GWAS analyses and then conducted a meta-analysis to pool the results. The pooled GWAS results were the primary outcomes. The investigators also

Table Selected relationships between SNPs and BMB

Pathology	Related SNP	OR (95% CI) for BMB
Deep ICH	rs2984613	1.12 (1.05–1.18)
Lacunar stroke	rs12445022	1.07 (1.00–1.13)
WMH	rs2984613	1.12 (1.05–1.18)

assessed the relationships between *APOE* genotypes and BMB with data from 13,028 individuals from the UK Biobank study and the Rotterdam Study.

Results and study limitations

In total, 3,556 individuals (13.7%) had BMB. A single-nucleotide polymorphism (SNP) in the *APOE* region (rs769449) exhibited an association with BMB (odds ratio [OR], 1.33; 95% confidence interval [CI], 1.21–1.45), and further analyses revealed an association between the *APOE* ϵ 4 allele and strictly lobar BMB counts (OR, 1.34; 95% CI, 1.19–1.50). Several variants associated with deep intracerebral hemorrhage (ICH) and lacunar stroke exhibited associations with BMB. The present study's limitations include a relatively modest number of individuals with BMB and between-cohort variability in the percentages of people with BMB. Most members of the analytic sample were of European ancestry, which may limit interracial generalizability.

Study funding and competing interests

This study was funded by the European Union. Some authors report additional competing interests. Go to Neurology.org/N for full disclosures.

A draft of the short-form article was written by M. Dalefield, a writer with Editage, a division of Cactus Communications. The corresponding author(s) of the full-length article and the journal editors edited and approved the final version.

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