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Role of single nucleotide polymorphisms (SNPs) in common migraine

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Abstract

Single nucleotide polymorphisms (SNPs) may act as biological markers, as they can relate to the genes that are associated with various complex diseases such as heart diseases, diabetes, cancer, schizophrenia, blood pressure, migraine, and Alzheimer. These SNPs mostly locate within a gene or in a regulatory region near a gene and can affect the gene's function to play a more direct role in disease. Hence, SNPs allow scientists to develop candidate drug therapy by evaluating an individual's genetic makeup to develop a particular disease. Gene-gene interactions generally complicate migraine and its genetics and further gene-environmental interactions that often misguide the true defying causes of this disease. Due to its complex nature, it is difficult for scientists to reveal a complete list of SNPs or even all the genes that are related with the pathogenesis of this disease. Nowadays, much work has been done in this direction and new variants of migraine are being constantly identified. In this review article, the role of various SNPs reported to be disease-associated in published migraine GWAS has been discussed. To understand the molecular mechanisms of migraine attack by identifying new genetic variants of migraine can be a key to develop new therapeutic strategies in the future.

Keywords: Migraine, Genetics, Single nucleotide polymorphisms, Genome-wide association studies (GWAS)

Introduction

Migraine is a common, chronic, polygenic neurovascular disorder in which both genetic and environmental factors play their roles. This disease affects about 15% of the population overall. The prevalence of migraine in women (18%) is higher when compared with men (6%), with attacks lasting from a few hours to some days [1]. The higher prevalence in women is typically attributed to hormonal fluctuations especially estrogen. Migraines typically begin during puberty or between the ages of 35 and 45 years [2, 3]. Migraine is a disabling disorder, which reduces the quality of life and significantly affects the ability to work and moreover results in higher cost and greater health care resource utilization [4–6]. Migraine can be classified into two types on the basis of aura: migraine without aura (MO) and migraine with aura (MA) and up to one-third of patients experience an aura prior or during the headache attacks. In migraine with aura (MA), patients can show transient facial neurological symptoms that mostly precede or in some cases accompany the headache. A premonitory phase having symptoms of depression, cravings for particular foods, fatigue, hyper or hypoactivity along with repetitive yawning, and neck stiffness is reported, which occur hours or days before the headache, and a headache resolution phase [7]. Migraine without aura (MO) is characterized by headache with specific features and associated symptoms such as unilateral location, pulsating quality, moderate, or severe pain intensity. During headache nausea, vomiting, photophobia, and phonophobia can occur [8]. The main criteria for the diagnosis of migraine with and without aura by the International Headache Society in 2013 [9] are given in Table 1.

Migraine and its genetics

Migraine has a direct impact on the lives of millions of people worldwide, and for most of them, there is still no effective treatment. Nowadays, genome-wide association studies have emerged as an important mean to uncover the genetic variants of complex disorders such as migraine. Whole exome sequencing is potentially an effective tool to identify coding variants underlying human

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Table 1 International classification of headache disorders 3rd edition [9]

Migraine without aura (MO)	Migraine with aura (MA)
Diagnostic criteria A. At least five attacks fulfilling criteria B–D B. Headache attacks lasting 4–72 h (untreated or unsuccessfully treated)2,3 C. Headache has at least two of the following four characteristics: 1. Unilateral location 2. Pulsating quality 3. Moderate or severe pain intensity 4. Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs) D. During headache at least one of the following: 1. Nausea and/or vomiting 2. Photophobia and phonophobia E. Not better accounted for by another ICHD-3 diagnosis	Diagnostic criteria A. At least two attacks fulfilling criteria B and C B. One or more of the following fully reversible aura symptoms: 1. Visual 2. Sensory 3. Speech and/or language 4. Motor 5. Brainstem 6. Retinal C. At least two of the following four characteristics 1. At least one aura symptom spreads gradually over 5 min, and/or two or more symptoms occur in succession 2. Each individual aura symptom lasts 5–60 min 3. At least one aura symptom is unilateral 4. The aura is accompanied, or followed within 60 min, by headache D. Not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack has been excluded

diseases like migraine. In several GWAS, common SNPs related with migraine have proved to be very useful. These SNPs even help in understanding the role of the glutamatergic system, sensitization of nociceptive nerve endings, and cortical spreading depression in the pathogenesis of migraine. Despite this fact that GWAS have revealed new candidate genes and various SNPs related with them that could be the reason for migraine pathogenesis, still, the outcomes from previous findings have not brought us closer to understand its molecular and genetic bases. The reason behind this may be the multigenetic and multi-factorial nature of this disorder. Further, more studies should be done for building a gene profile of the complex common migraine disorder which may provide new drug targets.

To better understand the genetics of migraine, approaches to study candidate genes and linkage studies are also widely used. For a large number of genes and its related SNPs, various replication studies have been done and these studies either confirmed or disproved the association. A criterion using the combination of physiological functions with genomic associations is widely used to find out the most possible variants related with common migraine pathogenesis. On this basis, three different groups of genes including neurological, hormonal, or vascular pathways have been identified for this disorder [10, 11]. Under the neurological group, genes that are involved with expression or control of ion channels (CACNA1A, KCCN3, Sodium-Potassium-ATPase), genes responsible for the synthesis/release and binding of neuropeptides (CGRP protein, glutamate), and the genes with functional effects in dopamine and serotonergic pathways have been reported. The second group of vascular genes is mostly functional in the regulation of blood pressure, endothelial cell expression, vasoconstriction, and vasodilation (MTHFR, ACE). Vascular genes are responsible for migraine particularly migraine with aura overlap with the genes that have a role in elevated risk of stroke and heart disease as a significant co-morbidity with risk for stroke and depression [12]. The third group of genes is typically related with women that can describe the sex-biased distribution of migraine. Genes that can regulate hormonal pathways in females and menstrual migraine include mostly those which can control estrogen and progesterone (ESR1, PGR) levels [13].

Migraine and its SNPs

Genome-wide association studies of migraine (MA and MO), family clustering, and twin studies have identified various migraine-associated common genetic variants [14, 15]. The first large migraine meta-analysis was performed by Anttila et al. [16] that had 29 studies with 23,285 migraineurs and 95,425 controls. In that study, 12 single nucleotide polymorphisms (SNPs) were revealed that were related with migraine susceptibility. Recently, a GWAS [17] had revealed 38 genomic variants mostly found in humans (with > 5% allele frequency) which can affect migraine risk. Previous studies [18, 19] have found additional variants that make the total number of genomic regions related with migraine as high as 47. These variants hint towards a remarkable progress in this direction and provide causes for optimism that the key mechanisms for this disorder can finally be understood. Thus, migraine-related GWAS and reported meta-analyses found different SNPs for this disease, which can be further classified into five pathways [20] on the bases of function:

- Genes involved in glutamatergic neurotransmission—rs1835740 in *MTDH*, rs11172113 in *LRP1*, and rs3790455 in *MEF2D*
- Genes for synapse development and neuroplasticity—rs6478241 in *ASTN2*, rs1320832 in *FHL5*

- Genes for pain sensitivity—rs10166942 in *TRPM8*
- Genes for metalloproteinases—rs10504861 near to *MMP16*, rs10915437 near to *AJAP1*, rs12134493 near to *TSPAN2*
- Genes responsible for vascular system and metabolism—rs4379368 in *C7orf10*, rs2651899 in *PRDM16*, rs9349379 in *PHACTR1*, rs7640543 near to *TGFBR2*

In this review, the most common genes and their variants involved as biomarkers for migraine have been discussed and listed in Table 2.

rs1835740

This SNP, present on 8q22.1 chromosomal region, is located in a 27 kb haplotype block between genes *MTDH* (metadherin, astrocyte elevated gene 1) and *PGCP* (plasma glutamate carboxypeptidase). This variant is mainly responsible for glutamate homeostasis and best known for harboring different genes involved in glutamate metabolism and transport. This SNP regulates the expression of *MTDH* gene and hence indirectly regulates the expression of the glutamate transporter gene *SLC1A2* which is also known as *EAAT2* or *GLT-1* that further encodes a major glutamate transporter protein in the brain. It has been reported in various studies that by increasing the release of glutamate or reduction in uptake of glutamate increase the risk of migraine attacks [21–23]. In astrocytes, *MTDH* downregulates *GLT-1*, the gene encoding the major glutamate transporter protein. SNPs in *MTDH* gene thus can contribute towards understanding the role of glutamate in this disorder. Higher levels of glutamate increase the susceptibility towards cortical spreading depression. Glutamate is one of the major excitatory neurotransmitters in the CNS and therefore has an important role to play in the mediation of excitatory synaptic transmission [24–26]. In the migraine pain pathway, the anatomic structures contain glutamate-positive neurons which include the trigeminal ganglion (TG), thalamus, and the trigemino-cervical complex (TCC) [27, 28]. Migraineurs have higher levels of glutamate and glutamine in their cerebrospinal fluids on comparing with controls and also shown a positive correlation between glutamate levels and mean headache scores [29, 30]. This SNP in *MTDH* gene increases the interest in glutamatergic pathways in migraine but can explain only a small fraction of the overall genetic variance.

rs1801133 and rs1801131

The *MTHFR* gene, on chromosome 1p36, has 11 exons of ~ 17 kb in size [31]. A common SNP (C677T) in *MTHFR* gene encodes for amino acid valine (Val) instead of alanine (Ala) at position 222. Migraineurs with the valine instead of alanine amino acid due to this SNP may exhibit a significantly reduced *MTHFR* enzyme activity which is 30% in the Val/Val homozygous state as compared to 65% in the Ala/Val heterozygote [32]. If the patients further have a low intake of dietary folate, then this reduced activity of *MTHFR* gene can result in mild elevation in plasma homocysteine levels [33]. Mild hyper homo-cysteinemia has been associated with an increased risk of cardiovascular diseases (CVD) that include cerebral, coronary, and peripheral vascular diseases [34]. It is

Table 2 Variants identified in common form of migraine and replicated in various studies

SNPs	Chromosome locus	Gene	Biochemical markers
rs1835740	8q22.1	MTDH	Glutamate
rs1801133	–	–	–
rs1801131	1p36.3	MTHFR	Homocysteine
rs11172113	12q13.3	LRP1	NMDA glutamate
rs10166942	2q37	TRPM8	Pain sensor protein
rs2651899	1p36.32	PRDM16	TGF-β signaling
rs4379368	7p14	C7orf10	Glutaric acid
rs10504861	8q21	MMp16	MT3-MMP protein
rs10915437	1p36	AJAP1	DFFB, TP73, and CEP104 protein
rs12134493 rs2078371	1p13	TSPAN2	Transmembrane protein
rs13208321	6q16	FHL5	CREM, CREB
rs3790455	1q22	MEF2D	–
rs7640543	3p24.1	TGFBR2	–
rs9349379	6p21	PHACTR1	PP1
rs6478241	9q33.1	ASTN2	–

reported that homocysteine may act like an excitatory amino acid in migraine pathophysiology. Homocysteine can cause vasodilation or temporary thrombosis of cerebral blood vessels and thus leading to reduce the supply of oxygen into the brain [35, 36]. Interestingly, an increased risk of ischemic stroke is also associated with the migraine disorder itself, particularly with MA in some studies [37]. Further, cortical spreading depression (CSD) in MA, with changes in cerebral blood flow and headache, can also occur along with a stroke episode [38]. On the basis of the co-morbidity between migraine and stroke and with the role of homocysteine in disturbing the cerebro-circulatory system, it is possible that the *MTHFR* C677T SNP may represent an important genetic variant for the vascular pathophysiologies of migraine representing both neurovascular conditions.

Similarly, rs1801131 and A1298C SNP can cause a point mutation in *MTHFR* gene at position 1298 and are responsible for encoding glutamine instead of alanine residue [39]. This polymorphism A1298C may affect the enzyme activity of *MTHFR* as well as folate concentrations, although less than those reported in SNP C677T. Additionally, A1298C SNP is located within the regulatory domain of *MTHFR* gene. In the previous studies, it has been shown that individuals homozygous only for the A1298C SNP do not report higher homocysteine levels in serum than that of controls but those who are heterozygous both for the A1298C and C677T SNPs tend to have a similar biochemical profile with C677T homozygotes, showing an increase in homocysteine levels and a decrease in folate concentrations in serum [40]. Hence, the investigation of *MTHFR* polymorphisms and their effects on metabolic pathway of folate has been considered as an interesting topic for research in recent years.

rs11172113

rs11172113, a SNP on chromosome 12q13.3, is located in the first intron of *LRP1* gene. This SNP is responsible for the lipoprotein receptor *LRP1* [41], which further showed interaction with neuronal glutamate receptors in the brain. Hence, this variant also shares a common link with the glutamate pathway via interaction of *LRP1* receptors with NMDA glutamate receptors in migraine. Both previous findings [15, 16] have discussed the role of glutamate in the pathophysiology of migraine and integrated well with various pharmacological approaches that can further target glutamate receptors for migraine treatment [26].

rs10166942

rs10166942, a SNP on chromosome 2q37, is located close to the gene *TRPM8* at the transcription start site. *TRPM8* gene encodes a sensor protein for a cold and cold-induced burning pain [42] that is primarily expressed in sensory neurons and the dorsal root ganglion in the brain [43]. It has been investigated that *TRPM8* can be a target in various animal models with neuropathic pain. As both migraine and neuropathic pain share some features, the role for *TRPM8* variant in this disease as well as its relation between both pain syndromes can be an interesting topic in future for research scientists [44, 45].

rs2651899

rs2651899 SNP, located on chromosome 1p36.32, is in the first intron of *PRDM16* (PR domain containing 16) gene. This gene codes for a zinc finger transcription factor, supposed to be associated with differentiation of brown adipose tissue along with repression of *TGF-β* (transforming growth factor beta) signaling [46, 47], but the role of this gene is still unclear in migraine. More case-control studies with a reasonable number of individuals from different geographical regions are needed to explore the relationship of this SNP with migraine.

rs4379368

rs4379368 SNP, on chromosome 7p14, is found within an intron in the transcript of the *C7orf10* gene and encodes enzyme succinic HMG coenzyme A transferase. It has been reported that mutations in *c7orf10* can cause glutaricaciduria type III which is a rare metabolic abnormality in individuals leading to persistent excretion of glutaric acid [48]. Different SNPs in this gene may differentially control the transcription and/or RNA processing and as a result affecting the risk of migraine [49].

rs10504861

rs10504861, a SNP located on chromosome 8q21, is 200 kb away from the matrix metalloproteinase *MMP16* gene. Metalloproteinase is an extended family of protease enzymes that are responsible for the breakdown of extracellular matrix in various normal physiological processes. This SNP has been linked with an elevated incidence of migraine without aura (MO) in genome-wide association studies (GWAS), as the protein encoded by *MMP16* gene is associated with the cleavage of the low-density lipoprotein receptor protein (*LRP1*) [50]. A SNP within *LRP1* (rs11172113) has already been revealed to be associated with migraine in a genome-wide association study (GWAS). Various studies have recently shown that MT3-MMP encoded by this gene is supposed to cause basal NgR1 (Nogo-66 receptor) shedding in cortical neurons and to increase axonal and synaptic plasticity [51]. Although for the mechanism showing association of *MMP16* to migraines, no conclusive evidence exists so far, these two findings may offer plausible reasons for the biological implication of rs10504861 SNP

in migraine pathology [14, 52]. More case-control studies are needed to associate this SNP with migraine.

rs10915437

The SNP rs10915437, on chromosome 1p36, is present approximately 500 kb telomeric from the adherens junction-associated protein 1 (*AJAP1*) gene and almost 300 kb centromeric from a gene cluster that encodes the apoptosis-related proteins DFFB and TP73 as well as centrosomal protein CEP104. *AJAP1* has been related with tumor invasion and supposed to control the regulation of metalloproteinase activity and is expressed in the brain [53]. Hence, indirectly, this SNP may link with the migraine pathology and much work is required to relate this association.

rs12134493

The SNP rs12134493 is on chromosome 1p13 and located 87 kb 5′upstream of the tetraspanin 2 (*TSPAN2*) gene. This gene encodes a four trans-membrane protein which causes the modulation of development, activation, growth, and movement of cells via the mediation of signal transduction. Esserlind et al. reported another SNP (rs2078371) that is located near gene *TSPAN2* in a GWAS and had shown the genome-wide significance of association with migraine in Danish and Icelandic populations and hence supported the indirect role of this SNP in migraine [14].

rs13208321

The SNP rs13208321, present on chromosome 6q16, is within the four and a half LIM domains protein 5 (*FHL5*) gene. This SNP is reported to influence protein function in cells. *FHL5* gene can encode a transcription factor which further regulates cAMP-responsive elements *CREM* and *CREB* [54], and those have a role to play in synaptic plasticity associated with migraine and memory formation [55, 56].

Another study by Freilinger et al. [57] revealed associations of migraine with four new SNPs and also replicated the findings of previously related associations with *TRMP8* and *LRP1* genes. These new variants with the strongest association at the respective locus were rs3790455 (*MEF2D*) on chromosome1q22, rs7640543 (*TGFBR2*) on chromosome 3p24.1, rs9349379 (*PHACTR1*) on chromosome6p21, and rs6478241 (*ASTN2*) on chromosome 9q33.1. Myocyte enhancer factor 2D (*MEF2D*), a transcription factor, is found to promote the survival of newly formed neurons in the brain [58]. *MEF2D* is also responsible for influencing the number of excitatory synapses in an activity-dependent manner, thus indirectly neuronal excitability, which is a common factor for a migraine candidate gene. Phosphatase and actin regulator 1 (*PHACTR1)* gene is supposed to regulate the activity of PP1 (protein phosphatase 1), which further influences synaptic activity and morphology in migraine [59, 60]. Transforming growth factor β receptor 2(*TGFBR2*) is a serine-threonine kinase enzyme that is active in proliferation, and Astrotactin 2 (*ASTN2)* gene codes for a protein which is supposed to influence neuronal migration [61, 62]. In endothelial samples, only two gene products (*TGFBR2* and *MEF2D*) exhibit moderate or greater expression.

In another study, which mainly reflects the known comorbidity between migraine and cardiovascular diseases [63], it is reported that two of the 12 most proximal genes (*TGFBR2* and *PHACTR1*) have also been related with cardiovascular traits: *TGFBR2* mutations have been found to cause monogenic Marfan's syndrome [64] and to be present in abdominal aortic aneurysms [65], while *PHACTR1* is linked with early onset myocardial infarction [66]. Whereas *TSPAN2* [67], *MEF2D* [68], *TRPM8* [69], *TGFBR2* [70], *PHACTR1* [71], *MMP16* [72], *ASTN2* [62], and *LRP1* [73] genes have been found to be functional in synaptic formation or its regulation. Mutations in *PRDM16* have been linked to oxidative stress response in brain cells and those of *AJAP1* in maintaining tissue borders.

Conclusions

Migraine is a common cause of headache, and early diagnosis and prompt treatment of migraine enhance the quality of life and prevent conversion of episodic migraine to chronic migraine. Single nucleotide polymorphism is a common form of allelic variation in human disease genes. SNPs may act as genomic biomarkers in search for variants that influence susceptibility to migraine. Diagnosis of migraine is still based on questionnaires and neuro-imaging mostly which should be replaced with various biomarkers. These biomarkers could easily be detected from saliva or blood samples of migraineurs by using biochemical or molecular methods. Various SNPs discussed in this review may reveal the phenotypic characters of migraineurs and have implications for functions of proteins coded by mutated genes. Each SNP may be genetically affected to a small group of migraineurs, but each one provides important information about migraine mechanism which can be further applicable to a wider population. These variants may further help in monitoring candidate drug response and in finding new targets for migraine pharmacotherapy. Hence, a better understanding of migraine genetics with rapid whole-genome sequencing in an individual could lead to personalize medicines in migraineurs.

Abbreviations

ACE: Angiotensin I-converting enzyme; AJAP1: Adherens junction-associated protein 1; ASTN2: Astrotactin 2; C7orf10: Chromosome 7 open reading frame 10; CACNA1A: Calcium voltage-gated channel subunit alpha1 A; cAMP: Cyclic adenosine monophosphate; CEP104: Centrosomal protein 104;

CGRP: Calcitonin gene-related peptide; CREB: cAMP response element binding; CREM: cAMP-responsive element modulator; CSD: Cortical spreading depression; CVD: Cardiovascular disease; DFFB: DNA fragmentation factor subunit beta; EAAT2: Excitotoxic amino acid transporter 2; ESR1: Estrogen receptor 1; FHL5: Four and a half LIM domains protein 5; GLT-1: Glutamate transporter 1; GWAS: Genome-wide association study; HMG: Hydroxy methyl glutarate; KCCN3: Potassium calcium-activated channel subfamily *N* member 3; LRP1: Lipoprotein receptor 1; MA: Migraine with aura; MEF2D: Myocyte enhancer factor 2D; MMP16: Matrix metalloproteinase16; MO: Migraine without aura; MT3-MMP: Membrane-type-3 matrix metalloproteinase; MTDH: Metadherin; MTHFR: Methylenetetrahydrofolate reductase; NgR1: Nogo-66 receptor 1; NMDA: *N*-methyl-D-aspartate receptor; *PGCP*: Plasma glutamate carboxypeptidase; PGR: Progesterone; PHACTR1: Phosphatase and actin regulator 1; PP1: Protein phosphatise; PRDM16: PR domain containing 16; SLC1A2: Solute carrier family 1 member 2; SNP: Single nucleotide polymorphism; TCC: Trigemino-cervical complex; TG: Trigeminal ganglion; TGFBR2: Transforming growth factor β receptor 2; *TGF-β*: Transforming growth factor beta; TP73: Tumor protein P73; TRPM8: Transient receptor potential cation channel, subfamily M, member 8; TSPAN2: Tetraspanin 2

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All authors contributed equally in the preparation of the manuscript and read and approved the final version.

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References

1. Kors E, Haan J, Ferrari M. Migraine genetics. Curr Pain Headache Rep. 2003;7:212–7.
2. Stewart WF, Shechter A, Rasmussen BK. Migraine prevalence: a review of population-based studies. Neurology. 1994;44(6 Suppl 4):S17–23.
3. Abu-Arefeh I, Russell G. Prevalence of headache and migraine in school children. BMJ. 1994;309:765–9.
4. Adams AM, Serrano D, Buse DC, Reed ML, Marske V, et al. The impact of chronic migraine: the Chronic Migraine Epidemiology and Outcomes (CaMEO) Study methods and baseline results. Cephalalgia. 2015;35(7):563–78.
5. Arslantas D, Tozun M, Unsal A, Ozbek Z. Headache and its effects on health-related quality of life among adults. Turk Neurosurg. 2013;23(4):498–504.
6. Stovner L, Hagen K, Jensen R, Katsarava Z, Lipton R, et al. The global burden of headache: a documentation of headache prevalence and disability worldwide. Cephalalgia. 2007;27:193–210.
7. Russell MB, Ulrich V, Gervil M, Olesen J. Migraine without aura and migraine with aura are distinct disorders: a population-based twin survey. Headache. 2002;42:332–6.
8. Russell MB, Rasmussen BK, Fenger K, Olesen J. Migraine without aura and migraine with aura are distinct clinical entities: a study of four hundred and eighty-four male and female migraineurs from the general population. Cephalalgia. 1996;16:239–45.
9. Headache Classification Subcommittee of the International Headache Society. The international classification of headache disorders, 3rd Edition (beta version). Cephalalgia. 2013;33(9):629–808.
10. Colson NJ, Lea RA, Quinlan S, Griffiths LR. The role of vascular and hormonal genes in migraine susceptibility. Mol Genet Metab. 2006;88(2):107–13.
11. Fernandez F, Colson NJ, Griffiths LR. Pharmacogenetics of migraine: genetic variants and their potential role in migraine therapy. Pharmacogenomics. 2000;8(6):609 (14).
12. Maher BH, Griffiths LR. Identification of molecular genetic factors that influence migraine. Mol Genet Genomics. 2011;285(6):433–46.
13. Colson N, Fernandez F, Griffiths L. Genetics of menstrual migraine: the molecular evidence. Curr Pain Headache Rep. 2010;14(5):389–95.
14. Esserlind AL, Christensen AF, Le H, Kirchmann M, Hauge AW, et al. Replication and meta-analysis of common variants identifies a genome-wide significant locus in migraine. Eur J Neurol. 2013;20(5):765–72.
15. Chasman DI, Schürks M, Anttila V, Vries B, Schminke U, et al. Genome-wide association study reveals three susceptibility loci for common migraine in the general population. Nat Genet. 2011;43(7):695–8.
16. Anttila V, Stefansson H, Kallela M, Todt U, Terwindt GM, et al. Genome-wide association study of migraine implicates a common susceptibility variant on 8q22.1. Nat Genet. 2010;42(10):869–73.
17. Gormley P, Anttila V, Winsvold BS, Palta P, Esko T, Pers TH, et al. Meta-analysis of 375,000 individuals identifies 38 susceptibility loci for migraine. Nat Genet. 2016;48:856–66.
18. Anttila V, Winsvold BS, Gormley P, Kurth T, Bettella F, McMahon G, et al. Genome-wide meta-analysis identifies new susceptibility loci for migraine. Nat Genet. 2013;45:912–7.
19. Pickrell JK, Berisa T, Liu JZ, Ségurel L, Tung JY, Hinds DA. Detection and interpretation of shared genetic influences on 42 human traits. Nat Genet. 2016;48:709–17.
20. Klimov E, Kondratieva N, Anuchina A, Skorobogatykh K, Azimova J, et al. Genetics of migraine - is there any progress? J Neurol Stroke. 2017;7(4):00245.
21. Goadsby PJ, Classey JD. Glutamatergic transmission in the trigeminal nucleus assessed with local blood flow. Brain Res. 2000;875:119–24.
22. Van den Maagdenberg AM, Haan J, Terwindt GM, Ferrari MD. Migraine: gene mutations and functional consequences. CurrOpinNeurol. 2007;20:299–305.
23. Martinez F, Castillo J, Rodriguez JR, Leira R, Noya M, et al. Neuroexcitatory amino acid levels in plasma and cerebrospinal fluid during migraine attacks. Cephalalgia. 1993;13:89–93.
24. Goadsby PJ. Migraine pathophysiology. Headache. 2005;45(Suppl 1):S14–24.
25. Lauritzen M. Pathophysiology of the migraine aura: the spreading depression theory. Brain. 1994;117(Pt 1):199–210.

26. Andreou AP, Goadsby PJ. Therapeutic potential of novel glutamate receptor antagonists in migraine. Expert Opin Invest Drugs. 2009;18(6):789–803.
27. Greenamyre JT, Young AB, Penney J. Quantitative autoradiographic distribution of L-[3H] glutamate-binding sites in rat central nervous system. J Neurosci. 1984;4(8):2133–44.
28. Kai–Kai MA, Howe R. Glutamate-immunoreactivity in the trigeminal and dorsal root ganglia, and intraspinal neurons and fibers in the dorsal horn of the rat. Histochem J. 1991;23(4):171–9.
29. Peres MF, Zukerman E, SenneSoares CA, Alonso EO, Santos BF, et al. Cerebrospinal fluid glutamate levels in chronic migraine. Cephalalgia. 2004; 24(9):735–9.
30. Rothrock JF, Mar KR, Yaksh TL, Golbeck A, Moore AC. Cerebrospinal fluid analyses in migraine patients and controls. Cephalalgia. 1995;15(6):489–93.
31. Goyette P, Summer JS, Milos R, Ducan AM, Rosenblatt DS, et al. Human methylenetetrahydrofolatereductase isolation of cDNA, mapping and mutation identification. Nat Genet. 1994;7:195–200.
32. Frosst P, Blom HJ, Milos R, Goyette P, Sheppard CA, et al. A candidate genetic risk factor for vascular disease: a common mutation in methylenetetrahydofolatereductase. Nat Genet. 1995;10:111–3.
33. Wald DS, Law M, Morris JK. Homocysteine and cardiovascular disease: evidence on causality from a meta-analysis. BMJ. 2002;325:1202.
34. Coull BM, Malinow MR, Beamer N, Sexton G, Nordt F, et al. Elevated plasma homocysteine concentrations as a possible independent risk factor for stroke. Stroke. 1990;21:572–6.
35. Kelly PJ, Rosand J, Kistler JP, Shih VE, Silveira S, et al. Homocysteine, MTHFR 677C-->T polymorphism, and risk of ischemic stroke: results of a meta-analysis. Neurology. 2002;59:529–36.
36. Schwaag S, Nabavi DG, Frese A, Husstedt IW, Evers S. The association between migraine and juvenile stroke: a case-control study. Headache. 2003;43:90–5.
37. Donaghy M, Chang CL, Poulter NJ. Duration, frequency, recency, and type of migraine and the risk of ischaemic stroke in women of childbearing age. NeurolNeurosurg Psychiatry. 2002;73:747–50.
38. Tzourio C, Iglesias S, Hubert JB, Visy JM, Alperovitch A, et al. Migraine and risk of ischaemic stroke: a case-control study. PMID. 1993;31:289–92.
39. Weisberg IS, Jacques FP, Selhub J, Bostom AG, Chen Z, et al. The 1298A→C polymorphism in methylenetetrahydrofolatereductase (MTHFR): in vitro expression and association with homocysteine. Atherosclerosis. 2001;156:409–15.
40. Friedman G, Goldschmidt N, Friedlander Y, Ben-Yehuda A, Selhub J, et al. A common mutation A1298C in human methylenetetrahydrofolatereductase gene: association with plasma total homocysteine and folate concentrations. JNutr. 1999;129(9):1656–61.
41. Lillis AP, Duyn LB, Murphy-Ullrich JE, Strickland DK. LDL receptor-related protein 1: unique tissue-specific functions revealed by selective gene knockout studies. Physiol Rev. 2008;88(3):887–918.
42. Proudfoot CJ, Garry EM, Cottrell DF, Rosie R, Anderson H, et al. Analgesia mediated by the TRPM8 cold receptor in chronic neuropathic pain. CurrBiol. 2006;16(16):1591–605.
43. Peier AM, Moqrich A, Hergarden AC, Reeve AJ, Andersson DA, et al. A TRP channel that senses cold stimuli and menthol. Cell. 2002;108(5):705–15.
44. Dray A. Neuropathic pain: emerging treatments. Br J Anaesth. 2008;101(1): 48–58.
45. Biondi DM. Is migraine a neuropathic pain syndrome? Curr Pain Headache Rep. 2006;10(3):167–78.
46. Seale P, Bjork B, Yang W, Kajimura S, Chin S, et al. PRDM16 controls a brown fat/skeletal muscle switch. Nature. 2008;15:961–7.
47. Takahata M, Inoue Y, Tsuda H, Imoto I, Koinuma D, et al. SKI and MEL1 cooperate to inhibit transforming growth factor-beta signal in gastric cancer cells. J BiolChem. 2009;15:3334–44.
48. Sherman EA, Strauss KA, Tortorelli S, Bennett MJ, Knerr I, et al. Genetic mapping of glutaricaciduria, type 3, to chromosome 7 and identification of mutations in c7orf10. Am J Hum Genet. 2008;83:604–9.
49. Marlaire S, Van Schaftingen E, Veiga-da-Cunha M. C7orf10 encodes succinate-hydroxymethylglutarate CoA-transferase, the enzyme that converts glutarate to glutaryl-CoA. J Inherit Metab Dis. 2004;37(1):13–9.
50. Rozanov DV, Hahn-Dantona E, Strickland DK, Strongin AY. The low density lipoprotein receptor-related protein LRP is regulated by membrane type-1 matrix metalloproteinase (MT1-MMP) proteolysis in malignant cells. J BiolChem. 2004;279:4260–8.
51. Borrie SC, Baeumer BE, Bandtlow CE. The Nogo-66 receptor family in the intact and diseased CNS. Cell Tissue Res. 2012;349:105–17.
52. Schreiner A, Ruonala M, Jakob V, Suthaus J, Boles E, et al. Junction protein shrew-1 influences cell invasion and interacts with invasion-promoting protein CD147. MolBiol Cell. 2007;18:1272–81.
53. Lafleur MA, Xu D, Hemler ME. Tetraspanin proteins regulate membrane type-1 matrix metalloproteinase-dependent pericellular proteolysis. MolBiol Cell. 2009;20(7):2030–40.
54. Fimia GM, De Cesare D, Sassone-Corsi P. A family of LIM-only transcriptional coactivators: tissue-specific expression and selective activation of CREB and CREM. Mol Cell Biol. 2000;20:8613–22.
55. Dash PK, Hochner B, Kandel ER. Injection of the cAMP-responsive element into the nucleus of Aplysia sensory neurons blocks long-term facilitation. Nature. 1990;345:718–21.
56. Lee YS, Silva AJ. The molecular and cellular biology of enhanced cognition. Nat Rev Neurosci. 2009;10:126–40.
57. Freilinger T, Anttila V, De VB, Malik R, Kallela M, et al. Genome-wide association analysis identifies susceptibility loci for migraine without aura. Nat Genet. 2012;15:777–82.
58. Flavell SW, Cowan CW, Kim TK, Greer PL, Lin Y, et al. Activity-dependent regulation of MEF2 transcription factors suppresses excitatory synapse number. Science. 2006;15:1008–12.
59. Allen PB, Greenfield AT, Svenningsson P, Haspeslagh DC, Greengard P. Phactrs 1–4: a family of protein phosphatase 1 and actin regulatory proteins. ProcNatlAcadSci U S A. 2004;15:7187–92.
60. Greengard P, Allen PB, Nairn AC. Beyond the dopamine receptor: the DARPP-32/protein phosphatase-1 cascade. Neuron. 1999;15:435–47.
61. Lin HY, Wang XF, Ng-Eaton E, Weinberg RA, Lodish HF. Expression cloning of the TGF-beta type II receptor, a functional transmembrane serine/ threonine kinase. Cell. 1992;15:775–85.
62. Wilson PM, Fryer RH, Fang Y, Hatten ME. Astn2, a novel member of the astrotactin gene family, regulates the trafficking of ASTN1 during glial-guided neuronal migration. J Neurosci. 2010;15:8529–40.
63. Schürks M, Rist PM, Bigal ME, Buring JE, Lipton RB, et al. Migraine and cardiovascular disease: systematic review and meta analysis. BMJ. 2009;339:b3914.
64. Mizuguchi T, Collod-Beroud G, Akiyama T, Abifadel M, Harada N, et al. Heterozygous TGFBR2 mutations in Marfan syndrome. Nat Genet. 2004;36: 855–60.
65. Biros E, Walker PJ, Nataatmadja M, West M, Golledge J. Downregulation of transforming growth factor, beta receptor 2 and Notch signaling pathway in human abdominal aorticaneurysm. Atherosclerosis. 2012;221:383–6.
66. Kathiresan S, Voight BF, Purcell S, Musunuru K, Ardissino D, et al. Genome-wide association of early-onset myocardial infarction with single nucleotide polymorphisms and copy number variants. Nat Genet. 2009;41:334–41.
67. Terada N, Baracskay K, Kinter M, Melrose S, Brophy PJ, et al. The tetraspanin protein, CD9, is expressed by progenitor cells committed to oligodendrogenesis and is linked to beta1 integrin, CD81, and Tspan-2. Glia. 2002;40:350–9.
68. Flavell SW, Kim TK, Gray JM, Harmin DA, Hemberg M, et al. Genome-wide analysis of MEF2 transcriptional program reveals synaptic target genes and neuronal activity-dependent polyadenylation site selection. Neuron. 2008;60:1022–38.
69. Tsuzuki K, Xing H, Ling J, Gu JG. Menthol-induced Ca2+ release from presynaptic Ca2+ stores potentiates sensory synaptic transmission. J Neurosci. 2004;24:762–71.
70. Diniz LP, Almeida JC, Tortelli V, Vargas Lopes C, Setti-Perdigão P, et al. Astrocyte-induced synaptogenesis is mediated by transforming growth factor beta signaling through modulation of D-serine levels in cerebral cortex neuron. J BiolChem. 2012;287(49):41432–41,445.
71. Allen PB, Greenfield AT, Svenningsson P, Haspeslagh DC, Greengard P. Phactrs. 1–4: a family of protein phosphatase 1 and actin regulatory proteins. ProcNatlAcad Sci USA. 2004;101:7187–92.
72. Ferraro GB, Morrison CJ, Overall CM, Strittmatter SM, Fournier AE. Membrane-type matrix metalloproteinase-3 regulates neuronal responsiveness to myelin through Nogo-66 receptor 1 cleavage. J BiolChem. 2011;286:31418–24.
73. May P, Rohlmann A, Bock HH, Zurhove K, Marth JD, et al. Neuronal LRP1 functionally associates with postsynaptic proteins and is required for normal motor function in mice. Mol Cell Biol. 2004;24:8872–83.

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