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Causes Of Migraine
(Genetic Basis)

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Abstract

The causes of migraine is genetic mutations although that the other factors such as food, stress, hormonal changes and other habits play role in stimulate the headache. Ans the studies found that the mutation that lead to migraine are many and the mutation is in the functional genes in nervous system or the mutation may be in vascular genes or mitochondrial genes, and with all of this we should mention that the migraine is familial disease and with high incidence with female than male, but it may be sporadic when the environmental factors lead to dysfunctioning of genes and to mutations.

Introduction

Migraine is a common multifactorial and polygenic neurological disabling disorder characterized by a genetic background and associated to environmental, hormonal and food stimulations. There are a number of different types of migraine, the most common being Migraine without Aura and Migraine with Aura. Other types of migraine include Basilar Migraine, Hemiplegic Migraine, Vestibular Migraine and Aura without Headache. Migraine without Aura the majority of migraine sufferers have Migraine without Aura. The most common symptoms of Migraine without Aura are: Intense throbbing headache, usually on one side of the head, worsened by movement and lasting from 4-72 hours. Migraine with Aura refers to a range of neurological disturbances that occur before the headache begins, usually lasting about 20-60 minutes . Migraine Aura Without Headache about 1% of migraineurs experience migraine aura without ever having a headache. The most common symptoms of migraine aura are visual disturbances such as: Blind spots Flashing lights Zig-zag patterns. Basilar migraine is a rare form of migraine that includes symptoms such as loss of balance, double vision, blurred vision, difficulty in speaking and fainting. During the headache, some people lose consciousness. Hemiplegic Migraine is a rare form of migraine where the person experiences many of the usual migraine symptoms, but may also suffer from temporary numbness, weakness or even paralysis on one side of their body. Vestibular Migraine or Migraine Association Vertigo (MAV) is a disorder which involves a problem with the coordination of the sensory information sent to your brain from the eyes, muscles & bones, and the vestibular organs inside the ears. Nearly 40% of all migraine sufferers experience some vestibular symptoms during their lifetime, such as dizziness, sensitivity to light/sound and stiffness of the neck. Ophthalmoplegic migraine is a very rare type of migraine that occurs mainly in young people in which there is weakness of one or more of the muscles that move the eye. In addition to headache, symptoms of ophthalmoplegic migraine include dilation of the pupils, inability to move the eye upward, downward or across, as well as a drooping of the upper eyelid[1,2,3].

Discussion

Inheritance of migraine

Hereditary factors play an important role in the development bof migraine .Relatives of such patients have migraine much more often than the population in general; if both parents have migraine, the risk that their offsprings will have this disease reaches 60-90% (vs. 11% in the control group), and the leading role belongs to the mother: in this case the risk of disease in children is 72%. Long-term studies have demonstrated familial aggregation of migraine symptoms, and in some cases a positive family history (presence of the disease in family history) is a diagnostic criterion for migraine. Studies of monozygotic and dizygotic twins also

demonstrated the presence of a significant genetic component in the development of migraine: in monozygotic twins with migraine, concordance value is 1.5-2 times higher than in dizygotic twins (for MWOA and MWA. A large study involving about 30,000 pairs of twins showed that genetics and environmental factors contribute almost equally to the development of migraine.
Studies of twins who grew up together or separately showed that general environmental factors play a secondary role[4,5,6].

Monogenic migraine syndromes

This section presents rare neurological disorders, in which migraine attacks are a part of a broader clinical spectrum and can be regarded as a monogenic subtype of migraine. These subtypes may help identify and understand the pathophysiological mechanisms of migraine.

CADASIL-syndrome

(Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts an Leukoencephalopathy) - a "cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy", characterized by recurrent subcortical ischemic strokes with severe white matter hyperintensity, seizures, cognitive decline, depression and other psychoneurological symptoms. Migraine, in particular migraine with aura, is a characteristic peculiarity of more than a third of patients, which occurs at least one decade prior to other symptoms .CADASIL is caused by mutations in the NOTCH3 gene that encodes the NOTCH3 receptor and plays a key role in the functioning of smoot muscle cells that make up small arteries and arterioles in the brain .Mutations lead to dysfunction of the signaling pathway that regulates the development of vessels during embryogenesis and supports th structural/functional stability of blood vessels in adults .A specific feature of CADASIL is th accumulation of NOTCH3 receptor due to its slow elimination, which leads to the formation of granular osmiophilic deposits, and this affects small blood vessels and results in reduced cell adhesion and cell death, as well as in the transformation of smooth muscle cells in the middle layer and in fibrosis Thus, CADASIL may be caused by vascular dysfunction, which results in the death of smooth muscle cells in the vessels and in the degeneration of the structure of vessels[7,8,9] .

Mitochondrial encephalopathy, lactic acidosis, and strokelike episodes (MELAS)

This disease I caused by mutations in several mitochondrial genes, most frequently in the MTTL1 gene encoding the mitochondrial tRNA for leucine (nucleotide A to nucleotide G transition in position 3243), and is characterized by seizures, stroke-like episodes and lactic acidosis . A typical picture of MELAS includes seizures with neurovisual manifestations of cortical infarcts, which are often combined with migraine-like headaches; as well as hemiparesis, hemianopsia, cortical blindness, episodic vomiting, and short stature. Systemic manifestations may include cardiac, renal, endocrine or gastrointestinal disorders .Cerebral hereditary angiopathy with vascular retinopathy and internal organ dysfunction[10].

Cerebral hereditary angiopathy with vascular retinopathy and internal organ dysfunction (CHARIOT)

A progressive systemic disease of small blood vessels, which is caused by mutations in the TREX1 gene .The TREX1 gene is located in chromosome 3p21 and encodes human DNAase III (3' repair exonuclease) - an autonomous, non-processive 3'-5' DNA specific exonuclease .Thi enzyme is localized in the perinuclear area of the cell, which plays a fundamental role in granzyme A-mediated cell death and, when mutated, indirectly activates the autoimmune reaction against the undigested double-stranded DNA from dying cells .The main peculiarities of this disease include a progressive blindness due to vascular retinopathy; focal and cerebral neurological symptoms associated with cerebral edema and white matter lesions; and premature death. Additional symptoms, such as migraine and Raynaud's syndrome, are observed in more than a half of patients and occur almost ten years before other symptoms. Patients with the familial advanced sleep-phase syndrome (FASPS) hav serious disturbances of the sleep-wake cycle and other circadian rhythms. The disease is caused by missense mutations in the CSNK1D

gene encoding Iδ (CK1δ) casein kinase that is involved in th phosphorylation of Per2 circadian rhythm protein .In two independent families, CSNK1 mutations were observed in 9 of 11 patients with the familial advanced sleep-phase syndrome and migraine wit aura .Screening of two families with migraine with aura and FASPS identified two missense mutations (c.44T> A and c.46H> R) in the CSNK1D gene, which lead decreased enzyme levels .Mice with T44A (Csnk1d) mutation a have lower threshold for cortical spreading depression, accompanied by increased spontaneous and induced activation of the calcium signaling pathway in astrocytes[11] .

COL4A1-related syndromes

The COL4A1 gene encodes alpha-1 subunit of type IV collagen.Mutations in this gene may lead to several autosomal dominant disorders with overlapping characteristics, including perinatal hemorrhage with porencephalia ,and small vessel disease, which result in hemorrhage and hemiparesis in childhood or adulthood .The association of COLA4A1 mutations with migraine I not quite reliable and may be a random discovery, despite the fact that 10 out of 52 COLA4A1 mutation carriers have confirmed migraines (with or without aura)[12].

Familial and sporadic hemiplegic migraine (FHM)

Is characterized by migraine attacks combined with transient unilateral motor weakness. Aura, headaches and associated symptoms are identical, and attacks can be caused by similar triggers; the same medicinal products are used for treatment and prevention. In 75% of FHM patients, hemiplegic episodes may alternate with migraine episodes without moto weakness. FHM and migraine are more common in women, and migraine rates increase among first-degree relatives. FHM patients may also have additional transient and persistent neurological disorders, such as ataxia, epilepsy, cognitive disorders or loss of consciousness.

FHMs are genetically heterogeneous. 5 types of FHM are distinguished:

1) Type 1 FHM - missense mutations in the CACNA1A gene (50-75% of families) .
2) Type 2 FHM -mainly deletions and frameshift in the ATP1A2 gene (20% to 30% of cases) .
3) Type 3 FHM - mutations in the SCN1A gene on 2q24 .
4) Type 4 FHM - mutations in the CACNA1E gene on 1q25-q31.
5) FHM induced by mutations in other genes: SLC1A3 ,SLC4A4 ,PRR2.

Approaches to studying candidate genes are widely used to study the genetics of migraine. Repeated studies were conducted for a significant number of genes, and those studies either confirmed or refuted the association. However, studies of candidate genes are interesting, as they can reveal the contribution of common genetic variants to the complex phenotype of specific ethnic groups, particularly genetic isolates Candidate genes were previously grouped into four functional families of genes, namely, neurological, cardiovascular, hormonal and inflammatory genes[13,14,15].

Genes involved in the nervous system functioning

This category includes mainly candidate genes, the products of which are needed for the functioning of the nervous system:

1) Ion channels. For example, genes encoding calcium (CACNA1A, CACNB2, CACNB4) or potassium (KCNAB3, KCNB2, KCNG4, KCNJ10, KCNK18, KCNN3) channels.
2) Subunits of Na+/K+ -ATPase,
3) Molecules involved in the synthesis, release and binding of neuropeptides (calcitonin gene-related peptide) or neurotransmitters (glutamate, GABA, dopamine, serotonin) connected with neuronal excitation and/or nociception.

Some case-control association studies gave positive results for the DBH, DDC, DRD2, DRD3, DRD4, GRIA1, GRIA3, HTR2, 5-HTTLPR, MAOA, SLC6A3, SLC6A4 and BDNF genes, although the results of most studies were negative, especially for the first two gene families[see 4] .

Vascular genes

Association studies of the genes involved in the regulation of blood pressure, endothelial cell function, vasoconstriction (narrowing of the blood vessels) and vasodilation (widening of the blood vessels) provided more consistent positive results.

i. Angiotensin converting enzyme (ACE) plays a key role in maintaining blood pressure and vessel wall pressure. Homozygous deletion (DD) in the human ACE gene increases the enzymatic activity of ACE and is associated with the frequency and duration of MWA attacks .

ii. A number of studies revealed association between variants of the 5-10-methylenetetrahydrofolate reductase (MTHFR) gene and migraine. MTHFR is a key component of remethylation of homocysteine to methionine and catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate Mutations in the MTHFR gene may lead to hyperhomocysteinemia due to lower enzymatic activity. Several studies involving different ethnic groups and several recent meta-analyzes have confirmed the contribution of the T677 allele in the MTHFR gene to the pathogenesis of migraine. However, it was reported that the absence of any connection with MTHFR gene variants can b due to age and selective survival.

iii. NOTCH3 encodes a transmembrane receptor that regulates the development of vessels and differentiation during embryogenesis, and also contributes to the integrity of vessels in adults . In addition to rare NOTCH3 mutations leading to MWA in the context of CADASIL, other variants are significantly associated with migraine .Therefore, NOTCH3 may play a more active role in the pathogenesis of common migraine without aura.

iv. Other endothelial genes assessed for association with migraine encode endothelin-1 (EDN1), endothelin receptor type A and B (EDNRA and EDNRB), inducible NO-synthase (NOS2), endothelial NO-synthase (NOS3), and vascular endothelial growth factor (VEGF) [56,78-84]. Several studies have found association between EDNRA alleles and migraine, and one study involving Finnish and German patients with migraine showed association between MWA and the rs2048894 (EDNRA) substitution especially with the age of diseases onset <20 years[see4,8,16] .

Conclusion

Due to the fact that the polymorphic variants of genes apparently have no significant effect on the pathogenesis of migraine individually, but rather there is an integrated effect of a complex genotype on pathogenesis, it is difficult to determine the contribution of polymorphic variants of individual genes. For example, the protein encoded by the LRP1 gene associated with migraine is cleaved by metalloproteinase that is encoded by another candidate gene, MMP16 . Also, for most genes their role in the disease development processes remains unclear, as their cellular processes are not linked with the currently available data on the pathogenesis of migraine: TGFBR2, PHACTR1, C7orf10, ADARB2, ZNF555.

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