



Genetics in Headache

Genetic Approaches in Headache

Migraine—the primary headache type most studied in genetics—is probably caused by a combination of environmental and genetic factors. Epidemiological family and twin studies indicate that the genetic component is higher in migraine with aura than in migraine without aura. Although genetic factors are also involved in other headaches, such as tension-type headache and cluster headache, gene discoveries in these headache types, unlike in migraine, are essentially lacking.

To identify genetic factors that confer susceptibility to migraine, several approaches have been used, which are also applicable to other headache types. First of all, one can perform *classical linkage analysis*, which aims at identifying segments of chromosomes shared by affected individuals using a family-based approach. This approach has been particularly successful for monogenic migraine types. A second commonly used strategy to identify gene variants involves *candidate gene association* studies. These studies test for significant differences between cases and controls in allele frequencies of genes expected to be involved in the disease. In the last two years or so, the technology to type DNA variants has advanced spectacularly, allowing the cost-effective analysis of hundreds of thousands of DNA variants in many thousands of patients in so-called *genome-wide association studies* (GWAS). Although GWAS have yielded hundreds of genes for many complex traits, especially for neurological diseases, results lag behind, likely because the quality of homogenous phenotyping of cases is more difficult for such diseases. GWAS is not the holy grail of headache genetics because the common gene variants can only explain a little of the genetic variance. To identify rarer gene variants with higher effect sizes, additional genetic approaches—although too expensive at the moment—are now being tried, such as next-generation sequencing of exons (*exome sequencing*) and *whole-genome sequencing*. Functional followup of gene discoveries in cellular and transgenic animal models will unravel how migraine genes cause disease.

Findings in Monogenic Migraine

Most gene discovery successes come from studies investigating monogenic familial hemiplegic migraine (FHM), a subtype of migraine with aura. In 1996, the first FHM gene was identified that encodes a subunit of voltage-gated $Ca_v2.1$ calcium channels. In the following decade, two other FHM genes, encoding a voltage-gated $Na_v1.1$ sodium channel subunit and a subunit of sodium-potassium ATPases were identified. Mutations in these FHM genes were not always associated with pure FHM, but sometimes also with additional phenotypes of epilepsy, cerebellar ataxia, or stroke, and sometimes even with lethal consequences. Functional genetic studies in cellular and transgenic mouse model systems point to a common pathway of increased glutamatergic neurotransmission that can explain the increased propensity for cortical spreading depression (CSD), the likely origin of the migraine aura. For instance, mutant $Ca_v2.1$ calcium channels from transgenic knock-in mice that carry an FHM1 gene mutation revealed increased CSD susceptibility and increased glutamate release from cortical neurons. Normalization of the release also normalized CSD parameters in mutant mice. Cellular model systems that showed reduced functioning of glial sodium-potassium pumps and reduced activity of inhibitory neuron $Na_v1.1$ sodium channels predicted an in vivo hyperexcitability of excitatory neurons, similar to that shown for FHM1 mutations.

Findings in Complex Migraine

Many candidate gene association studies have been performed, for example in testing genes encoding components of the serotonin and dopamine pathways, but the majority of the associations could not be replicated, suggesting that many of the original results represent false-positive findings. Best results came from the 5',10'-methylene tetrahydrofolate reductase (*MTHFR*) gene, which encodes a key enzyme in folate and homocysteine metabolism. Most—but certainly not all—studies found an association of the T-allele of the *MTHFR* C677T polymorphism with migraine (with aura). The first GWAS investigated several thousands of patients who had migraine with aura and identified a single migraine susceptibility locus on chromosome 8 close to the *MTDH* gene, which may affect glutamate levels in the brain. A

subsequent GWAS in a population-based cohort of female migraineurs identified three additional candidate migraine loci pointing to *PRDM6*, *LPR1*, and *TRPM8* as potential migraine genes. Additional GWAS are underway, and the number of migraine genes will quickly expand. As a GWAS is designed to detect only gene variants that are common (>5%), it will leave rarer gene variants undetected. Such rare variants are expected to have a larger effect size and may shed further light on migraine pathophysiology. The technology to detect them, i.e., next-generation sequencing (NGS), has been developed, but successes with NGS thus far come from rare monogenic recessive disorders. So far, none have been reported for migraine.

Findings from Other Headache Types

Genetic discoveries in other headache types are still in their infancy. At first, cluster headache (CH) was considered a sporadic disorder, but since the 1990s, a familial occurrence has been recognized. Family studies have revealed that there is a 14-fold increased risk for CH in first-degree family members of CH patients, and a twofold increased risk in second-degree family members, which indicates a genetic component in CH. There is now also good evidence that genetic factors are involved in tension-type headache (TTH), particularly for the “frequent tension-type headache” phenotype. Only a few molecular genetic studies have been performed in nonmigraine headache types. In addition to several negative candidate gene association studies, a significant, replicated association was found with a hypocretin receptor 2 (*HCRTR2*) gene polymorphism and CH.

Conclusion

Genetics of primary headache syndromes, such as migraine and nonmigraine headaches such as cluster headache, have provided a better understanding of the molecular basis of these conditions. Most insight has come from the identification of gene mutations in FHM patients with mutations in calcium and sodium channel subunits, as well as a sodium-potassium ATPase. Functional studies of these gene mutations in cellular and/or transgenic animal models point to an important role of disturbed neurotransmitter release—more specifically, increased excitatory glutamatergic neurotransmission in FHM. Support for the possibility that similar mechanisms may also cause common migraine types comes from recent GWAS findings that identified the *MTDH* gene, which (through downregulation of glutamate transporter EAAT2) may result in hyperexcitation in migraineurs. A more recent GWAS revealed the true potential of genetics studies, as genetic associations with *TRPM8*, *LRP1*, and *PRDM6* highlighted additional pathological mechanisms, including pain pathways already known in neuropathic pain. Similar exciting findings are expected from GWAS in other primary headache types in the coming years. GWAS technology only detects common variants with a low effect size, leaving rarer, higher-risk, variants undetected. However, due to further advances in genotyping technology, it has become feasible to detect these DNA variants with “next-generation sequencing” approaches. Integrating these novel technologies in genetic research of headache is expected to have a dramatic positive effect on gene discoveries. The real challenge will be to combine genetic and neurobiology research to functionally characterize the newly discovered headache gene variants to understand how they cause headache. Surely, in the coming decade we will unravel many molecular disease mechanisms in headache that will be a rich source of targets for drug discovery.

References

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