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Genetics of migraine - is there any progress?

Abstract

Nowadays migraine ranks 9th in the list of leading causes of disability among population. In Russia migraine prevalence is two times higher than the world index and inflicts a considerable damage on the state economy. Despite almost one-century history of studying migraine, science until now cannot explain many cases of attack occurrence. It causes difficulties both for diagnosis and treatment – the therapy of patients with migraine is not sufficiently effective. Today one of the investigation directions is searching of migraine biomarkers confirming diagnosis. In this review we attempted to generalize the results of available works targeted at searching genetic markers of migraine.

Keywords: migraine, gene,polymorphism

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Introduction

Migraine is now one of the leading causes of disability (ranks 9th according to the WHO), comparable to such diseases as cancer, diabetes, cardiovascular diseases and others. In the female population, migraine-related disability ratio promotes this disease to 3rd place. According to epidemiological studies, migraine prevalence in the world for 1 year in the adult population ranges on average from 10.2%[1] to 14.7 %.[2] In Russia, migraine prevalence exceeds world figures almost 1.5-2 fold, being 20.3%, and annual indirect costs (days lost due to disability) related to primary headaches total US $22.8 billion (1.75% of Russia's gross domestic product).[3] Thus, migraine is not only a medical, but also a significant economic problem.

Until now, the diagnosis of "migraine" is exclusively clinical, and any diagnostic tests are aimed only at excluding other causes of headache.[4] There are also problems with migraine treatment and although both traditional analgesics and specific anti-migraine products are available in the market, treatment of migraine patients is still not sufficiently effective. For example, specific anti-migraine agents (triptans) help control only two out of three attacks, and migraine prevention products are considered effective, if they reduce the frequency of attacks by 50% or more. The chronification of migraine attacks and the development of chronic daily headaches, occurring in 1% of patients per year,[5] are a significant clinical problem. However, about 10% of migraine patients in the population and 40-60% of patients visiting specialized headache centers are resistant to standard therapy.[6] Treatment of such patients is the most expensive.

Thus, searching for migraine biomarkers that confirm such diagnosis, instead of refuting other diagnoses, is the principal vector in this scientific field. In this review, we attempted to summarize the available information about studies aimed at searching for genetic markers of migraine.

Discussion

Inheritance of migraine

Hereditary factors play an important role in the development of migraine.[7] 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).[8,9] A large study involving about 30,000 pairs of twins showed that genetics and environmental factors contribute almost equally to the development of migraine.[10] Studies of twins who grew up together or separately showed that general environmental factors play a secondary role.[11,12]

Differences in migraine prevalence between populations also may serve as an indirect evidence of the genetic basis of migraine pathogenesis; such differences may be due to the differences in allele frequencies between populations. According to foreign researchers.[13,14] the genetic component in migraine with aura is stronger than that in migraine without aura. Some authors define migraine as a polygenic multiple-factor disease.[15,16] Currently, there is a belief that it is not the disease itself that is inherited, but rather a predisposition to respond to external stimuli of the nervous and vascular systems.

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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 and 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.[17] CADASIL is caused by mutations in the NOTCH3 gene that encodes the NOTCH3 receptor and plays a key role in the functioning of smooth muscle cells that make up small arteries and arterioles in the brain.[18] Mutations lead to dysfunction of the signaling pathway that regulates the development of vessels during embryogenesis and supports the structural/functional stability of blood vessels in adults.[19,20] A specific feature of CADASIL is the 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.[21] 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.

Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS): This disease is 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.[22] 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.[23]

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.[24,25] 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.[26] This 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.[27] 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.[25-28]

Patients with the familial advanced sleep-phase syndrome (FASPS): Have 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 the phosphorylation of Per2 circadian rhythm protein.[29-31] In two independent families, *CSNK1D* mutations were observed in 9 of 11 patients with the familial advanced sleep-phase syndrome and migraine with aura.[29] 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.[30] 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.[29]

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,[32-35] and small vessel disease, which result in hemorrhage and hemiparesis in childhood or adulthood.[36] The association of *COLA4A1* mutations with migraine is 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).[35]

Familial and sporadic hemiplegic migraine (FHM) ischaracterized 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 motor 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.[37]

FHMs are genetically heterogeneous.

5 types of FHM are distinguished:

1. Type 1 FHM - missense mutations in the *CACNA1A*gene (50-75% of families).[15,38]
2. Type 2 FHM -mainly deletions and frameshift in the *ATP1A2* gene (20% to 30% of cases).[39]
3. Type 3 FHM - mutations in the *SCN1A*gene on 2q24.[40]
4. Type 4 FHM - mutations in the *CACNA1E*gene on 1q25-q31.[41]
5. FHM induced by mutations in other genes: *SLC1A3*,[42] *SLC4A4*,[43] *PRR2*.[44]

Association studies

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.[45]

A. 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.

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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 he *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.[46-54] Nevertheless, careful screening of 150 genes expressed in the brain and involved in ion homeostasis (channels, transporters, antiporters and auxiliary subunits) made it possible to identify three potassium channel encoding genes associated with migraine, namely *KCNK18*, *KCNG4* and *KCNAB3*.[55] *KCNK18* is particularly interesting in terms of its expression in the trigeminal and dorsal root ganglia, and its relationship with the MWA was detected also by analyzing the linkage groups.

B. 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. Many vascular genes associated with migraine also pose a risk of stroke and heart diseases.[56-58] Common functional variants in several vascular genes can predispose the person to migraine and at the same time influence the type and frequency of attacks:[58]

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.[59-61]

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[62-68] and several recent meta-analyzes[65-71] have confirmed the contribution of the T677 allele in the *MTHFR* gene (rs1801133) to the pathogenesis of migraine. However, it was reported that the absence of any connection with *MTHFR* gene variants can be due to age and selective survival.[72]

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 (19-20). In addition to rare *NOTCH3*mutations leading to MWA in the context of CADASIL, other variants are significantly associated with migraine.[73-77] 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.[78]

C. Hormones and genes: Genes controlling the metabolism of estrogen and progesterone theoretically may be associated with migraine and at least partially may explain gender distribution, as well as menstrual migraine.[85] However, the results of studies of genetic association are controversial, although there are some positive results.[86-93] In a recent study, three estrogen receptor 1 (*ESR1*) haplotypes were associated with the disease. In addition to the *ESR1* gene, other hormonal genes were studied: estrogen receptor 2 *(ESR2)*, progesterone receptor *(PGR)*, androgen receptor *(AR)*, follicle-stimulating hormone receptor *(FSHR)*, nuclear receptor interacting protein 1 *(NRIP1)* and cytochrome P450, family 19, subfamily A, polypeptide 1 *(CYP19A1)*. However, a meta-analysis of these genes showed association only with polymorphic variants c.594G>A and c.325C>G of the *ESR1* gene, with no difference between MWA and MWOA found.[93]

D. Inflammation and genes: In animal and human studies, it is supposed that inflammation and immune system components may play a role in the pathogenesis of migraine. In case of CSD (cortical spreading depression), for example, this process causes a local neurogenic inflammation with the activation of mast cells and macrophages, accompanied by the release of pro-inflammatory cytokines, ultimately leading to sensitization of meningeal nociceptive nerve endings.[94] For the *COX-2, HLA-DRB1, LTA, TNFA, TNFB*and*TNFRSF1B* genes, positive associations with migraines were detected.[95-102]

Genome-wide association studies (GWAS)

To date, six GWAS have been conducted, which studied migraine:

1. The first GWAS was prepared by the International Headache Genetics Consortium (IHGC) in 2010. Anttila et al.,[103] conducted a two-stage association study on six clinical and one European population samples.[103] When comparing 2,748 patients with migraine from three European headache clinics (Finland, Germany and Denmark) and the control sample (n=10,747), the minor allele of rs1835740 on chromosome 8q22.1 was identified, which is associated with migraine. This association was obtained on 3,202 patients and 40,062 controls, and the combined results showed that the risk of migraine increases by 18% in the presence of the minor allele of rs1835740, with a stronger effect in MWA than in MWOA. This substitution is between the *MTDH* and *PGCP* genes.

Interestingly, these genes may simultaneously participate in glutamate homeostasis. In cultured astrocytes, *MTDH* (metadherin) suppresses the transcription of the *EAAT2* gene that is main transporter of glutamate in astrocytes: this, in turn, causes an increase in glutamate concentrations in the synaptic cleft due to a delay in glutamate removal, thereby reducing the threshold for cortical spreading depression (CSD) that plays an important role in the pathophysiology of migraine.[104,105] However, subsequent studies failed to confirm the association between the *MTDH* gene and migraine,[106-108] although its role in the development of clinical characteristics of migraine[107] and in the pathogenesis of other types of headaches[108] was demonstrated.

2. The sample in a subsequent population GWAS consisted of women only and included 5,122 female patients and 18,108 controls.[109] Substitutions of rs2651899 (locus 1p36.32, gene *PRDM16*), rs2078371 (locus 1p13.2), rs10166942 (locus 2q37.1, gene *TRPM8*), rs17172526 (locus 7p14.2, gene *SEPT7*),

rs2203834 (locus 8p22, gene *C8orf79*), rs13290757 (locus 9q33.3), rs11172113 (locus 12q13.3, gene *LRP1*) showed association with migraine at the first stage of the study. The association was confirmed for three out of seven substitutions in repeated analysis of three samples and with a combination of samples from the initial stage and repeated analysis (rs2651899, rs10166942 and rs11172113). For none of the three substitutions, association with migraine type (MWA and MWOA) or clinical features of migraine was demonstrated. *TRPM8* is expressed in sensory neurons and neurons of the spinal ganglia. This gene encodes cold- and menthol-activated ion channels and participates in the generation of cold-induced pain.[110] Studying the role of *TRPM8* in animal models with neuropathic pain also confirms the functional association with migraine.[111] *LRP1* expresses in the brain tissues and in many other tissues,[31] modulates synaptic transmission and interacts with the NMDA glutamatergic receptors. *PRDM16* is a pleiotropic gene that is important for craniofacial development, fat determination and the proliferation of cardiac myocytes, neural and leukocyte neural progenitor cells.[112] It was shown that the *Prdm16* mouse homologue acts as a negative TGF-β regulator (the *TGFBR2* gene is also a candidate gene of migraine).[113] Association with *PRDM16*, but not with *LRP1* and *TRPM8*, has been recently reproduced in a Chinese Han sample.[114] At the same time, association with *LRP1* and *TRPM8* was found in Denmark and Iceland in a sample consisting of 2,523 patients and 38,170 controls, and meta-analysis confirmed the association for all the three loci.[115]

3. Lighthart et al.,[116] conducted meta-analysis of migraine GWAS; in their work, they studied six European samples from the Dutch Icelandic migraine genetics consortium, involving 2,446 patients and 8,534 controls.[116] 32 SNP demonstrated a weak association with migraine. The best result was obtained for rs9908234 localized in the nerve growth factor receptor (NGFR) gene. However, this association was not repeated in three samples from the Netherlands and Australia. In repeated analysis of 18 SNP in two samples, the association was not reproduced. This study confirmed the association between migraine and the metadherine gene (*MTDH*), identified in the first GWAS.

4. Freilinger et al.,[117] tried to find SNP associated with MWOA and conducted a GWAS that included 2,326 patients with MWOA and 4,580 controls from the population of Germany and the Netherlands.[117] The association was verified additionally in four independent repeated European samples that included 2,508 patients with MWOA and 2,652 controls. The 1q22 locus contains 6 SNP, a considerable genome-wide association for which was received at the first stage of the study. Association for rs1050316 and rs3790455 was reproduced in repeated samples. All associated SNP were localized within the myocyte enhancer factor 2D gene (*MEF2D*). The *MEF2D* protein is a transcription factor and is highly expressed in the brain, where it regulates the differentiation of neurons and limits synaptic excitation.[118,119] Taking into account the involvement of glutamatergic neurotransmission in CSD and in the pathogenesis of migraine,[104] and elevated plasma levels of glutamate in patients with migraine,[120] *MEF2D* can be considered as a candidate gene of migraine. The 3p24 locus contains rs7640543 that showed association at an early stage in repeated samples and genome-wide significance in meta-analysis of pooled samples. This polymorphic variant is located in the gene encoding the transforming growth factor-beta receptor (*TGFBR2*). The *TGFBR2* is involved in the regulation of cell proliferation, differentiation and extracellular matrix production.[121] The missense mutation p.Arg460His is associated with migraine headaches in 11 out of 14 carriers of the mutation in a large pedigree.[122] Locus 6p24, rs9349379 reached genome-wide significance in meta-analysis of pooled samples. This SNP is localized in the gene encoding phosphatase and actin regulator 1 (*PHACTR1*). The gene product controls synaptic activity and synaptic morphology by regulating binding of phosphatase 1 and actin proteins and is involved in the functioning of endothelial cells.[123-125] Locus 9p33, rs6478241 also reached genome-wide significance in meta-analysis of pooled samples. The rs6478241 substitution is localized in the *ASTN2* gene that is a member of the astroactin gene family. This gene plays an important role in glial-directed migration that is necessary for the development of laminar architecture of the cortical regions in the brain.[126] For two SNP in the 2q37 locus, genome-wide significance was shown in meta-analysis that pooled all the samples (rs10166942 and rs17862920). The substitutions are localized in the *TRPM8* gene. The 12q13 locus contains rs11172113, genome-wide significance of which was shown in meta-analysis.

5. Cox et al.,[127] conducted a GWAS based on pedigrees of an isolated population of Norfolk Island with high migraine prevalence (25.5%).[127] During their work, they identified association with the substitution of rs4807347 localized in the *ZNF555* gene encoding the "zinc finger 555" protein, which was confirmed in an independent sample (Women's Genome Health Study, WGHS). This study also demonstrated association between the *ADARB2* (rs883248, rs2271275, rs1046914, rs10903399), *GRM7* (rs1391950 and rs11713183) and *HTR7*(rs2800143) genes and migraine phenotype in the population of Norfolk Island. The *HTR7* and *GRM7* genes related to the serotonergic system. These genes are expressed mainly in the brain, function in the presence of positively activated adenylate cyclase in a cell and may play a role in regulating the circadian rhythms and the neuroendocrine function, as well as in the development of affective mood disorders.[128,129]

6. The sample in a large meta-analysis was 23,285 patients with migraine and 95,425 controls.[130] The study identified 12 loci associated with susceptibility to migraine. Five loci were not previously associated with migraine (near to *AJAP1* - 1p36, near to *TSPAN2* - 1p13, inside *FHL5* - 6q16, inside *C7orf10* - 7p14 and near to *MMP16* - 8q21). The remaining loci confirmed previous associations with migraine (*PRDM16, MED2D, TRPM8, TGFBR2, PHATCTR1, ASTN2* and *LRP1*). The *FHL5* gene encodes a transcription factor that regulates cAMP dependent elements CREM and *CREB6*, which play a role in synaptic plasticity and memory formation.[131,132] The *c7orf10* (or *SUGCT*) gene encodes succinyl-CoA-glutarate-CoA transferase. Mutations in this gene are associated with phenotypically mild or even clinically asymptomatic glutaraciduria type III, a rare metabolism abnormality leading to a constant excretion (elimination) of glutaric acid.[133] *AJAP1* is expressed in the brain and is associated with tumor invasion and the regulation of metalloproteinase activity.[134] *TSPAN2*, a member of the tetraspanin family, encodes a cell surface protein that mediates signal transduction in the regulation of cell development, activation, growth and motility. It was shown that *TSPAN2*acts as a metalloproteinase activity regulator.[135] The protein encoded by the *MMP16* gene belongs to the metalloproteinase family, the members of which are widely expressed in human tissues and participate in the destruction of extracellular matrix in normal physiological processes. This protein cleaves the LRP1 protein encoded by another candidate gene of migraine.[109]

Thus, migraine-related GWAS and subsequent meta-analyses identified associated polymorphic variants of susceptibility genes, which can be grouped into five pathways:

a. Glutamatergic neurotransmission (rs1835740 - *MTDH*, rs11172113 - *LRP1*, rs3790455 - *MEF2D*);

b. Synapse development and neuroplasticity (rs6478241 - *ASTN2*, rs13208321 - *FHL5*);

c. Pain sensitivity (rs10166942 - *TRPM8*);

d. Metalloproteinases (rs10504861 - near to *MMP16*, rs10915437 - near to *AJAP1*, rs12134493 - near to *TSPAN2*);

e. Vascular system and metabolism (rs4379368 - *C7orf10*, rs2651899 - *PRDM16*, rs9349379 - *PHACTR1*, rs7640543 - near to *TGFBR2*).

Common variants demonstrated in several GWAS proved to be very valuable and underlined the glutamatergic role in the pathogenesis of migraine, with such role probably underlying cortical spreading depression and sensitization of nociceptive nerve endings.[27] Despite the fact that GWAS have identified new candidate genes responsible for the pathogenesis of migraine, the results of these studies have not brought us closer to understanding its molecular and genetic bases.

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*.[136] 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,* etc.

Conflicts of interest

No conflict.

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None.

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