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Interpreting a migraine GWAS using gene expression in healthy human brain

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Summary
Migraine is a common brain disorder, with a heritability of 50%. Genome-wide association studies have identified several loci, but interpretation remains challenging. We integrated migraine GWAS data with spatial gene expression data of adult brains from the Allen Human Brain Atlas, to identify specific brain regions and molecular pathways involved in migraine. We used two complementary methods. First, we clustered all genes into co-expression modules and identified those associated with migraine. Second, we constructed local co-expression networks around high-confidence migraine genes. Both approaches converge on functions and anatomy.

Migraine GWAS
GWAS data1 from 23,285 migraine patients - 95,425 controls.
Calculate p-values per gene with GATES2:
- LD and gene size corrected.
- SNPs within 15 kb flanks.
Define migraine genes:
- “High confidence genes”
  Bonferroni corrected p < 0.05
- “Candidate genes”
  uncorrected p < 0.05

Healthy brain gene expression
Gene expression data3 from the Allen Human Brain Atlas.
Expression in 3702 samples from six healthy human donors, covering most of the brain.
Use these samples to calculate spatial co-expression between genes.
If genes are co-expressed, they share a spatial expression pattern.

Approach 1
Using co-expression data from the healthy brains, we clustered all genes into 18 co-expression modules.
All modules were tested for enrichment in migraine “candidate genes”. Five modules of interest were identified (A - E).
These modules are involved in:
- Neurotransmission, protein catabolism and mitochondria in the cortex.
- Transcription regulation in the cortex and cerebellum.
- Oligodendrocytes and mitochondria in subcortical areas.

Approach 2
We selected the 14 “high confidence migraine genes” to serve as seeds in local co-expression networks.
Each of these genes was connected to its most co-expressed genes in the healthy brains.
The network shows considerable overlap with modules A, B and D of Approach 1. It also points to the same anatomical regions and biological functions.