Contribution of Common Genetic Variants to Risk of Early Onset Ischemic Stroke

Thomas Jaworek, MS, Huichun Xu, MD, PhD, Brady J. Gaynor, MS, et al. for the Cervical Artery Dissections and Ischemic Stroke Patients (CADSIP) Consortium for the INVENT Consortium, and the Early Onset Stroke Genetics Consortium of the International Stroke Genetics Consortium (ISGC)

Cite as: Neurology® 2022;99:e1738-e1754. doi:10.1212/WNL.0000000000201006

Correspondence
Dr. Kittner
skittner@som.umaryland.edu

Study Question
What are the major genetic determinants of early onset ischemic stroke (onset < age 60 years) and do they differ from older onset stroke?

What Is Known and What This Paper Adds
Our study’s results show genome-wide associations of early onset stroke (EOS) with variants that tag ABO blood subgroups O1 and A1. Although ABO is a known stroke locus, effect sizes of both variants were larger in EOS compared with late onset stroke (LOS). We further observed that a higher genetic propensity for venous thrombosis was more strongly associated with EOS than with LOS, supporting a stronger role of prothrombotic factors in EOS.

Methods
We performed a meta-analysis of genome-wide association studies of EOS, ages 18–59 years, in 16,730 cases and 599,237 controls from The Early Onset Stroke Consortium, an international collaboration of 48 different studies. Cases believed to be due to known monogenic or nongenetic causes were excluded. Logistic regression was performed to test for association between stroke occurrence and single variants, adjusting for sex and up to 10 principal components to account for population stratification. For comparison with LOS (age at stroke onset ≥ 60 years), we performed a parallel analysis in 9,272 LOS cases and 25,124 controls from the SiGN Consortium. ABO blood groups were defined using established tagging single-nucleotide polymorphisms. We evaluated the relation of venous thromboembolism (VTE), another prothrombotic condition, with blood group-associated variants and EOS first by testing associations of blood group-associated variants with early and late onset VTE in the UK Biobank (UKB) and second by testing whether a VTE polygenic risk score was more strongly associated with EOS than with LOS.

Results and Study Limitations
Two separate loci associated with EOS, both mapping to the ABO gene. Odds ratios were 0.88 (0.85–0.91; p = 4.3 × 10⁻⁴) for the rs529565 O1-tagging variant and 1.26 (1.11–1.21; p = 6.5 × 10⁻¹³) for the rs635634 A1-tagging variant. Their effect sizes were significantly larger for EOS than for LOS (p < 0.001 for difference in ORs between EOS and LOS). The strongest differences between EOS and LOS were for cardioembolic and undetermined stroke. In the UKB, both the O1-tagging and A1-tagging variants were more strongly associated with early compared with late onset VTE (p = 2.2 × 10⁻⁶ and 4.0 × 10⁻⁷, respectively, for difference in ORs). A previously developed polygenic risk score for VTE was more strongly associated with EOS than with LOS (p = 0.0002). Study limitations include the absence of mechanistic support linking ABO to increased risk of EOS, the limited ancestral diversity of our sample, and the limited sample size for subtype-specific analyses.

Study Funding and Competing Interests
This study was funded by the NIH, Department of Veterans Affairs, and multiple international government agencies and medical research foundations. Some authors report competing interests. Go to Neurology.org/N for full disclosures.
Contribution of Common Genetic Variants to Risk of Early-Onset Ischemic Stroke
Thomas Jaworek, Huichun Xu, Brady J. Gaynor, et al.
Neurology 2022;99:e1738-e1754 Published Online before print August 31, 2022
DOI 10.1212/WNL.0000000000201006

This information is current as of August 31, 2022

Updated Information & Services
including high resolution figures, can be found at:
http://n.neurology.org/content/99/16/e1738.full

References
This article cites 41 articles, 11 of which you can access for free at:
http://n.neurology.org/content/99/16/e1738.full#ref-list-1

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
Association studies in genetics
http://n.neurology.org/cgi/collection/association_studies_in_genetics
Infarction
http://n.neurology.org/cgi/collection/infarction
Stroke in young adults
http://n.neurology.org/cgi/collection/stroke_in_young_adults

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://www.neurology.org/about/about_the_journal#permissions

Reprints
Information about ordering reprints can be found online:
http://n.neurology.org/subscribers/advertise