

VIII

Genetics

Are there genetic factors associated with migraine?

Recommendation

Migraine occurs commonly among family members. The existence of genetic factors in migraine is almost certain from linkage analyses and twin studies. Multiple genes are speculated to be involved in the development of migraine. However, the definitive causative genes and susceptibility genes have not been identified.

Grade B

Background and Objective

Many studies have been conducted with the aim to identify the causative genes and susceptibility genes of migraine. Three causative genes have been identified for familial hemiplegic migraine, but the association of these genes with “normal” migraine has been ruled out. Many association analyses using the candidate gene approach have also been conducted, and some of the findings have been subjected to meta-analysis. In addition, linkage analyses and large-scale genome-wide association studies (GWAS) are ongoing, and multiple chromosomal loci and genes have been reported. However, the detailed pathophysiological mechanisms remain unclear.

Comments and Evidence

Although it has long been noted that migraine commonly occurs within the family, whether this phenomenon is based on genetic factors or environmental factors, or simply due to coincidence because of the high prevalence of migraine has been much debated.

More recently, pedigree analysis¹⁾ and twin analyses²⁾³⁾ suggested that migraine is a multi-factorial genetic disease likely to be associated with a combination of multiple genetic factors and environmental factors. It has been reported that both genetic and environmental factors are involved in migraine without aura, while genetic factors are more strongly associated with migraine with aura, but some reports showed no difference between migraine with and without aura.⁴⁾⁵⁾

Since the first report of a causative gene found in some families with familial hemiplegic migraine (FHM, a special type of migraine with aura),⁶⁾ several genes; *FHMI*, *FHM2* and *FHM3*, have so far been identified (for details, see Comments and Evidence of CQ VIII-4, page 239). All the genes are related to membrane channel function, suggesting a relationship between the excitability of neurons and pathophysiology of migraine.⁷⁾ These findings were the driving force that promoted the great advances in genetic research on migraine. However, association analyses have ruled out the association between the causative genes of FHM and “normal” migraine.⁸⁾

A pedigree analysis focusing on the K⁺ channel in patients with familial migraine other than FHM reported new finding of a significant relationship with mutation in *KCNK18*.⁹⁾

As for the migraine susceptibility genes, many investigations and verification studies using a candidate gene approach have been conducted, but most yielded inconsistent results. Some of the reports have been subjected to meta-analysis, and a significant relationship has been reported for multiple genes including *ACE*,¹⁰⁾ *MTHFR*,¹⁰⁾¹¹⁾ *ESR-1*¹²⁾ and *5-HTT*.¹³⁾

Linkage analyses have reported multiple chromosomal loci, but the exact genes have not been identified.

Genome-wide association study has revealed associations of *PRDM16*, *TRPM8* and *LRPI* with migraine,¹⁴⁾ but the contribution of individual genes was low, and the detailed pathophysiology mechanisms remain unclear.

• References

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• Search terms and secondary sources

- Search database: PubMed (2011/10/07)

Search was conducted using the same search terms as for Chronic Headache VIII-1 in the Clinical Practice Guidelines 1st edition, narrowed to after 2004 only.

migraine

& association 877

& genetics 897

& polymorphisms 213

& (genetic factor OR genetic factors) 287

& genetic influence 44

& familial occurrence 239

& inheritance 59

& twin 48

& segregation 6

& adoption 3

& linkage 108

Are there genetic factors associated with cluster headache?

Recommendation

Cluster headache occurs significantly more commonly among family members, and the involvement of genetic factors is highly probable. Due to the coexistence of environmental factors and the genetic heterogeneity, the causative genes and susceptibility genes for cluster headache have not been identified.

Grade B

Background and Objective

Family-based and twin studies have reported the involvement of genetic factors in cluster headache, but the mode of inheritance and other details remain unclear. Some reports have indicated the involvement of gene polymorphism, but analysis is difficult due to the clinical diversity and the low prevalence of cluster headache.

Comments and Evidence

Summarizing reports of genetic epidemiological surveys on cluster headache, first-degree relatives of patients with cluster headache are 5 to 18 times, and second-degree relatives are 1 to 3 times more likely to have cluster headache than the general population, suggesting that in addition to environmental factors, genetic predispositions are involved in the development of cluster headache.¹⁾

Many studies have investigated the causative genes and susceptible genes of cluster headache.

In relation to the pathophysiological hypothesis of cluster headache, research has focused on orexin (hypocretin), a physiologically active peptide closely associated with the hypothalamus. It has been shown that patients with cluster headache have a significantly higher frequency of GG genotype of 1246G>A polymorphism [rs2653349] in the hypocretin receptor 2 gene (*HCRTR2*: MIM ID 602393). A meta-analysis of two reports that confirmed such association²⁾ and one report that found no such association³⁾ verified an association between cluster headache and *HCRTR2*.⁴⁾

A genetic study also reported two-fold higher frequency of GG genotype of 925A>G polymorphism [rs1126671] in exon 7 of the alcohol dehydrogenase 4 gene (*ADH4*: MIM ID 103740) in patients with cluster headache.⁵⁾

In relation to treatment, carriers of CT genotype of 825C>T polymorphism [rs5443] in the guanine nucleotide-binding protein $\beta 3$ gene (*GNB3*: MIM ID 139130) was three times more responsive to triptan compared to carriers of CC genotype.⁶⁾

Further clinical genetic data have to be accumulated to determine whether these genes are the causative genes or susceptibility genes of cluster headache. One genome-wide association study of cluster headache was conducted, and found no significant genes associated with cluster headache.³⁾

References

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Search terms and secondary sources

- Search database: PubMed (2011/10/11)

Search was conducted using the same search terms as for Chronic Headache VIII-2 in the Clinical Practice Guidelines 1st edition, narrowed to after 2004 only.

cluster headache

& association 73
& genetics 60
& polymorphisms 14
& (genetic factor OR genetic factors) 21
& genetic influence 4
& familial occurrence 24
& inheritance 4
& twin 9
& segregation 0
& adoption 0
& linkage 7

Are there genetic factors associated with tension-type headache?

Recommendation

Environmental factors are considered to be strongly associated with the development of tension-type headache. However, the presence of genetic factors in some subtypes is possible.

Grade C

Background and Objective

There is less research on the genetic factors for tension-type headache compared to migraine and cluster headache. Reports are limited to some twin studies. Although environmental factors are mainly involved in the development of tension-type headache, the involvement of genetic predisposition has been reported for frequent episodic tension-type headache.

Comments and Evidence

A study using the New Danish Twin Register of 5,360 twins found no significant difference in concordance of tension-type headache in both monozygotic and dizygotic twin pairs.¹⁾ The report concluded that genetic factor, if it exists, has minor effect.

In a subsequent study using the same Register, of 11,199 twin pairs with tension-type headache and no migraine, the concordance rate of frequent episodic tension-type headache was higher in monozygotic than in dizygotic twin pairs.²⁾ The concordance rate of infrequent episodic tension-type headache was significantly higher in monozygotic than in dizygotic twin pairs in women only, and the difference was small in men. The report concluded that genetic factors play a role in frequent episodic tension-type headache, while infrequent episodic tension-type headache is caused primarily by environmental factors, and that no firm conclusion could be drawn for chronic tension-type headache.

Further accumulation of clinical genetic data for different regions and various races is required to elucidate whether genetic element is involved in tension-type headache.

• References

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• Search terms and secondary sources

- Search database: PubMed (2011/10/11)

Search was conducted using the same search terms as for Chronic Headache VIII-3 in the Clinical Practice Guidelines 1st edition, narrowed to after 2004 only.

tension-type headache

& association 102

& genetics 30

& polymorphisms 11

& (genetic factor OR genetic factors) 27

& genetic influence 2

& familial occurrence 42

& inheritance 1

& twin 9

& segregation 0

& adoption 1

& linkage 2

Does familial (hereditary) migraine caused by single gene mutations exist?

Recommendation

Familial hemiplegic migraine type 1, type 2 and type 3 have been reported to be familial migraine caused by single gene mutations. In addition, single gene disorders that may coexist with migraine include cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), retinal vasculopathy with cerebral leukodystrophy (RVCL), hereditary hemorrhagic telangiectasia type 1 (HHT1), mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), and myoclonus epilepsy associated with ragged-red fibers (MERRF).

Grade A

Background and Objective

Genetic diseases causing migraine due to single gene mutations exist, and the causative genes have been identified in recent years.

Comments and Evidence

1. Familial migraine caused by single gene mutations

(1) Familial hemiplegic migraine type 1 (FHM1; MIM ID 141500)

The causative gene of FHM1, *CACNA1A*, is located on chromosome 19p13 and encodes $Ca_v2.1$, the $\alpha 1$ subunit of P/Q type voltage-gated calcium channel.¹⁾ *CACNA1A* is also known to be the causative gene of spinocerebellar ataxia type 6 (SCA6), episodic ataxia type 2 (EA2) and progressive cerebellar ataxia (PCA). FHM1 is complicated with diverse symptoms including disturbance of consciousness, fever, and cerebella ataxia. Among the mutations, the frequency of p.T666M point mutation (substituting methionine for threonine at codon 666) is high.

(2) Familial hemiplegic migraine type 2 (FHM2; MIM ID 602481)

The causative gene of FHM, *ATP1A2*, is located on chromosome 1q21-23 and encodes the $\alpha 2$ subunit of ATP-dependent Na,K-ATPase.²⁾ Unlike FHM1, most of the FHM2 patients manifest a clinical picture of pure hemiplegic migraine, although some cases are complicated with cerebellar ataxia, epilepsy and mental retardation.

(3) Familial hemiplegic migraine type 3 (FHM3; MIM ID 609634)

The causative gene of FHM3, *SCN1A*, is located on chromosome 2q24 and encodes $Na_v1.1$, the $\alpha 1$ subunit of voltage-gated sodium channel.³⁾ *SCN1A* is also known to be the causative gene of generalized epilepsy febrile seizures plus (GEFS+) or Dravet syndrome. Apart from pure familial hemiplegic migraine, cases of FHM3 are complicated with epilepsy and elicited repetitive transient daily blindness (ERDB) have been reported.

2. Genetic diseases with concurrent migraine

(1) Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL; MIM ID 125310)

The causative gene of CADASIL is *NOTCH3* located on chromosome 19p13.⁴⁾ Twenty to 30% of CADASIL patients manifest migraine with aura concurrently. With onset at 30 to 50 years of age, CADASIL is characterized by recurrent subcortical infarction and transient ischemic attack, as well as diverse symptoms including impaired cognitive function, psychiatric symptoms, and pseudobulbar palsy. CADASIL is an autosomal dominant disease. On brain MRI, characteristic hyperintense signals in external capsule and temporal pole white matter on T2-weighted and FLAIR images are observed.

(2) Retinal vasculopathy with cerebral leukodystrophy (RVCL, MIM ID 192315)

The causative gene of RVCL is *TREX1*, located on chromosome 19p13.⁵⁾ RVCL is an autosomal dominant disorder. With

onset symptoms of retinal vasculopathy and progressive visual disturbance at 30 to 40 years of age, migraine is added to the clinical picture together with diverse neurological symptoms including cognitive decline due to multiple infarcts in cerebral cortex, convulsion, spastic paralysis and dysarthria, as well as systemic symptoms including Raynaud symptom, renal disease and cirrhosis. On brain MRI, multiple contrast-enhancing lesions in cerebral subcortical white matter and surrounding edema are observed.

(3) Hereditary hemorrhagic telangiectasia (HHT)

So far four genetic loci (HHT1 to 4) have been reported, and the causative genes for HHT1 and HHT2 have been identified. Approximately 40% of patients with HHT1 manifest migraine concurrently. The causative gene of HHT1 (MIM ID 187300) is *ENG*, located on chromosome 9q34.⁶ HHT1 is an autosomal dominant disease previously known as Osler-Rendu-Weber disease. The disorder is characterized by arteriovenous malformations in the lung, brain, liver and spinal cord, as well as multiple telangiectases and hemorrhages in the skin, mucous and internal organs.

(4) Mitochondrial disorder

Migraine has been reported to occur concurrently with subtypes of mitochondrial disorder: MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes) characterized by episodic vomiting, headache, convulsion and stroke-like symptoms, and MERRF (myoclonic epilepsy associated with ragged-red fibers) with myoclonus, cerebellar ataxia and myopathy as main symptoms. Eighty percent of MELAS cases are caused by A3243G mutation of *MTTL1* that encodes mitochondrial tRNA-leucine.⁷ Mutations of *ND5* that encodes the subunit 5 of electron transport complex 1 are also known. On the other hand, the major causative mutation in MERRF is A8344G mutation of *MTTK* that encodes mitochondrial tRNA-lysine.

3. Other genes associated with familial migraine

Using candidate gene approach or pedigree analysis, mutations in various other genes such as *EAAT1*,⁸ *SLC4A4*,⁹ and *KCNK18*¹⁰ have been reported in pedigrees with familial migraine. To determine whether these genes are causative genes of migraine, further accumulation of clinical genetic data is necessary.

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- **Search terms and secondary sources**

- Search database: PubMed (2011/12/21)
 - Migraine & CACNA1A 253
 - Migraine & ATP1A2 115
 - Migraine & SCN1A 41
 - Migraine & Notch 3104
 - TREX 168
 - Migraine & HHT 10
 - Migraine & MELAS 70
 - Migraine & MERRF 7
 - Migraine & genome-wide association study 29

Is genetic diagnosis for migraine possible?

Recommendation

Genetic diagnosis of familial hemiplegic migraine may be possible by analyzing *CACNA1A*, *ATP1A2* and *SCN1A*. While it is rare to find causative mutations in sporadic hemiplegic migraine patients, genetic diagnosis is possible in some young-onset cases. Although migraine susceptibility genes have been identified by genome-wide association study, the contribution of individual gene is low and not useful for genetic diagnosis.

Grade B

Background and Objective

With advances made in the identification of causative genes for familial hemiplegic migraine, genetic diagnosis of this disorder has become possible. For common migraine also, susceptibility genes are gradually being identified.

Comments and Evidence

In general, for conducting genetic diagnosis, detailed explanations and various supports such as genetic counseling have to be provided to the subjects, according to the guideline for genetic diagnosis of neurological diseases (2009). In addition, since the causative genes of hemiplegic migraine; *CACNA1A*, *ATP1A2* and *SCN1A*^(1,2) are relatively large genes, it is inefficient to conduct genetic diagnosis on all the cases. Careful consideration of the indication for genetic diagnosis is recommended, by reviewing genetic epidemiological and clinical information including frequency of disease, age of onset and associated symptoms.

Among the causative genes for hemiplegic migraine, the mutation frequencies of *CACNA1A* and *ATP1A2* are high, and that of *SCN1A* is low. Therefore, in conducting genetic diagnosis, analyzing *CACNA1A* and *ATP1A2* first, and then proceeding to *SCN1A* is recommended.

In a large-scale epidemiological survey of the whole Danish population of 5.2 million people, a total of 44 families with familial hemiplegic migraine (FHM) were identified.⁽³⁾ When mutation analyses of all exons of *CACNA1A* and *ATP1A2* as well as p.Q1489K mutation of *SCN1A* were conducted in 43 families, 14% of the families were positive for these mutations. The mutation frequencies for *CACNA1A* and *ATP1A2* were similar, and no *SCN1A* mutation was detected. In the same population, 105 individuals with sporadic hemiplegic migraine were identified.⁽⁴⁾ Mutation analysis was conducted in 100 individuals, and causative gene mutations were found in only 2 individuals.

Therefore, FHM is a genetically heterogeneous disease, and so far genetic diagnosis has not identified mutations in the majority of the affected families. This point has to be explained when obtaining informed consent for genetic diagnosis.

Causative mutations identified in FHM are rarely detected in patients with SHM. However, when analysis was conducted in early-onset SHM only, *de novo* mutation was identified in 19 of 25 (76%) SHM patients aged 16 years or younger.⁽⁵⁾ Therefore genetic diagnosis has clinical significance in early-onset SHM. However, whether amino acid substitutions identified in SHM represent true causative mutations has to be examined carefully.

No large-scale genetic epidemiological study on hemiplegic migraine has been conducted in Japan, and the frequency of mutation in Japanese remains unknown. As of November 2011, reports of mutations in hemiplegic migraine among Japanese included two families with p.T666M mutation in *CACNA1A*, one family with p.S218L mutation in *CACNA1A*, and one family with p.H916L mutation in *ATP1A2*.

Regarding the involvement of FHM-related causative mutations in common migraine, linkage analysis, association study and direct sequencing analysis yielded negative results.⁽⁶⁾ Therefore analysis of FHM-related genes in common migraine has no relevance. As for migraine susceptibility genes, candidate gene approach suggested an association with *MTHFR*⁽⁷⁾ and *5-HTT*.⁽⁸⁾ Genome-wide association study reported an association with *TRPM8* and *LRPI*.⁽⁹⁾ However, the odds ratios were 1.3 to 1.5 at the highest, not sufficiently accounting for the heritability of migraine. Therefore, at this time, they are not useful for genetic diagnosis.

• References

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• Search terms and secondary sources

- Search database: PubMed (2011/12/21)
 - hemiplegic migraine AND epidemiology 38
 - (hemiplegic migraine) AND Japanese 24
 - familial hemiplegic migraine AND sporadic 77
 - (common migraine) AND (CACNA1A OR ATP1A2 OR SCN1A) 206
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