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MIGRAINE

New susceptibility loci associated with migraine

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A meta-analysis of data from 29 genome-wide association studies has identified 12 genetic loci associated with common forms of migraine. Approximately 14% of the adult population is affected by migraine, but the causal molecular mechanisms and pathophysiology are still poorly understood.

The meta-analysis involved over 23,000 patients with migraine and almost 100,000 population-matched control individuals. The investigators also analysed data from several subgroups of patients, including those who had migraine with or without aura, and clinic-based individuals (who are considered particularly likely to have severe forms of migraine).

The investigators identified 12 loci, including five that were previously unknown (near *AJAP1*, in *C7orf10*, in *FHL5*, near *MMP16* and near *TSPAN2*), associated with migraine susceptibility. 11 of the 12 genes nearest to these loci are at least moderately expressed in migraine-relevant brain regions and several are involved in synapse function or regulation. Notably, two of the loci have previously been associated with cardiovascular traits. "The identified gene regions stimulate a so far speculative hypothesis about how response to hypoxia might be connected to migraine susceptibility," comments Aarno Palotie, one of the lead investigators.

Quantitative mRNA expression analyses of 394 brain tissue samples revealed that four of these 12 loci regulate the expression of other genes—namely, *APOA1BP*, *ATP5B*, *TBC1D7*, *FUT9* and *STAT6*—suggesting that these loci might represent further susceptibility genes. Furthermore, several of the single nucleotide polymorphisms associated with migraine are located in DNase I hypersensitivity sites or known transcription factor binding motifs, indicating that alterations in genetic regulation might be causative in migraine pathology.

4 of the 12 new loci were exclusively identified in subgroup analyses. Interestingly, no variants were identified that exclusively predispose individuals to migraine with aura, despite the fact that this type of migraine is considered more heritable than migraine without aura. The investigators speculate that migraine with aura might be influenced less by common variants and more by rare variants than is migraine without aura. Two of the loci were identified in the migraine without aura subgroup, and the other two in the clinic-based subgroup, which suggests that analysis of samples from clinic-based patients with migraine could be useful to detect low-frequency genetic variants with moderate effect sizes.

The researchers hope that identification of the causal pathways will lead to the development of new, more directed, treatment options for migraine. "The next step is to perform an even larger study combined with a denser marker set and new statistical tools," says Palotie. "This should provide us with an opportunity for meaningful pathway analyses to identify critical cellular mechanisms related to migraine susceptibility."

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Original article Anttila, V. *et al.* Genome-wide meta-analysis identifies new susceptibility loci for migraine. *Nat. Genet.* doi:10.1038/ng.2676