

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

## A targeted gene panel study

Rhea Y.Y. Tan, PhD, Matthew Traylor, PhD, Karyn Megy, PhD, et al.,  
NIHR BioResource: Rare Diseases Consortium

### Correspondence

Dr. Tan  
yyrt2@medschl.cam.ac.uk

Cite as: *Neurology*® 2019;93:e2007-e2020. doi:10.1212/WNL.00000000000008544

### 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  $\leq 70$  years (mean age at first stroke,  $56.3 \pm 8.7$  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*, *FOXCl*, *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
<i>NOTCH3</i>	8	11
<i>HTRA1</i>	2	2
<i>COL4A1</i>	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

This study was funded by the UK National Institute for Health Research; the British Heart Foundation; the Singaporean Agency for Science, Technology and Research; and the UK National Health Service. The authors report no competing interests. Go to [Neurology.org/N](http://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 authors of the full-length article and the journal editors edited and approved the final version.

# Neurology®

## How common are single gene mutations as a cause for lacunar stroke?: A targeted gene panel study

Rhea Y.Y. Tan, Matthew Traylor, Karyn Megy, et al.

*Neurology* 2019;93:e2007-e2020 Published Online before print November 12, 2019

DOI 10.1212/WNL.00000000000008544

**This information is current as of November 12, 2019**

<b>Updated Information &amp; Services</b>	including high resolution figures, can be found at: <a href="http://n.neurology.org/content/93/22/e2007.full">http://n.neurology.org/content/93/22/e2007.full</a>
<b>References</b>	This article cites 50 articles, 11 of which you can access for free at: <a href="http://n.neurology.org/content/93/22/e2007.full#ref-list-1">http://n.neurology.org/content/93/22/e2007.full#ref-list-1</a>
<b>Subspecialty Collections</b>	This article, along with others on similar topics, appears in the following collection(s): <b>All Cerebrovascular disease/Stroke</b> <a href="http://n.neurology.org/cgi/collection/all_cerebrovascular_disease_stroke">http://n.neurology.org/cgi/collection/all_cerebrovascular_disease_stroke</a> <b>All Genetics</b> <a href="http://n.neurology.org/cgi/collection/all_genetics">http://n.neurology.org/cgi/collection/all_genetics</a> <b>CADASIL</b> <a href="http://n.neurology.org/cgi/collection/cadasil">http://n.neurology.org/cgi/collection/cadasil</a> <b>Stroke in young adults</b> <a href="http://n.neurology.org/cgi/collection/stroke_in_young_adults">http://n.neurology.org/cgi/collection/stroke_in_young_adults</a>
<b>Permissions &amp; Licensing</b>	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: <a href="http://www.neurology.org/about/about_the_journal#permissions">http://www.neurology.org/about/about_the_journal#permissions</a>
<b>Reprints</b>	Information about ordering reprints can be found online: <a href="http://n.neurology.org/subscribers/advertise">http://n.neurology.org/subscribers/advertise</a>

*Neurology*® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2019 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.

