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Genetic and lifestyle risk factors for MRI-defined brain infarcts in a population-based setting

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Study objective

To identify genetic and lifestyle risk factors for MRI-defined brain infarcts (BI).

Summary results

This study identified 2 genetic risk loci and found that high blood pressure (BP) is the major risk factor for BI.

What is known and what this paper adds

The predictors of BI remain poorly understood, with past studies reporting inconsistent results. This meta-analysis study identifies the key risk factors for BI.

Participants and setting

This study was a meta-analysis of 18 prospective population-based cohort studies participating in the Cohorts for Heart and Aging Research in Genomic Epidemiology consortium. Collectively, these studies had 20,949 participants of European (n = 17,956), African (n = 1,834), Hispanic (n = 737), Malay (n = 215), or Chinese (n = 207) ancestry, of whom 3,726 had MRI-defined BI.

Design, size, and duration

The study participants underwent brain MRI assessments. BI and white matter hyperintensities (WMH) were estimated from this MRI. The participants were also assessed for vascular risk factors including BP, diabetes, cholesterol levels, body mass index, and cardiovascular event histories. The genotypes of the participants were imputed to the 1,000 Genomes reference panel. This study conducted a multiethnic genome-wide association studies (GWAS) meta-analysis to identify genetic risk factors for BI and assess relationships between genetically determined vascular risk factor levels and BI.

Primary outcome measures

The primary outcomes were the genetic and vascular risk factors for BI identified in the multiethnic GWAS meta-analysis.

Main results and the role of chance

This study identified 2 genetic loci as BI risk factors: rs39938 in *FBN2* (chr5q23) and rs12583648 in *LINC00539* and near *ZDHHC20* (chr13q12) ($p < 0.0001$ for both), although these could not be replicated in a smaller follow-up sample. After adjustments for age and sex, associations with BI were found for hypertension, smoking, diabetes, histories of cardiovascular disease (especially stroke), and WMH burden ($p < 0.0001$ for all). Genetically determined high BP was associated with BI.

Table Selected risk factors for BI in the meta-analysis

Factor	Odds ratio (95% confidence interval) for BI
rs39938 in *FBN2*	1.21 (1.13–1.30)
rs12583648 in *LINC00539/ZDHHC20*	1.21 (1.13–1.29)
Hypertension	1.62 (1.48–1.78)
History of cardiovascular disease generally	1.62 (1.46–1.81)
History of stroke specifically	5.72 (4.71–6.95)

Bias, confounding, and other reasons for caution

This study was underpowered for the discovery and replication of novel, robust genetic risk loci, partly due to the heterogeneity of BI etiologies.

Generalizability to other populations

This study's large, international, multiethnic sample favors the generalizability of the results.

Study funding/potential competing interests

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

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