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How common are single gene mutations as a cause for lacunar stroke?

A targeted gene panel study

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Study objective and summary result

This study investigated the prevalence of rare disease-causing variants in small vessel disease (SVD)-associated genes in patients with younger-onset presumed-sporadic SVD stroke and found that rare monogenic variants are present in ~1.5% of such stroke cases.

What is known and what this paper adds

Genetic SVD most commonly results from *NOTCH3* variants, but various other SVD-associated genes have been reported. This investigation clarifies the prevalence of rare variants in patients with younger-onset presumed-sporadic SVD stroke.

Participants and setting

The investigators analyzed samples from 950 patients (70.9% male) with MRI-confirmed SVD stroke and onset ages ≤70 years (mean age at first stroke, 56.3 ± 8.7 years). These patients participated in the UK DNA Lacunar Stroke Study, which recruited patients of European ancestry through 72 stroke centers located throughout the UK.

Design, size, and duration

The investigators used a gene panel to analyze the participants' DNA samples for mutations in 7 genes known to cause SVD (*NOTCH3*, *HTRA1*, *FOXC1*, *COL4A1*, *COL4A2*, *TREX1*, and *GLA*) and 8 genes associated with disorders involving SVD-related phenotypes (*APP*, *CST3*, *ITM2B*, *ATP1A2*, *CACNA1A*, *SCN1A*, *ABCC6*, and *COL3A1*). Variants were filtered according to their frequencies in control databases, their predicted impacts, their presence or absence in curated variant lists, and their degrees of deleteriousness according to Combined Annotation Dependent Depletion scores.

Table Identified variants in genes known to cause SVD

Gene	No. of identified variants	No. of affected patients
NOTCH3	8	11
HTRA1	2	2
COL4A1	1	1

Primary outcome measures

The primary outcome was the prevalence of identified variants.

Main results and the role of chance

Eleven previously reported variants were identified in 14 patients (1.5%), and 29 variants of unknown clinical relevance were identified in 32 patients (3.4%).

Bias, confounding, and other reasons for caution

The present study lacked a control group.

Generalizability to other populations

The present study's focus on individuals of European ancestry limits the generalizability of the results to people of different ethnic backgrounds.

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.

