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

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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; \( p = 4.3 \times 10^{-13} \)) for the rs529565 O1-tagging variant and 1.26 (1.11–1.21; \( p = 6.5 \times 10^{-13} \)) 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 (\( p = 2.2 \times 10^{-6} \) and \( 4.0 \times 10^{-7} \), 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.

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