
Genetics of Migraine

Genetics of Migraine: An Update

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Observations including the long-recognized tendency of migraine to run in families, the high concordance rates for migraine in twins reared together or apart, and the association of specific mutations with a rare migraine form are consistent with a genetic contribution to the disorder. This paper summarizes major findings to date on the genetics of migraine. Study of the heritability of migraine, particularly the common forms of migraine, is beset by several challenges including the absence of easily measurable biological markers, uncertainty about the etiologic and clinical overlap among migraine types, and the apparently complex interplay of environmental and genetic factors in determining migraine phenotype. Nevertheless, significant progress has been realized in recent years. Familial hemiplegic migraine, a rare migraine variant, appears to be transmitted by a Mendelian, autosomal dominant mode of inheritance involving mutations in at least 2 genes. These genes do not seem to be critically involved in the other forms of migraine; however, several other susceptibility loci for more common forms of migraine have been identified in recent genome-wide screens and candidate-locus studies. These and other data suggest that the genetic contribution to migraine is complex, multifactorial, and subject to significant modification by environmental factors.

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Migraine, which affects approximately 20% of adults,¹ is among the most common of neurologic disorders. Observations including the long-recognized tendency of migraine to run in families, the high concordance rates for migraine in twins reared together or apart, and the association of specific mutations with the rare migraine form familial hemiplegic migraine are consistent with a genetic contribution to the disorder.²⁻⁴ These and other data also suggest that the genetic contribution to migraine is complex, multifactorial, and subject to significant modification by environmental factors. This paper summarizes major findings to date on the genetics of migraine including both

familial hemiplegic migraine and more common migraine variants.

FAMILIAL HEMIPLEGIC MIGRAINE

Familial hemiplegic migraine is a rare type of migraine with aura. It appears to be transmitted by an autosomal dominant mode of inheritance and has been important in constituting a Mendelian model for migraine research.² Familial hemiplegic migraine has been linked to mutations in the calcium channel gene *CACNA1A* on chromosome 19 and the sodium/potassium pump gene *ATP1A2* on chromosome 1.⁴ Mutations in *CACNA1A* alter calcium channel dynamics, an effect that potentially could explain the altered brain excitability in individuals with migraine. Assessment of physiology and behavior of animals having mutations analogous to those in humans with familial hemiplegic migraine have helped to advance knowledge into the mechanisms of migraine. For example, the potential phenotypic importance of

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the mutation in *CACNA1A* is illustrated by the finding that the tottering mouse strain, an animal model of migraine, has a mutation in the mouse ortholog of *CACNA1A* and is resistant to the induction of cortical spreading depression.^{5,6} Cortical spreading depression, characterized by an initial spike in cortical electrical activity followed by spreading depression of electrical activity, is a hypothesized physiologic trigger of migraine. The calcium channel encoded by *CACNA1A* and the sodium/potassium pump encoded by *ATPIA2* likely modulate electrical potentials determining the threshold of neuronal firing and thus influence susceptibility to cortical spreading depression.⁴

Additional mutations linked to familial hemiplegic migraine have been identified. That mutant gene products of *CACNA1A* and *ATPIA2* can affect glutamatergic neurotransmission suggests a possible role of glutamate in familial hemiplegic migraine. In a recent investigation, a mutation in the gene *SLC1A3*, which encodes the glutamate transporter excitatory amino acid transporter (EAT)1 that removes glutamate from the synaptic cleft, was identified in patients with episodic ataxia and hemiplegic migraine but no mutation in either *CACNA1A* or *ATPIA2*.⁷ This mutation was associated with substantially reduced capacity for glutamate uptake. In another study of familial hemiplegic migraine in individuals without mutations in either *CACNA1A* or *ATPIA2*, a mutation in the neuronal voltage-gated sodium channel gene *SCN1A*, which has also been associated with epilepsy, was identified.⁸ The authors suggested that the finding substantiates the molecular links between epilepsy and migraine.

The clinical manifestations of familial hemiplegic migraine and more common types of migraine with and without aura are similar but do not wholly overlap. Attacks of familial hemiplegic migraine resemble attacks of migraine with aura but are also characterized by motor symptoms including unilateral weakness or paralysis. In addition, impaired consciousness (eg, confusion), fever, and seizures can occur with attacks of familial hemiplegic migraine. The degree to which familial hemiplegic migraine and more common migraine types are etiologically and genetically similar remains to be elucidated. Possibly, familial hemiplegic

migraine constitutes the most severe phenotype of the spectrum of migraine disorders.² In that case, familial hemiplegic migraine and more common migraine types should share some pathogenic mechanisms, and advances in understanding of the molecular genetics of familial hemiplegic migraine should be useful for understanding more common migraine types.

COMMON TYPES OF MIGRAINE

Inheritance of migraine has been investigated from an epidemiologic perspective in both family studies and twin studies and from a molecular genetic perspective with genome-wide screens and candidate locus testing.

Family Studies.— Family studies assess the genetic contribution to migraine by evaluating the relative risk, defined in these studies as the prevalence of migraine in first- or second-degree family members of an index case (proband) with that in the general population. As first- or second-degree family members are genetically more similar to the index migraine case than the general population, the prevalence of migraine among these family members should be higher than that in the general population in the event of a genetic contribution to migraine. Results of family studies have been mixed regarding the genetic contribution to the more common migraine types.⁹⁻¹⁴ In most of these studies, a higher frequency of migraine was observed among first-degree relatives of index migraine cases than among control groups, although the frequencies ranged widely across studies. Across studies, the relative risk for migraine in family members of migraine probands ranges from approximately 1.4 in migraine without aura to approximately 4.0 in migraine with aura. While migraine was often more frequent among first-degree relatives than controls, other research shows no significant differences in the frequency of migraine between first-degree relatives of probands with migraine and control groups.¹³

Early family studies generally employed varying methods and migraine case definitions. Furthermore, many are characterized by limitations including failure to use migraine diagnostic criteria, selection of index cases from groups that might be nonrepresentative, and assessment of migraine occurrence through questionnaires or through family histories obtained from

the index case—both of which are subject to bias.¹² These shortcomings may account for the wide variation among studies, particularly earlier ones, in frequency of familial cases of migraine.

Several of the limitations of earlier studies were overcome in a general population-based study undertaken in Copenhagen county, Denmark.¹⁴ Occurrence of migraine with or without aura was assessed among first-degree relatives ($n = 1109$) and spouses ($n = 229$) of probands with migraine with or without aura ($n = 378$) and probands who had never had migraine. The presence of migraine in relatives and spouses was determined through interview by a blinded neurology resident who used International Headache Society criteria for classifying migraine cases. The results show that

- First-degree relatives of probands with migraine without aura had 1.9 times higher risk of migraine without aura and 1.4 times higher risk of migraine with aura than the general population.
- First-degree relatives of probands having migraine with aura had almost 4 times greater risk of migraine with aura but no greater risk of migraine without aura than the general population (Table 1).
- First-degree relatives of probands having migraine without aura had 1.4 times greater risk of migraine without aura and no greater risk of migraine with aura than the general population (Table 1).
- Spouses of probands having migraine without aura had 1.4 times the risk of migraine without aura, but spouses of probands with migraine with aura had no increased risk of migraine with aura.
- First-degree relatives of probands who never had migraine had no increased risk of migraine with or without aura.

The authors concluded that this pattern of results suggests differing etiologies of migraine with aura, which appears to have a large genetic determinant, and migraine without aura, which appears to be determined both by genetic and environmental factors.¹⁴

Familial data have been used to undertake segregation analysis, a method of investigating the mode of

inheritance of specific phenotypes. Segregation analysis tests deviation of the calculated ratio of the proportion of offspring with a phenotype (in this instance, migraine) from the Mendelian segregation ratio, which assumes that 2 alleles at a single locus account for a phenotype. Deviation from Mendelian segregation can occur when more than 1 locus accounts for the phenotype, when both genetic and environmental factors contribute to the phenotype, or in the event of incomplete penetrance. In a segregation analysis of 126 probands of migraine without aura and 127 probands of migraine with aura from the general Danish population, both types of migraine were determined to have multifactorial inheritance without generational difference.¹⁵

Twin Studies.— Twin studies have also helped to elucidate the hereditary contribution to migraine.^{2,16-22} Twin studies compare concordance rates (ie, the probability that both twins have a specific phenotype) between monozygotic twins, whose genetic make-up is identical, and dizygotic twins, whose genetic make-up is not identical but is comparable to that of siblings. If migraine is inherited, then the concordance rate for migraine in monozygotic twins should exceed that in dizygotic twins. While some of the twin studies in migraine share the methodological limitations of the family studies described above, they are consistent in showing higher concordance rates for migraine among monozygotic twins than among dizygotic twins.^{2,16-23} Heritability estimates (ie, the proportion of phenotypic variance explained by variations in genotype) ranged from 28% to 65% across studies. In the GenomEUtwin project, which combines twin registers and cohorts from several European countries and Australia to yield 29,717 twin pairs, heritability ranged from 34% to 57%.²³ Higher concordance rates for migraine between monozygotic twins than between dizygotic twins were found even among twins raised apart,^{24,25} a finding that supports the importance of genetics over environmental factors in the high concordance rates for migraine in monozygotic twins. Together, the results of twin studies suggest approximately 50% heritability of migraine with multifactorial, polygenic inheritance.

Genome-Wide Screens.— Unlike familial hemiplegic migraine, which has been associated with

Table 1.—Sex- and Age-Standardized Risk of Migraine With and Without Aura Among First-Degree Relatives of Various Probands¹⁴

Disease in Proband	Disease in First-Degree Relative	Observed	Expected	Relative Risk (Estimated 95% Confidence Interval)
Migraine without aura	Migraine without aura	102	54.84	1.86 (1.56 to 2.16)
	Migraine with aura	42	29.17	1.44 (1.03 to 1.85)
Migraine with aura	Migraine without aura	56	55.10	1.02 (0.77 to 1.26)
	Migraine with aura	111	29.26	3.79 (3.21 to 4.38)
Co-occurrence of migraine with and without aura	Migraine without aura	16	9.77	1.64 (0.94 to 2.33)
	Migraine with aura	11	5.07	2.17 (0.98 to 3.36)
Never had migraine	Migraine without aura	58	52.41	1.11 (0.83 to 1.39)
	Migraine with aura	18	27.73	0.65 (0.36 to 0.94)

mutations in the *CACNA1A* and *ATP1A2* genes, common types of migraine have not to date been linked to a mutation in a specific gene. Nevertheless, several susceptibility loci have been identified in gene-mapping studies (Table 2).²⁶⁻³⁰ Autosomal loci have been identified at regions including Chr4q24 for migraine with aura among 50 Finnish families, 6p12.2 to 6p21.1 for migraine with and without aura in a Swedish family, 11q24 for migraine with aura in 43 Canadian families, and 14q21.2 to 14q22.3 for migraine without aura in an Italian family. The loci involved in familial hemiplegic migraine have not figured as prominent contributors to common forms of migraine in genome-wide screens, a result that might be attributed to the greater complexity and genetic heterogeneity of common forms of migraine.⁴

Data from genome-wide screens in samples with common forms of migraine are inconsistent such that specific linkages demonstrated in 1 sample often are not replicated in other samples. The inconsistency among studies may reflect the contribution of multiple

loci and the interaction of genetic and environmental determinants affecting the correspondence between genotype and phenotype. The findings also are consistent with the possibility that migraine is a genetically heterogeneous disorder that may be determined by different genes in different families. The finding in genome-wide screens that, in some families, the same major effect locus mutation can be associated with phenotypic variability in migraine is consonant with an interaction of environmental and genetic contributors to migraine.

Candidate Locus Testing.— Several small case-control gene-association studies have been conducted to assess polymorphisms in candidate loci for migraine. In these studies, target loci or genes are selected for assessment based on hypotheses about the pathophysiology of migraine. Like findings with the genome-wide screens, results of candidate-locus studies have been inconsistent and difficult to replicate.^{2,4} The inconsistency may reflect the possibility that, in migraine, a genetically complex disease, disease

Table 2.—Summary of Results of Genome-Wide Screens on Migraine Families²⁶⁻³⁰

Reference Number	Migraine Subtype	Population	Number of Families	Identified Locus
30	Migraine without aura	Icelandic	103	4q21
26	Migraine with aura	Finnish	50	4q24
27	Migraine with and without aura	Swedish	1	6p12.2-p21.1
29	Migraine with aura	Canadian	43	11q24
28	Migraine without aura	Italian	1	14q21.2-q22.3

susceptibility could be conferred through minor, additive protein changes that become clinically manifest only under particular environmental circumstances.

As recently reviewed elsewhere,⁴ genes with polymorphisms thought to be associated with migraine include dopamine type 2 receptor (a result not consistently replicated), glutathione-S-transferase, dopamine type 4 receptor, tumor necrosis factor- β /lymphotoxin- α , serotonin transporter, the C677T methyl-tetrahydrofolate reductase allele, the dopamine- β -hydroxylase gene, and the angiotensin-converting enzyme allele. Polymorphisms found not to be associated with migraine include interleukin-6, dopamine receptor types 1, 3, and 5, apolipoprotein E, 5HT_{1B} receptor, inducible nitric oxide synthase, cytochrome P450/2D6, glutathione S-transferase M1, 5HT_{2A} receptor, 5HT_{2B} receptor, and a nitric oxide synthase polymorphism.

Results of candidate-locus studies of involvement of the *CACNA1A* region in common forms of migraine are inconsistent. Whereas some studies report linkage to the familial hemiplegic migraine locus on Chr19p13,³¹⁻³³ other studies find no linkage or association.³⁴⁻³⁶ Furthermore, no mutations in the *CACNA1A* gene have been demonstrated in patients with common types of migraine.²

In a recent, large, case-control study, the insulin receptor gene *INSR*, which lies in a Chr19p13 region near *CACNA1A*, was identified as a susceptibility gene for migraine.³⁷ Five single-nucleotide polymorphisms within the insulin receptor gene were significantly associated with migraine. However, no functional consequences of these polymorphisms were identified: the insulin resistance protein made from DNA containing these single-nucleotide polymorphisms appeared to function normally.

CONCLUSIONS

Study of the genetics of migraine, particularly the common forms of migraine, is beset by several challenges including the absence of easily measurable biological markers of migraine, uncertainty about the etiologic and clinical overlap among migraine types, and the apparently complex interplay of environmental and genetic factors in determining migraine phenotype. Nevertheless, significant progress in under-

standing the heritability of migraine has been realized in recent years. Familial hemiplegic migraine, a rare migraine variant, appears to be transmitted by a Mendelian, autosomal dominant mode of inheritance involving mutations in at least 2 genes. These genes do not seem to be critically involved in the other forms of migraine; however, several other susceptibility loci for more common forms of migraine have been identified in recent genome-wide screens and candidate-locus studies.

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