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Interpreting a migraine GWAS using gene expression in healthy human brain

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Summary

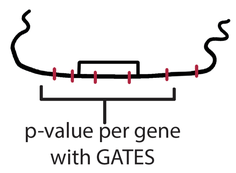
Migraine is a common brain disorder, with a heritability of 50%. Genome-wide association studies have identified several loci, but interpretation remains challenging. We integrated migraine GWAS data with spatial gene expression data of adult brains from the Allen Human Brain Atlas, to identify specific 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 data[1] from
23,285 migraine patients - 95,425 controls.

Calculate p-values per gene with GATES[2]:
- 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 data[3] 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).

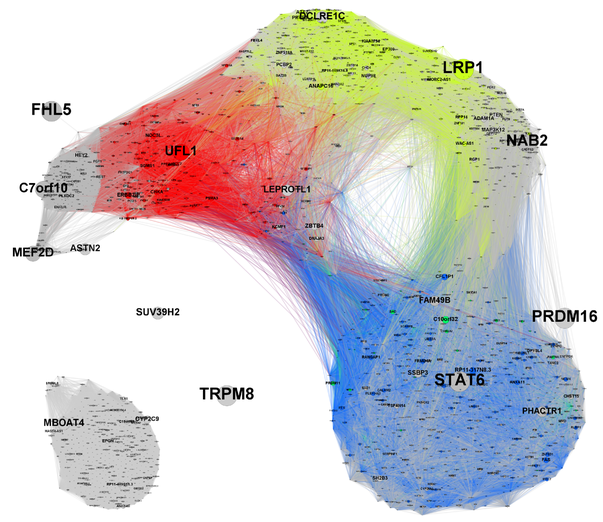
These modules are involved in:
- Neurotransmission, protein catabolism and mitochondria in the cortex.
- Transcription regulation in the cortex and cerebellum.
- Oligodendrocytes and mitochondria in subcortical areas.

Approach 2

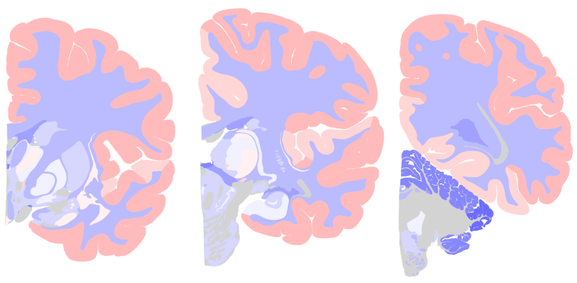
We selected the 14 "high confidence migraine genes" to serve as seeds in local co-expression networks.

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.



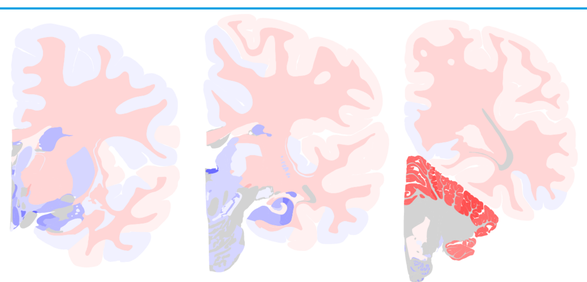
Module A



1,556 genes / 205 candidate genes
$p = 9.22 \times 10\text{-}4$
LD corrected $p = 5.47 \times 10^{-4}$

Function	EASE
Integration of energy metabolism	3.84
Mod.-dep. protein catabolic process	2.61
Proteasome	2.57
Synapse	2.09
Voltage-gated cation channel activity	2.08

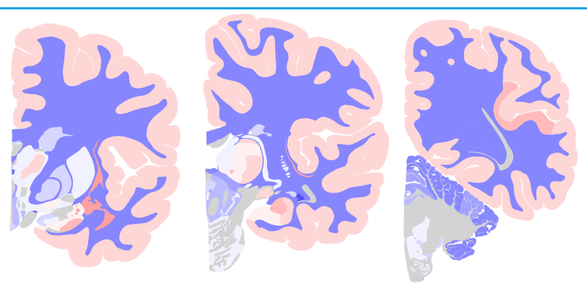
Module B



1,595 genes / 198 candidate genes
$p = 0.015$
LD corrected $p = 7.18 \times 10^{-3}$

Function	EASE
Nuclear lumen	16.46
Zinc finger transcription factor	13.85
Transcription	13.19
Zinc ion binding	9.18
Chromatin modification	8.02

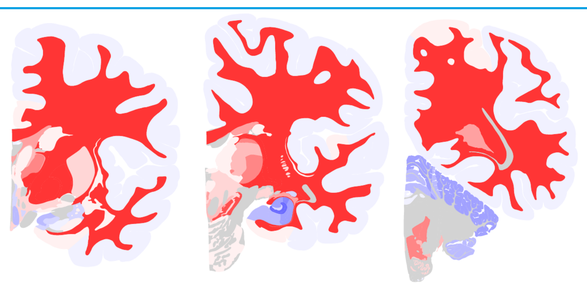
Module C



497 genes / 67 candidate genes
$p = 0.020$
LD corrected $p = 7.77 \times 10^{-3}$

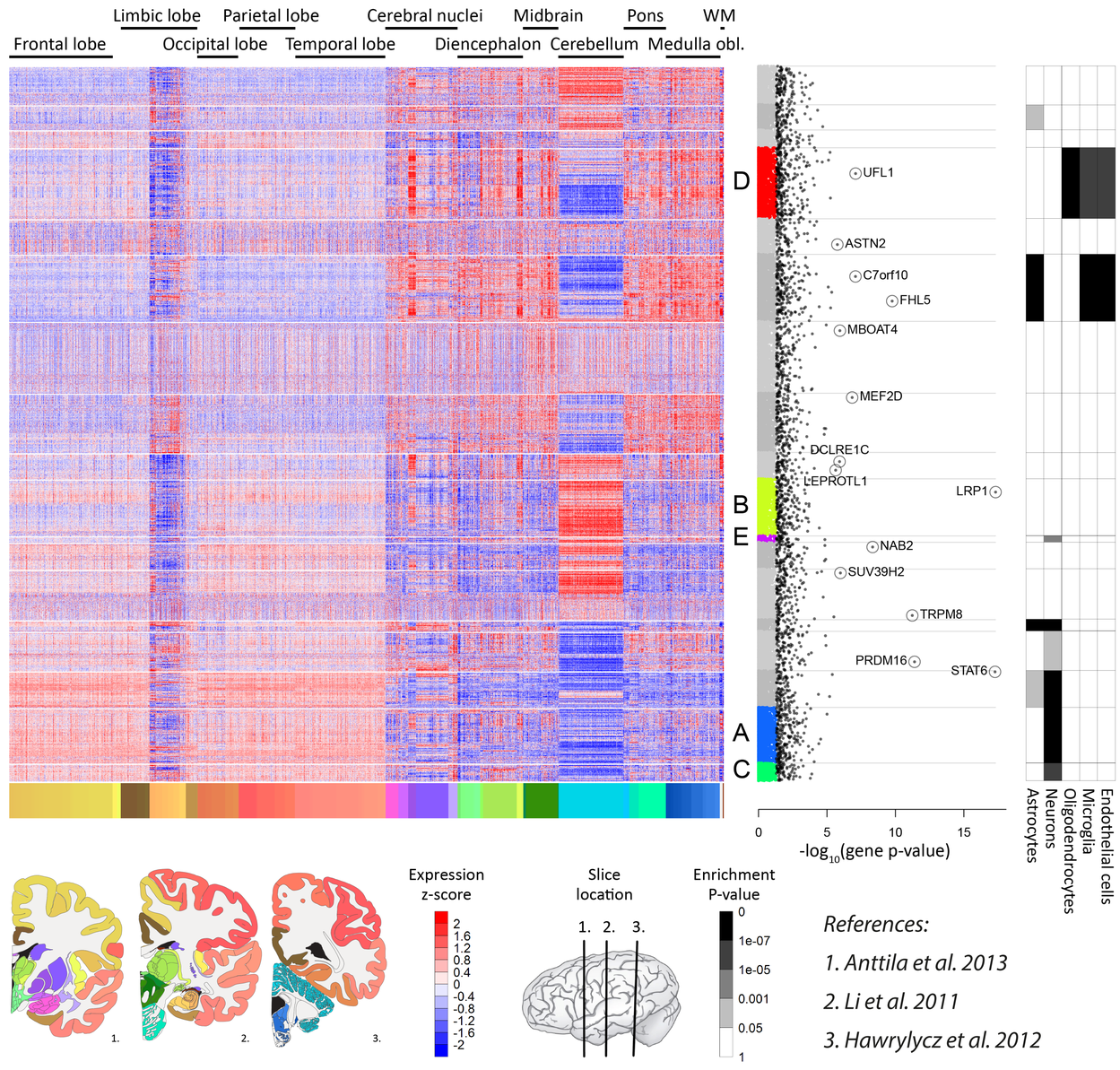
Function	EASE
Membrane fraction	3.21
Mod.-dep. protein catabolic process	3.13
Purine ribonucleotide binding	2.61
Cerebellar cortex formation	1.71
Regulation of synaptic plasticity	1.70

Module D



1,984 genes / 240 candidate genes
$p = 0.024$
LD corrected $p = 5.82 \times 10^{-3}$

Function	EASE
Mitochondrial part	4.26
Mitochondrion	3.76
Actin filament-based process	3.68
Apoptosis	3.44
Ensheathment of neurons	2.97



References:

1. Anttila et al. 2013

2. Li et al. 2011

3. Hawrylycz et al. 2012

Enabling new technology

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