Genetics of Migraine Headache

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Abstract: Migraine is a common form of chronic headache syndrome. Although the pathogenesis of migraine still remains enigmatic, there has been remarkable progress in genetic research. Point mutations of the P/Q-type $\text{Ca}^{2+}$ channel alpha 1 subunit (CACNA1A) gene have been identified in familial hemiplegic migraine (FHM). The CACNA1A gene has been noticed as a possible candidate genetic locus related to common forms of migraine headache. Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) is an autosomal dominant inherited disorder that is often accompanied by migraine-like headache. Point mutations of the notch-3 gene have been identified as the cause of CADASIL. The trigemino-vascular theory is a modern theory of migraine headache that claims that neurogenic inflammation of the meningeal blood vessels is triggered by excitation of trigeminovascular fibers. Neurotransmitters such as serotonin (5HT), CGRP, and substance P likely play major roles in these events during the early stage of migraine attacks. An association study of the allelic variation at Codon 23 (Cys or Ser) of the 5HT$_2$C-R gene in Japanese samples revealed that the Ser allele frequency in migraine with aura was significantly higher than that in the non-headache controls. However, a negative association of this polymorphism has been reported in Caucasian migraineurs. An increased frequency in the dopamine D2 receptor (DRD2) Ncol C allele has been reported in Caucasian samples. The C677T allelic variation of 5,10-methylenetetrahydrofolate reductase (MTHFR) increased the risk for migraine. Discovery of new genes that are responsible or susceptible to migraine will also open an avenue to develop a new therapeutic strategy for migraine.

Key words: Migraine; Gene; $\text{Ca}^{2+}$ channel; CACNA1A; Methylenetetrahydrofolate (MTHFR)

Introduction

Traditionally, headache was considered a mere symptom of disease, and it was not duly recognized as a disease in itself, but with the development of tryptans and other drugs, which exhibit a specific effect on migraine, the clinical entity of chronic headache has come to receive

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is classified as a subgroup of migraine with aura (MA) by the International Headache Society, fulfills the diagnostic criteria for MA by definition, because it exhibits an aura, in this case hemiplegia, and has a history of at least one first degree relative (parent, sibling or child) with similar attacks. Different families exhibit different symptoms, and it is known that some families exhibit symptoms like nystagmus or cerebellar atrophy, while convulsions or disturbed consciousness may appear in other families. With FHM relatively slight external trauma or a procedure like brain angiography may trigger a severe attack, resulting in irreversible brain damage.

In 1993, Joutel et al. linked FHM to chromosome 19p13, and in 1996 Ophoff et al. identified a point mutation of the P/Q type Ca\(^{+2}\) channel alpha 1 subunit (CACNA1A) on chromosome 19 (Fig. 1). Ducros et al. analyzed the available genetic data and clinical presentations of FHM

Familial Hemiplegic Migraine

Familial hemiplegic migraine (FHM), which

considerable attention. A study conducted in Daisen-cho, Tottori-prefecture, showed that 28.8% of the population experienced some kind of chronic headache, while 6.0% suffered migraine, a figure that matches the prevalence of high blood pressure.

Efforts are made to understand the pathophysiology of migraine, and research on a genetic level is also progressing recently. The discovery of the mutations of calcium channel gene in familial hemiplegic migraine (FHM) was a breakthrough. Other genes that are also studied as possible migraine-related susceptibility genes include the serotonin receptor, dopamine receptor, and methylene-tetrahydrofolate reductase (MTHFR) genes, as well as the angiotensin-converting enzyme (ACE) gene, etc.
in 28 families with a known family history of FHM. Migraine attacks with hemiplegia appeared in 89% of the members with the CACNA1A mutation, and a third of them experienced particularly severe migraine attacks accompanied by coma or delayed hemiplegia.

The 28 families that were analyzed showed a total of 9 mutation types, including 5 newly identified mutations; 6 of these mutations were related to hemiplectic migraine and cerebellar signs, and 83% of the patients presented with nystagmus or ataxia. The other three gene mutations caused “pure type” hemiplegic migraine (pure hemiplegic migraine),” and it was shown that they do not cause lasting cerebellar signs. Apart from the involvement of chromosome 19, a familial gene locus was also reported on chromosome 1q21–23, and a familial FHM locus on chromosome 1q31.

**CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy)**

This is an autosomal dominant hereditary disease with onset from a young age to middle age, that presents predominantly with cerebral leukoencephalopathy and recurring infarcts of the cerebral white matter. It does not exhibit high blood pressure, hyperlipidemia or any of the other risk factors for atherosclerosis. It is reported that migraine-like headaches are associated with it at a high frequency in affected families in Europe and America. Approximately half of the cases presented with a migraine-like attack and as the disease progresses, hemiplegia, ataxia, epilepsy, and cognitive dysfunction develop.4)

There are very few reports on this disease in Japanese, but even so, very few Japanese cases seem to be associated with headache.5)

If the perivascular presence of granular osmiophilic material (GOM) can be demonstrated on skin biopsy, the diagnosis is confirmed. CADASIL is caused by a point mutation of the Notch 3 gene.

It is reported that Americans of Chinese heritage suffer a hereditary disease similar to CADASIL, called hereditary endotheliopathy with retinopathy, nephropathy, and stroke (HERNS). There is also a report of a large family in Holland that showed symptoms of an autosomal dominant hereditary disease with retino-vascular degeneration, migraine, and Raynaud’s phenomenon. In both these conditions, migraine (migraine-like headache) features prominently, and although the gene involved has not been identified, it is linked to chromosome 3p21.6)

**Mitochondrial Gene**

The mitochondrial encephalomyopathy like the syndrome of mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS), are known for their frequent association with headache. There is a view that migraine is either a mitochondrial disease or a symptom of mitochondrial encephalomyopathy. This view is supported by reports suggesting mitochondrial dysfunction of the brain and muscles due to 31P-MRS in migraine patients, while cases of patients with cluster headache and an A3243G MELAS mutation, have also been reported.

It was considered that the mtDNA11084A-G polymorphism, which is frequently found in Japanese, may be a migraine-susceptible gene, but after studying many cases, the frequency of G polymorphisms was found to be the same as that in the control group, and it was concluded that it does not play a role in migraine.7) The possibility that mitochondria may be involved in migraine is an important one, and we anticipate the results of future studies.

**Susceptibility Genes in General Migraine**

FHM and CADASIL are hereditary diseases that are associated with migraine-like headaches and are caused by an abnormality of a
specific gene. On the one hand, many genetic studies in common form of migraine are under way. The familial occurrence of migraine is empirically well known, and it is assumed that genetic factors, as well as environmental factors like diet, etc. play a role.

Russell et al.\(^8\) conducted a study on familial migraine and found that, compared to the general population, patients with migraine with aura (MA), had a 3.8 times higher frequency of first degree relatives with MA and a 0.8 times higher frequency of spouses with MA; while patients with migraine without aura (MO) had a 1.9 times higher frequency of first degree relatives with MO and a 1.5 times higher frequency of spouses with MO (Fig. 2). Genetics seems to play the most important role in MA, while genetic and environmental factors both play a role in MO.

**Serotonin (5-hydroxytriptamine; 5-HT)-Related Genes**

Serotonin plays a major role in the clinical presentation of migraine and the serotonin receptor gene is actively investigated. Serotonin receptors are classified into subtypes 5HT\(_1\) through 5HT\(_7\). Sumatriptan (succinate), a drug that is specifically used for the treatment of migraine, is an agonist of the 5HT\(_{1B/D}\) receptor subtypes; stimulation of the 5HT\(_{1B}\) receptor causes vasoconstriction in the brain, while stimulation of the 5HT\(_{1D}\) receptor inhibits neurogenic inflammation, thus, by inhibiting neural activity it exerts an aborting effect on migraine attacks. Based on such facts as that the 5HT\(_{2C}\) receptor agonist m-chlorophenyl piperazone (mCPP) induces a high incidence of migraine attacks in migraine patients, and that the 5HT\(_{2C}\) receptor antagonists methylsergide and pizotyline are effective as prophylactic agents against migraine attacks, it is thought that the 5HT\(_{2C}\) receptor, with its gene locus on chromosome Xq24, is involved in the induction of migraine attacks.

The study by Burnet et al.\(^9\) of the Cys/Ser polymorphisms of the 5HT\(_{2C}\) receptor codon23, could not establish a significant relation with migraine, but the domestic study by Kusumi et al.\(^10\) showed that the frequency of the Ser allele was significantly increased in MA. These results can be attributed to racial differences, but it is not clear how the function of the receptor is changed by the Ser type, and we are anticipating the progress of future research.

Ogilvie et al. have also studied the relation between serotonin transporter gene polymorphism and migraine, and reported a significant relationship with both MA and MO.

**Dopamine Receptor Gene**

Peroutka et al. studied dopamine receptor (DRD2) gene polymorphism, and reported that the C/C type is significantly increased in migraine.\(^11\) According to the studies by Kusumi et al.\(^10\) this gene was not involved in migraine.

**Methylenetetrahydrofolate Reductase Gene**

Methylenetetrahydrofolate reductase (MTHFR), an enzyme involved in the metabolism of homocysteine, is known for its C677T (Ala->Val) gene polymorphism. The T-mutation causes significantly increased blood levels of homocysteine, and the homozygous T/T presence is receiving attention as a risk factor for coronary
artery disease and cerebrovascular disease.

The authors’ study\(^{12}\) showed that the frequency of the T/T type was high in MA. In other words, the T/T type MTHFR gene is a risk factor for hereditary migraine.

Also, when the blood homosysteine value was measured in migraine patients, it was found to be slightly, yet significantly, increased. Abnormalities in the MTHFR gene are presumably involved in the altered trigeminal nerve activity associated with migraine, and the modified threshold for the onset of migraine.

**Angiotensin Converting Enzyme**

The angiotensin converting enzyme (ACE) gene is related to blood pressure via the metabolic enzymes of the angiotensin system, but it is also known for its involvement in the metabolism of the trigger substance, substance P.

There are both insertion (I) and deletion (D) mutations of the Alu base-pair sequence of the ACE gene; with the D type the blood levels of ACE are increased, and the homozygous D type (DD type) is attracting attention as a risk factor for myocardial infarction. When the presence of this polymorphism was investigated in migraine patients, the frequency of the DD type was significantly elevated in MA. In Europe, Paterna et al.\(^{13}\) reported similar results in MO patients.

**Endothelin Receptor Gene**

Endothelin-1 (ET-1) is a potent vasoconstrictor substance and it is known that blood levels of ET-1 are elevated during a migraine attack. During the intermission of attacks of migraine, the levels of ET-1 have been reported to be both decreased and increased.

There are two types of ET-1 receptors, namely ET-A and ET-B. The ET-A receptor mediates the response to ET-1 and the production of nitric oxide (NO), which is involved in migraine, is suppressed. A study of the ET genes involved in migraine, the ET-A and ET-B receptor genes, showed that polymorphisms of the ET-A receptor gene played a significant role.

**Other Genes**

The NO synthase (NOS) gene was studied as a migraine-related candidate, but a significant relationship was not established. Study of the prothrombin gene 20210A→G polymorphism, which is involved in blood coagulation, showed that it does not play a role in migraine. It is reported that the insulin receptor gene, which is located close to the CACNA of FHM (19p13.3/2) plays a role in migraine.

**The Genetic Locus of Migraine with Aura Is 4q24**

It was reported that a genome-wide sequence analysis using 350 types of microsatellite markers was performed on a sample of Finnish migraine patients and the gene was located on chromosome 4q24.\(^{10}\) Future identification of the gene as such is anticipated.

**Conclusion**

Genetic research of hereditary disorders that present as specific kinds of migraine has been successful, as in the identification of the genes that cause FHM and CADASIL.

Apart from familial migraine, families that demonstrate hereditary (familial) disorders with pathognomonic symptoms are meticulously examined clinically to establish separate syndromes, followed by a genetic search. It is therefore likely that new genetic mutations will continue to be identified.

On the one hand, based on the biochemical evidence involved in migraine, the use of single nucleotide polymorphisms (SNP) or microsatellite markers are progressing in the mutual analysis of possibly related candidate genes, and the susceptibility genes of migraine are gradually established. One aim of the molec-
ular genetic research of migraine is to understand the molecular level of clinical migraine in order to develop a more selective approach to the treatment of migraine.

We expect that the medical consultation of migraine will also include genetic testing in the future in order to rationalize the diagnostic process and allow selection of the most effective therapeutic drugs.

REFERENCES


