Comment: Tackling shared genetic underpinnings of migraine and ischemic stroke

In this large collaborative effort, Malik et al.[1] explore shared genetic variation underlying 2 common conditions: migraine and ischemic stroke (IS). Numerous studies have shown an increased risk of stroke in patients with migraine, but the contribution of genetic factors to this relationship is unclear.[2] The authors used the 2 largest existing meta-analyses of genome-wide association studies (GWAS) for both phenotypes.

First, they tested whether genetic variants showing genome-wide significant association with migraine also influence the risk of IS and vice versa. Second, they constructed a polygenic risk score, combining genetic variants associated with one disease at lower significance levels, and tested whether it predicts an increased risk of the other disease. Third, they used cross-phenotype spatial mapping (CPSM) to identify genomic regions exhibiting similar association patterns across phenotypes.

Although only one genome-wide significant locus for IS (in the chromosome 9p21 region) was associated with migraine, the CPSM approach showed various genomic regions affecting both the risk of IS and migraine. An important result emerging from the polygenic and CPSM approaches is that more shared genetic variation was observed between IS and migraine without aura (MO) than between IS and migraine with aura (MA). This is surprising, as phenotypic associations between migraine and IS were shown to be stronger for, or even restricted to, MA.[2] One potential explanation is that rare variants that are not captured by genome-wide chips may be influencing the risk of MA and its genetic correlation with IS. This is consistent with the fact that GWAS failed to reveal a large number of risk loci for MA, while numerous loci were discovered for MO.[3] Nongenetic factors may also contribute to the association between IS and MA.

While more data are needed to unravel the specific biological pathways underlying the association between IS and migraine, this study sheds new light on the pattern by which common variants jointly contribute to both diseases and their subtypes.

1. Malik R, Freilinger T, Winsvold BS, et al. Shared genetic basis for migraine and ischemic stroke: a genome-wide analysis of common variants. Neurology 2015;84: xxx–xxx.
2. Schürks M, Rist PM, Bigal ME, et al. Migraine and cardiovascular disease: systematic review and meta-analysis. BMJ 2009;339:b3914.
3. Anttila V, Winsvold BS, Gormley P, et al. Genome-wide meta-analysis identifies new 578 susceptibility loci for migraine. Nat Genet 2013;45:912–917.

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