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Genome-wide association meta-analysis of functional outcome after ischemic stroke

Martin Söderholm, MD, PhD,* Annie Pedersen, MD,* Erik Lorentzen, MSc, et al., on behalf of the International Stroke Genetics Consortium, the NINDS-SiGN Consortium, and the Genetics of Ischaemic Stroke Functional Outcome (GISCOME) Network

Correspondence
Dr. Pedersen
annie.pedersen@gu.se

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Study objective and summary result

This study aimed to identify genetic variants associated with functional outcomes in patients with ischemic stroke (IS), and it found that an intronic variant (rs1842681) in the *LOC105372028* gene is associated with worsened functional outcomes.

What is known and what this paper adds

Candidate gene studies have reported individual genetic variants associated with poststroke functional outcomes. This study provides the first large international genome-wide association (GWA) evidence for a genetic variant being associated with functional outcome after overall ischemic stroke.

Participants and setting

This study analyzed data from 12 studies conducted in Europe, the US, and Australia included in the Genetics of IS Functional Outcome (GISCOME) network. The GISCOME studies collectively included 6,165 adults with IS who were mainly of European ancestry.

Design, size, and duration

This study collected genotyping and outcome data from the GISCOME studies, which assessed functional outcomes ~3 months after stroke with the modified Rankin scale (mRS), on which lower scores reflect better outcomes. The mRS scores were dichotomized into categories of 0–2 and 3–6 and analyzed with logistic regression. In addition, the full mRS scale was analyzed using ordinal logistic regression. Analyses were adjusted for baseline stroke severity, age, sex and ancestry. This study conducted an inverse-variance weighted fixed-effects meta-analysis to combine the results for separate GWA analyses of each individual study. Statistical significance was defined as $p < 5 \times 10^{-8}$.

Primary outcome measures

The primary outcomes were dichotomized mRS (0–2 vs 3–6) and the full mRS scale.

Main results and the role of chance

The rs1842681 variant in the *LOC105372028* was associated with the dichotomized mRS. No other significant associations were found, but several variants demonstrated suggestive association with outcome ($p < 10^{-5}$), some of which are within or near genes with experimental evidence of influence on ischemic stroke volume and/or brain recovery (e.g., *NTN4* and *PTCH1*).

Table Genetic variants significantly associated and selected variants suggestively associated with functional outcome in patients with IS

Genetic variant	Odds ratio for minor allele for mRS score > 2	*p* Value	Nearest gene
rs1842681	1.40	5.27×10^{-9}	*LOC105372028*
rs2236406	1.27	3.43×10^{-6}	*PTCH1*
rs13299556	1.25	6.25×10^{-5}	*PLAA*
rs78734480	0.57	4.79×10^{-4}	*NTN4*

Bias, confounding, and other reasons for caution

This study's sample size is probably insufficient for detecting some additional genetic variants with relevance to poststroke functional outcomes. The mRS is a crude outcome measure, and the assessment timepoints varied between 60 and 190 days poststroke.

Generalizability to other populations

The participants in the GISCOME studies were mostly of European ancestry, and this may limit the interracial generalizability of this study's results.

Study funding/potential competing interests

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*These authors contributed equally to this work.

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