EDITORIAL

Common Genetic Variants and Early Onset Stroke

Clues but No Answers

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The incidence of stroke in young adults (early-onset stroke [EOS]) is increasing, and survivors face increased mortality risks and potentially decades living with a disability. Despite this, few studies focus on this population. In approximately 40% of people with EOS, the stroke is cryptogenic,[2] and there are scant data from clinical trials to guide the selection of preventative strategies in this population because people with EOS are often excluded from trials. Genetic determinants of EOS have long been suspected, but remain elusive. Monogenic causes (e.g., CADASIL, Fabry disease, and sickle-cell disease) have been implicated in some people with EOS, but the proportion of overall EOS cases with established etiologies remains low.

In this issue of *Neurology*®, Jaworek et al. report a transethnic meta-analysis of 48 genome-wide association studies (GWASs) of ischemic stroke (IS).[3] The consortium analyzed approximately 17,000 IS cases, split between EOS (age 18–59 years) and late-onset stroke (LOS: age older than 60 years) and 25,000 nonstroke controls. The analyses uncovered novel and previously known associations between common genetic variants and EOS, including a strong association between EOS and serologically defined ABO blood groups (A, B, AB, and O). A common variant tagging a 12-base pair insertion/deletion at the ABO locus was located in a biologically and clinically important region of the genome previously associated with IS. The notable finding is that the effect of the ABO association was larger in EOS compared with LOS. Specifically, in EOS cases vs nonstroke controls, the prevalence of blood group A increased from 0.444 to 0.484, and the prevalence of blood group O decreased from 0.411 to 0.355. These differences in blood groups distributions between EOS cases and controls indicate a link between the ABO locus, IS risk, and age at onset.

The ABO association with IS, identified in prior GWAS,[4] is found for both EOS and LOS, suggesting it is not specific to EOS, but rather enriched in EOS cases. This begs the question of whether EOS has a distinct genetic etiology from LOS, or if they lay on the same genetic spectrum, with varying degrees of effect from overlapping loci. Although further functional studies are required to understand the mechanism linking the ABO locus to EOS risk, a prothrombotic mechanism is likely at play. This makes sense because many of the IS subtypes prevalent in EOS, such as paradoxical embolism, pregnancy, and migraine, are likely linked to IS by a prothrombotic state.

The hypothesis that different genes may drive the age of IS onset is plausible. Yet, the present study uses a common but almost over-lapping age cutoff to separate EOS from LOS at age 60 years. The increasing prevalence of vascular risk factors in patients in the upper half of this EOS age range[5] shifts the stroke subtype architecture toward that of LOS, diluting phenotypic differences between the 2 groups. An alternative approach of using more extreme age cutoffs (e.g., EOS age younger than 45 years; LOS age older than 70 years) could boost the genetic signal. Although an extreme phenotyping approach requires larger overall sample sizes, it has been effective in other diseases, such as dementia.[6]

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Strengths of this meta-analysis include well-adjudicated EOS cases and samples sourced from 5 different continents, including 35% of subjects with non-European ancestry. Further increasing racial diversity in subsequent stroke GWAS is particularly important because the racial disparities in Black and Hispanic White stroke incidence and mortality are more pronounced in EOS vs LOS.[5]

Jaworek et al. excluded EOS cases with suspected monogenic causes. This is appropriate for common variant association discovery. It is likely, however, that EOS is at least partially driven by rare variants, as seen in breast cancer (BRCA1) and coronary artery disease (LDLR). It is possible that yet uncharacterized monogenic EOS-associated genes exist and could explain a portion of EOS cases that are undetected by GWAS methodology, which limits analysis to common variants with minor allele frequency >1%. If rare variants do contribute to excess EOS risk, conducting rare variant GWAS using whole-exome or whole-genome sequencing data will be useful.

This work has deepened our understanding of EOS pathophysiology. Future research will surely build on it, with the goal of a more precise understanding of stroke pathophysiology, leading to targeted preventative treatments for EOS and a reduction in disability in patients' most productive years.

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