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Current Issues in Migraine Genetics

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Migraine often runs in families and is associated with both genetic and environmental factors. Clinical and genetic heterogeneity as well as the influence of environmental factors have hampered the identification of the gene responsible for migraine disorder. Family /twin studies suggest the presence of hereditary susceptibility. Several different types of mutations or association studies with genetic polymorphism in neurotransmitters, inflammatory cytokines, homocysteine metabolism, mitochondria, or other risk genes in cerebrovascular disorders have been reported. Recently, progress of molecular genetics in familial hemiplegic migraine has provided important insights, a channelopathy, and now extending to a growing list of membrane excitability disorders. Further identification of candidate genes for migraine and exploring the correlation between phenotype and genotype are expected in the future for the understanding of migraine pathophysiology.
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INTRODUCTION

Migraine is a common neurological disorder disabling about 10~20% of general population. According to a population based epidemiological study of migraine in Korea, 20.2% of males and 24.3% of females were reported to have migraine or probable migraine.[1] It is well known that migraine runs in families and is related to both genetic and environmental factors. There have been several attempts to disclose the genetic factors in the pathophysiology of migraine. However, no clear diagnostic marker or objective method to assess the status of the migraineurs has been established. In the studies about migraine, variable clinical manifestations and penetrance have posed major difficulties.[2]

To overcome this problem, many studies have used the international headache society (IHS) classification in selecting patients. The IHS classification distinguishes different types of migraine, migraine with aura (MA), without aura (MO), etc. Some patients have attacks of only one type while one third of patients experience both types of attacks during their life. Therefore, classification of individuals simply as affected or unaffected is difficult. Due to clinical heterogeneity of migraine, controversies still remain among the several studies using different methodologies, for example, including or excluding criteria, or grouping migraineurs into MA vs. MO without consideration of probable migraine or accompanying secondary headache.

While migraine seems to be a polygenic multi-factorial disorder in most cases, there is an exception. Familial hemiplegic migraine (FHM) is a rare type of

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Table 1. Spectrums of migraine genetics and reported data during recent decades

Epidemiological study	
Familial risk pattern	MA>MO
Twin study	monozygote>dizygote
Segregation analysis	mode of inheritance:non-mendemian multifactorial
Molecular study	
Genome wide screen on migraine families	4q21,4q24,6p12.2-p21.1,11q24,14q21.2-q22.3
Association analysis with polymorphisms of alleged genes	D2,D4 receptors, dopamine β hydroxylase, angiotensin converting enzyme, serotonin transporter, serotonin receptor, endothelin type A receptor, insulin receptor, tumor necrosis factor, MTHFR gene
Linkage analysis on candidate region	1q31,X124-28, X22
SNP investigation	exon 8 of CACNA1A gene and epilepsy
Genetics of FHM	mutations on 9p13, 1q23
Linkage analysis between FHM and SHM/or other migraines	new locus on 19p13 distinct from CACNA1A
Association with hereditary diseases with known genetic abnormalities	CADASIL, MELAS, CVS

CADASIL; cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, MELAS; mitochondrial encephalopathy with lactic acidosis and stroke-like episode, CVS; cyclic vomiting syndrome, MA; migraine with aura, MO; migraine without aura, MTHFR; methylene-tetrahydrofolate reductase, SNP; single nucleotide polymorphism, FHM; familial hemiplegic migraine, SHM; sporadic hemiplegic migraine

migraine with aura which is the only form with established Mendelian inheritance. The progress in molecular findings in FHM has provided important insights, the concept of channelopathy, and the basic pathogenic mechanisms of migraine disorders. Thus it provoked further studies searching for possible genetic factors in migraine. Here the recent studies regarding the genetics in migraine will be reviewed (Table 1).

EPIDEMIOLOGICAL STUDY

The first step to genetics in migraine is to show the genetic influences in this disorder by means of epidemiological survey.

Familial risk patterns

A population-based epidemiological study showed that MO and MA are distinct disorders.[3] In that study, the relative risk of MO and MA among first-degree relatives was estimated. Compared with the general population, first-degree relatives of probands with MO had a 1.9 fold increased risk of MO and 1.4 fold increased risk of MA. Whereas first degree relatives of probands with MA had a 3.8 fold increased risk of MA but no increased risk of MO.

Population-based twin studies

In a population-based twin study, the concordance rates of diagnosis of MA or MO by two physicians were estimated. The pair-wise concordance rate was significantly higher in monozygotic twins than in dizygotic twins.[4,5] The result indicates that a genetic factor is a major contributor to the pathogenesis of both MO and MA. Several epidemiological studies, in spite of different methods in classifying migraine and demographical factors, have shown similar results.[6,7] To overcome the limitation of small sample sizes, the GenomEUtwin consortium was founded combining twin registers and twin cohorts from seven European countries and Australia. This project will provide powerful information about standardized phenotypic data from nearly 30,000 twin pairs for migraine studies.[8]

Population-based segregation analysis

A population-based segregation analysis was done to show the mode of inheritance of migraine. According to the report, MA and MO have a non-mendelian multifactorial inheritance.[9]

POSSIBLE GENETIC LOCI

Because migraine is a common disorder showing complex genetic traits and the influence of environmental factors, it is difficult to discover genetically susceptible loci.

Genome-wide screens on migraine families

There have been several genome-wide screens so far to randomly search for genetically susceptible loci in common forms of migraine. A well-defined diagnosis of MA, MO or other types of headache is important because genetic susceptibility among each subtypes may be different. As shown in epidemiological studies, MA may have a stronger genetic component than MO or other types of headache. Identified foci included: 4q21 in MO Icelandic, 4q24 in MA Finnish, 6p12.2-p21.1 MA and MO in Swedish, 11q24 in MA Canadian and 14q21.2-q22.3 in MO Italian.[10-13] However the genome-wide studies in migraine have not yet reached reliable data. It may be due to the variability of disease definition and study population among these studies.

Association studies with genetic polymorphism

Several association studies have used one or two polymorphic sites per candidate gene. Case-control studies compared the frequency of alleles of a polymorphic genetic marker between patients and healthy controls. In most studies, the prevalence of gene polymorphisms is higher in migraineurs than in controls. The candidate genes known to have a significant association with migraine included: Dopamine D2, D4 receptors,[14,15] dopamine β hydroxylase,[16] angiotensin converting enzyme,[17] serotonin transporter,[18] serotonin receptor,[19] the endothelin type A receptor,[20] the insulin receptor,[21] tumor necrosis factor-α,[22] and methylene-tetrahydrofolate reductase (MTHFR) gene.[23,24] An association study conducted in Korea suggested that both elevated homocysteine level and the homozygous C677T mutation in the MTHFR gene were associated with MA (adjusted odds ratio: 4.70, 95% CI 1.44~15.29, $p<0.01$).[25] Although not specific to migraine, some polymorphisms may increase susceptibility to migraine attack and induce endophenotypic vulnerability markers.[26] However, the role of these polymorphisms remains to be determined and most of these results need confirmatory replication studies with a larger number of patients.

Candidate region linkage studies on common types of migraine

Some candidate region linkage studies showed that loci 1q31, X124-28, X22 have been linked to MA or MO.[27,28,29]

Single nucleotide polymorphisms in CACNA1A and epilepsy

A single nucleotide polymorphism in exon 8 of the CACNA1A gene was investigated. There is one report that by logistic regression, two SNPs in the immediate vicinity of exon 8 are responsible for the association with epilepsy.[30]

THE GENES RESPONSIBLE FOR FAMILIAL HEMIPLEGIC MIGRAINE

Chromosome 19p13

In 50~70% of FHM families, mutations in the CACNA1A gene located at chromosome 19p13 have been identified. More than 15 different mutations have been discovered so far.[31,32] CACNA1A gene encodes the pore-forming α1 subunit of Cav2.1 (P/Q-type Ca^{2+}) channels, which are expressed in the cell bodies, dendrites and presynaptic terminals of most of the central neurons, most prominent in the cerebellar

Purkinje cells.[32] CACNA1A mutations are related to two other neurologic diseases such as episodic ataxia type 2 and spinocerebellar ataxia type 6. Moreover, all FHM type 1 families with cerebellar signs have shown linkage to chromosome 19. These results suggest that progressive cerebellar ataxia may be a symptom exclusively related to type 1, not to other type of FHM.[32]

Voltage-gated Ca^{2+} channels control important neuronal functions including excitability, neurotransmitter release, activity-dependent gene expression, neuronal survival, differentiation and plasticity.[31] The metabolic and biochemical changes of this calcium channel dysfunction may depress neuronal excitability of noradrenergic system in locus ceruleus, periaqueductal grey and raphe nucleus which are associated with nociceptional modulation of trigeminal nucleus.[31] A recent study with CACNA1A knock out mice showed the increase in Ca^{2+} influx through a single channel and decrease in maximal Cav2.1 current density in neurons.[33] However, the overall effect of the mutation has not been established.

Chromosome 1q23

The ATP1A2 is another responsible gene for FHM. The mutations were found to co-segregate with the FHM in three French families. The ATP1A2 gene on the chromosome 1q23 encodes the alpha subunit of the Na+/K+ ATPase pump and its mutations are associated with FHM type 2.[34,35,36] However there are FHM families that are not linked either to 19p13 or 1q23. At least a third locus may be present.

NONFAMILIAL HEMIPLEGIC MIGRAINE: SPORADIC CASES

Sporadic hemiplegic migraine (SHM) is a heterogenous disease. More than half of the SHM patients also had non-hemiplegic attacks of migraine with aura and one third had additional attacks of migraine without aura.37 Families of SHM patients had an increased risk of migraine both with and without aura. The clinical symptoms of SHM are more similar to FHM than MA.[38]

THE ASSOCIATION BETWEEN THE FHM AND MA / OR MO

Some of the patients with FHM also experience either MA or MO. It can be hypothesized that FHM is an extreme of MA.[32] Linkage analysis for MA with FHM/or SHM showed a new locus on 19q13 distinct from CACNA1A.[39] According to the epidemiological data, there is still controversy in the risk of developing specific migraine phenotype in specific migraine families. Thus, the link between mendelian FHM and MA/or MO remains to be consolidated.[32]

HEREDITARY DISEASES ASSOCIATED WITH MIGRAINE

CADASIL

MA occurs in many patients with CADASIL. However, it is not clear whether migraine attacks are directly related to the genetic abnormality in CADASIL (Notch 3 gene mutation). MA may be a secondary phenomenon due to underlying vascular changes. A mutation in the Notch 3 gene was recently found in an Italian family affected by migraine with prolonged aura but without other neurologic deficits.[40]

Mitochondrial disease

MELAS is a well-known mitochondrial disease with migrainous headache. The association between migraine and mitochondrial gene is inferred by another example of cyclic vomiting syndrome (CVS), which is thought to be mitochondrial in its origin. There is a survey of 62 children with severe CVS showing migraine, myopathy, seizures and dysautonomia-like symptoms. The report stated that it was far more common in matrilineal versus non-matrilineal relatives. Therefore, it was suggested that mitochondrial DNA sequence variants may be risk factors for a severe end of the CVS.[41,42]

CONCLUSION

During the past decades, epidemiological and molecular studies have brought us to new insights in understanding migraine. First, migraine is a complex disorder associated with certain genetic backgrounds interrelated with multiple environmental factors. Second, the genetic heterogeneity is confirmed by many molecular studies using linkage analysis with alleged genes or genome-wide screens, SNP analysis with polymorphisms and association studies. Third, although migraine has variable clinical phenotypes, it may share common pathophysiology. After discovering CACNA1A gene mutation, a P/Q type calcium channel dysfunction and its role in migraine pathogenesis at the genetic level suggests that migraine may be a channelopathy. Exploring the correlation between phenotype and genotype of migraine may be an important next step in studying migraine genetics.

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