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Review article

Biomarkers of migraine: Part 1 – Genetic markers

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ABSTRACT

Background: Migraine is a multifactorial socially significant disease affecting the peripheral and central nervous system. The diagnosis of "migraine" is still the only clinical, and additional methods of inspection are only required to avoid secondary headaches if certain "signs of danger". Accordingly, the search for biomarkers of migraine, confirming the diagnosis, rather than refuting others, is the leading vector in this scientific field.
Aim: In this paper we have analyzed the literature data on the genetic markers associated with migraine.
Methods: List of genes was compiled using Pathway Studio 10® software and abstract database ResNet12 ® made by Elsevier. Addition search (last time on 15 March 2016) was performed by using PubMed or TargetInsights. Information about 185 polymorphic loci in 98 genes associated with migraine was extracted and described.
Results: The genes associated with migraine could be classified into 8 major groups: homeostasis of blood vessels - 26.5%, metabolism of neurotransmitters - 11.2%, transport and reception of neurotransmitters - 24.5%, neurogenesis - 5.1%, inflammation - 8.2%, sex hormones - 5.1%, ion channels and membrane potential - 11.2%, other - 8.2%.
Conclusion: These findings parallel the range of mechanisms implicated in migraine pathogenesis.

Contents

1. Introduction

Reliable biomarkers of migraine, especially genetic markers, will allow predicting predisposition to the disease and its severity. This study provides the information about genetic markers associated with migraine.

The original list of genes was compiled using Pathway Studio 10 ® software and abstract database ResNet12 ® made by Elsevier. ResNet12 ® database contains information from literature sources freely available on the Internet, as of December, 2015. All genes found by the program to have "GeneticChange" relationship with migraine were selected, to the total of 148 genes. The amount of referenced articles was 497; 3 or less articles referenced 115 relations (80 relations – 1 reference). Addition search (last time on 15 March 2016) was performed by using PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) or TargetInsights (https://demo.elseviertextmining.com/).

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Table 1
Genes associated with migraine. Description is in the text.

Official symbol	Probable reasons for association with migraine	Markers	Sample parameters	Comments/reference
ACE (angiotensin I converting enzyme)	Regulates arterial pressure level by indirect activation of strong vasoconstrictors and vasodilators.	rs1799752	MWOA = 1951, MWA = 1275, nC = 20423. USA.	Increased risk of CVD (cardiovascular disease) among patients with MWA having DD, DI genotypes. [1]
			nP = 502, nC = 323. Italy.	Genotype II affects the clinical pattern of the disease that is associated with a reduction in the use of prophylactic agents in patients with MWA and chronic migraine. [2]
			nP = 240, nC = 200. Taiwan.	DD genotype is protective in males. [3]
			nP = 53, nC = 22. Turkey.	DD genotype is more common in patients with MWA. [4]
			nP = 302, nC = 201. Italy.	The frequency of DD genotype is higher in MWOA ($P < 0.05$). The incidence of migraine (average number of attacks per week) is greater in patients with DD, than in patients with ID ($P < 0.05$). ACE activity in plasma is increased in patients with DD. [5]
			ACE: nP = 6120 (MWA = 1761; MWOA = 2853), nC = 22,310.	II is a protective genotype. [6]
			nP = 254 (MWA = 54, MWOA = 122, TH = 78), nC = 248. Japan.	D allele and DD genotype ($P < 0.01$) are more common in patients with MWA. [7]
			nP = 91 (MWA = 24, MWOA = 67), nC = 119. Japan.	The distribution of genotypes II + ID vs DD differed in the group of patients with migraine ($P = 0.082$) and MWA ($P = 0.025$) as compared to the control group. [8]
		Interaction with MTHFR	nP = 103 (MWOA = 81, MWA = 9, MAO = 13), nC = 336 (CC3). Italy.	MTHFR and ACE polymorphism is associated with migraine. [9]
		rs1799752, interaction with MTHFR (rs1801133) and vWF	MWA = 61, MWOA = 64. USA.	Patients with DD (ACE) genotype had a high level of vWF activity (152%) as compared with ID and II genotypes. The level was higher (179%) in the combined ACE DD and MTHFR TT genotype. ACE DD genotype was associated with a high incidence of headaches. [10]
		rs4646994, interaction with MTHFR (rs1801133)	nP = 150, nC = 220 patients with non-migraine headache headache (disease control), nC = 150 normotensive. India.	ACE DD genotype is associated with MWA, but insignificantly in women with MWA as compared to the control group. DD * CT (MTHFR, rs1801133) positive association in patients with common MWA, women with MWA as compared with the control. [11]
			nP = 270 (MWA = 63%, MWOA = 37%), nC = 270. Australia.	DD/ID genotype (rs4646994) is more common in the group with migraine as compared to the control group ($P = 0.048$). The combination of TT (MTHFR, rs1801133) and ID/DD genotypes (ACE) increases the risk of migraine ($P = 0.018$), especially MWA ($P = 0.002$). [12]
		rs4646994, interaction with MMP3 (−1171 5 A > 6 A)	nP = 180 (MWOA = 109, MWA = 59, basilar type = 10, complicated = 2), nC = 210. Turkey.	Interaction between ACE (287 bp ID) and MMP3 (-1171 5A> 6A) is associated with migraine. Combined DD/5A5A and ID/5A5A genotypes increase the risk of migraine. Genotypes II and/or 6A6A are protective. [13]
ADH1B (alcohol dehydrogenase 1B (class I), beta polypeptide)	Takes part in metabolism of dopamine	rs1229984	nP = 197 (MWA = 98, MWOA = 99), nC = 255. Spain.	The frequency of Arg/His genotype and His allele is significantly lower in patients than in controls. The frequency of His allele is significantly higher among patients whose migraine trigger is alcohol. [14]
ANKK1 (ankyrin repeat and kinase domain containing 1)	Is involved in signal transduction	rs1800497, interaction with rs7239728 (DBH)	nP1 = 208, nP = 127, nC = 200.	rs1800497 results in reduced aggregation of ANKK1 protein. Interaction with rs7239728 (DBH) increases the risk of migraine. [15]
AOC1 (amine oxidase, copper containing 1)	Is involved in histamine metabolism	rs2052129, rs10156191, rs1049742, rs1049793	nP = 197, nC = 245. Spain.	Genotype CC of rs10156191 (related to decreased DAO enzyme activity) is associated with the risk of developing migraine (OR = 1.61), particularly in women (OR = 2.08). [16]
APEX1 (APEX nuclease (multifunctional DNA repair enzyme) 1)	Participates in DNA reparation	rs3136820	nP = 135 (MWOA = 88, MWA = 47), nC = 101. Turkey.	The frequency of genotypes differed significantly in patients with migraine as compared to the control group ($P = 0.048$). T+ genotype increases the risk of migraine ($P = 0.026$). [17]
APOE (apolipoprotein E)	The expression of molecules involved in headache pathogenesis (nitric oxide and interleukin) occurs under influence of apolipoprotein E (ApoE) and is gene-specific	E2-E4 HhaI polymorphism	nP = 241 (MWA = 18, MWOA = 135, mixed headaches (migraine associated with TH) =88), nC = 587. Italy.	ε2–ε4 genotype is significantly increased only in patients with mixed headaches. [18]
			nP = 50, nP = 50 (TH), nC = 50. India.	ε2 increases the risk of migraine in comparison to the control group ($P < 0.001$) and TH ($P = 0.01$). ε4 is protective. [19]
			nP = 217, nP = 179 TH. nC = 217. India.	E3E4 and E2E3 genotypes are associated with common migraines and MWA. [20]
ASTN2 (astrotactin 2)	Takes part in glia-controlled migration and alterations in architecture of brain cortex regions	rs6478241	1) nP = 2326 with MWOA, nC = 4580. Germany and Netherlands. 2) nP = 2508 with MWOA, nC = 2652. Europe.	Association with MWOA ($P < 0.05$). [21]

Table 1 (*continued*)

Official symbol	Probable reasons for association with migraine	Markers	Sample parameters	Comments/reference
BDNF (brain-derived neurotrophic factor)	BDNF protein interacts with CALCA. It takes part in generation and modulation of pain	rs2049046, interaction with CGRP (rs1553005)	nP = 188 (MWA = 77, MWOA = 111), nC = 287. Portugal.	Combined presence of AT (BDNF) and GC (CGRP) genotypes increases the risk of migraine. [22]
		rs2049046	nP = 855 (MWOA = 210. MWA = 645), nC = 857. Australia.	An increased frequency of TT genotype and allele T in migraine patients (P = 0.013), in particular with MWA (P = 0.015), as compared to controls. [23]
CACNB2 (calcium channel, voltage-dependent, beta 2 subunit)	Involved in ion homeostasis, plays important role in neuronal excitability	rs7076100, interaction with KCNB2 (rs1431656)	1) nP = 841 MWA, nC = 884. Finland. 2) nP = 2835, nC = 2740. Netherlands, Germany, Australia.	Interaction between rs1431656 (KCNB2) and rs7076100 (CACNB2) increases the risk of migraine. [24,25]
CACNB4 (calcium channel, voltage-dependent, beta 4 subunit)		D29D	nP = 14, nC = 46. USA.	A silent substitution of D29D was found in 2 patients, and was not found in any control sample. [26]
CALCA (=CGRP) (calcitonin-related polypeptide alpha = calcitonin gene-related peptide)	Has a vasodilatory effect, is responsible for neurogenic inflammation and vasodilation of cranial blood vessels in the pathophysiology of migraine. Is associated with the activation of the trigeminal vascular system	rs1553005, interaction with BDNF (rs2049046)	nP = 188 (MWA = 77, MWOA = 111), nC = 287. Portugal.	The combined presence of AT (rs2049046, BDNF) and GC (rs1553005, CGRP) genotypes increases the risk of migraine. [22]
CCKAR (cholecystokinin A receptor)	Regulates the release of beta-endorphin and dopamine	rs1800857	nP = 144, nC = 197. Russia.	Association of C allele with migraine ($p < 10^{-10}$). [27]
CNR1 (cannabinoid receptor 1 (brain))	Has an inhibitory effect on the trigeminal vascular activation	rs806369, rs1049353, rs4707436, rs12720071, rs806368, rs806366, rs7766029, rs806379, rs1535255, rs2023239	nP = 195, nC = 684. USA.	10 SNP haplotype are associated with migraine (P = 0.008). rs7766029 T allele (P = 0.063) and rs806368 C/C genotype (P = 0.008) were in association with migraine. [28]
COMT (catechol-*O*-methyltransferase)	Inactivates catecholamines and catecholamine-containing drugs	rs4680	2 nP samples: 1) 75 patients with MWOA were treated with frovatriptan. 2) 123 patients were treated with other triptans. Italy.	rs4680 affects the clinical response to drugs. Met/Met increases the risk of a weak response to triptans. [29]
			nP = 62 (MWA = 33, MWOA = 29), nC = 64. Turkey.	L/H (Met/Val) and L/L (Met/Met) genotypes are more common in migraine patients (P = 0.013). L/L (Met/Met) genotype was more common in patients with family history of migraine (P = 0.003). [30]
			nP = 97 MWOA, nC = 94. Korea.	L allele is associated with headache intensity (P = 0.001) and the incidence of accompanying nausea/vomiting (P = 0.026). [31]
CSNK1D (casein kinase 1, delta)	Association with CSD (cortical spreading depression)	p.Thr44Ala, p.His46Arg	USA.	2 families with migraine and an early onset of sleep phase, carrying missense mutations T44 A and H46R, were found. As a result of mutations, a decrease in enzyme activity is observed. [32]
CYP1A2 (cytochrome P450. family 1, subfamily A, polypeptide 2)	Metabolizes triptans	rs762551	nP = 104. Italy.	Association with chronic migraine. [33]
CYP19A1 (cytochrome P450. family 19, subfamily A, polypeptide 1)	Catalyzes the final step of estrogen biosynthesis	rs10046, rs4646, interaction with ESR1 (rs2234693, rs9340799)	nP1 = 207, nP2 = 127, nC = 200. India.	rs10046 - T allele and TT genotype are associated with migraine; rs4646 - protective effect of T allele in patients with MWA. The combination of heterozygous ESR1 variants (rs2234693 and rs9340799) - CYP19A1 (rs10046) is associated with migraine, while genotype CYP19A1 (rs4646) - ESR1 (rs9340799) has a protective effect. [34]
		interaction with ESR2 (rs1271572)	nP1 = 207, nP2 = 127, nC = 200. India.	CYP19A1 rs10046 - ESR2 rs1271572 interaction increases the risk of susceptibility to migraine. [34]
DBH (dopamine beta-hydroxylase (dopamine beta-monooxygenase))	Dopamine plays an important role in the pathophysiology of migraine, antimigraine agents (neuroleptics) affect the dopamine system The dopamine hypothesis of migraine development	STR (AC)n	nP = 177 (MWA = 98, MWOA = 79), nC = 182. Australia.	The distribution of (AC)n alleles is associated with migraine (P = 0.019). [35]
		rs141116007	nP = 275, nC = 275. Australia.	Association with migraine (P = 0.011), in particular with MWA (P = 0.003). Risk of migraine is 3-fold higher in men with DD genotype than in women. [36]
			nP = 301 (MWOA = 202, MWA = 99), nC = 202. India.	DD genotype has a significant association with migraine (P = 0.027), especially in women (P = 0.016). [37]

(*continued on next page*)

Table 1 (*continued*)

Official symbol	Probable reasons for association with migraine	Markers	Sample parameters	Comments/reference
	is based on the signs of central dopamine hypersensitivity in patients with migraine and the presence of effects of dopamine on the nociceptive system, vascular tone and autonomic responses.	rs2097629	nP = 270 + 380 (MWA), nC = 272 + 378. Germany.	Association with MWA (P = 0.0116). [38]
		rs7239728, interaction with ANKK1 (rs1800497)	nP1 = 208 nP2 = 127, nC = 200.	rs7239728 has a significant association with migraine, the interaction between rs7239728 and rs1800497 (ANKK1) increases the risk of migraine. [15]
		rs1611115	1) nP = 200 (MWA = 115, MWOA = 85), nC = 200; 2) nP = 300. nC = 300. Australia.	A significant association with migraine. [39]
DRD2 (dopamine receptor D2)		rs7131056	nP = 270 + 380 (MWA), nC = 272 + 378. Germany.	Association with MWA (P = 0.0058). [38]
		NcoI polymorphism	nP = 129 (MWA = 52, MWOA = 77), nC = 121. USA.	The frequency of C allele is increased in patients with MWA (P < 0.005) as compared to the control group. [28]
		rs6275	nP1 = 208 nP2 = 127, nC = 200.	T allele reduces the risk of migraine. [15]
DRD3 (dopamine receptor D3)		rs6280	nP = 197, nC = 282. Spain.	The frequency of Gly9Gly9 genotype was significantly higher in patients with MWA as compared with MWOA patients. [40]
DRD4 (dopamine receptor D4)		exon 3 VNTR	190 families with migraine (MWOA = 145, MWA = 45). Great Britain.	Seven-repeat allele is a protective factor against migraine without aura. [41]
		48-base-pair tandem repeat in exon 3	nP = 194 (MWA = 93, MWOA = 101), nC = 117. Italy.	The distribution of alleles in the MWOA group is significantly different from that in MWA groups (P = 0.002) and controls (P = 0.053). [42]
			nP = 101 c MWOA, nC = 117. Italy.	A significant association with MWOA. [43]
EDN1 (endothelin 1)	Potent vasoactive mediator	rs2070699, rs1626492	Women. nP = 312 (MWA = 243, MWOA = 69), nC = 407. USA.	Substitutions of rs2070699 and rs1626492 are associated with MWA (P = 0.03, P = 0.02). [44]
EDNRA (endothelin receptor type A)	Potent vasoconstrictor	-231G > A	nP = 440, nP = 222 (TH). nC = 1323.	Association of AA genotype with migraine. [45]
			nP = 217, nP = 179 (TH). nC = 217. India.	AA genotype and A allele are associated with common migraines and MWOA. [20]
EDNRB (endothelin receptor type B)	Regulation of vascular tone and cerebral circulation	rs9544636	Women. nP = 312 (MWA = 243, MWOA = 69), nC = 407. USA.	Association with migraine (P = 0.02). [44]
ESR1 (estrogen receptor 1)	Expressed in trigeminal neurons; receptors are associated with the hormonal system	rs2234693	nP = 217 (MWA = 84, MWOA = 133), nP = 179 (TH), nC = 217. India.	Association of TT genotype (P = 0.0003) and T allele (P = 0.0001) with migraine, especially in women (P = 0.002) and in patients with MWA (P = 0.002, P = 0.001). [46]
		rs6557170, rs2347867, rs6557171, rs4870062, rs1801132	nP = 898 MWA, nC = 900. Finland.	Association of 5 SNP of ESR1 gene (rs6557170. Rs2347867, rs6557171, rs4870062 and rs1801132) with MWA (P = 0.007–0.034). [47]
		rs2234693, rs9340799, interaction with CYP19A1 (rs10046, rs4646)	nP1 = 207; nP2 = 127. nC = 200. India.	rs2234693 – association with MWA. The combination of heterozygous variants of ESR1 (rs2234693 and rs9340799) - CYP19A1 (rs10046) is associated with migraine, while CYP19A1 (rs4646) - ESR1 (rs9340799) has a protective effect. [34]
		interaction with ESR2, FSHR	nP = 356 (MWA = 198, MWOA = 158), nC = 374. Spain.	ESR2-ESR1-FSHR interaction is associated with MWA. [48]
		p.Gly594Ala	1) nP = 224, nC = 224. 2) nP = 260, nC = 260. Australia.	Associated with susceptibility to migraine. [49]
			nP = 91 (MWA = 24, MWOA = 67), nC = 119. Japan.	The distribution of G594A genotypes (P = 0.001) differed in patients with migraine and controls. The distribution of G594A genotypes (P = 0.001) differed in the group with MWOA and controls. [8]
		p.Gly325Cys	Spain.	In women, increases the risk of migraine 3-fold. [50]
ESR2 (estrogen receptor 2)		interaction with ESR1, FSHR	nP = 356 (MWA = 198, MWOA = 158), nC = 374. Spain.	ESR2-ESR1-FSHR interaction is associated with MWA. [48]
		rs1271572, interaction with CYP19A1 (rs10046)	nP1 = 207; nP2 = 127. nC = 200. India.	CYP19A1 rs10046- ESR2 rs1271572 interaction increases the risk of susceptibility to migraine. [34]

Table 1 (*continued*)

Official symbol	Probable reasons for association with migraine	Markers	Sample parameters	Comments/reference
F2 (coagulation factor II (thrombin))	During migraine attacks, the activation of platelets and plasma coagulation increases	rs1799963	nP = 294 (MWA = 71, MWOA = 223). nC = 1162. France.	Association with MWA (P = 0.04). [51]
F5 (coagulation factor V (proaccelerin, labile factor))		rs6025	nP = 35 (children), nC = 50. Italy.	Increases the risk of migraine. [52]
			nP = 294 (MWA = 71, MWOA = 223), nC = 1162. France.	Association with MWA (P = 0.04). [51]
FHL5 (four and a half LIM domains 5)	Spermatid's specific transcription factor, involved in spermatogenesis	rs11759769, rs2983896	nP = 2328, nC = 95,425. Europe. IHGC GWA meta-analysis.	Association of allele A of rs11759769 with MWA. Association of allele A of rs2983896 with MWOA. [53]
FSHR (follicle stimulating hormone receptor)	Associated with the hormonal system	interaction with ESR2, ESR1	nP = 356 (MWA = 198, MWOA = 158), nC = 374. Spain.	Association with MWA as part of haplotypes ESR1-ESR2 (P = 0.009), ESR2-FSHR (P = 0.011), and ESR2-ESR1-FSHR (P = 0.037). [48]
GABRA3 (gamma-aminobutyric acid (GABA) A receptor, alpha 3)	GABA is the major inhibitory neurotransmitter in the brain; disorders of this system may cause increased neuronal excitability	rs3902802, rs2131190	nP = 188 (MWA = 77, MWOA = 111), nC = 286. Portugal.	CT (rs3902802) and GA (rs2131190) genotypes are protective (P = 0.006, P = 0.013). [54]
GABRQ (gamma-aminobutyric acid (GABA) A receptor, theta)		rs3810651	nP = 188 (MWA = 77, MWOA = 111), nC = 286. Portugal.	AT genotype is associated with an increased risk of migraine (P = 0.002). [54]
GRIA1 (glutamate receptor, ionotropic, AMPA1)	Involved in excitability needed for CSD and activation of the trigeminal vascular system	rs2195450, rs548294	nP = 244 (MWA = 135, MWOA = 109), nC = 260. Italy.	rs2195450 is associated with MWA (P = 0.00002). rs548294 is associated with MWOA (P = 0.0003). [55]
		rs2195450	nP = 331 (female), nC = 330 (female). Han-Chinese.	rs2195450 allele C is associated with migraine (P = 0.001), also allele C associated with MWA (P = 0.012, compared with control) and MWOA (P = 0.002, compared with control). [56]
GRIA3 (glutamate receptor, ionotropic, AMPA3)		rs3761555	nP = 472, nC = 472. Australia.	Associated with MWOA (P = 0.008). [57]
			nP = 244 (MWA = 135, MWOA = 109), nC = 260. Italy.	Associated with MWA (P = 0.0001). [55]
HCRTR1 (hypocretin (orexin) receptor 1)	Acts via PKC to phosphorylate voltage-activated calcium channels	rs2271933	nP = 384 (MWA = 54, MWOA = 330), nC = 259. Italy.	The presence of A allele was associated with an increased risk of migraine, including MWOA. [58]
HFE (hemochromatosis)	Involved in the regulation of iron	p.His63Asp	nP = 256, nC = 237. Italy.	Patients carrying the Asp/Asp genotype showed a later age of onset and an increased number of migraine attacks. [59]
HLA-DRB1 (major histocompatibility complex, class II, DR beta 1)	Association of migraine with certain diseases related to the HLA system, such as asthma and narcolepsy	HLA-DRB1 alleles	nP = 255 (MWA = 41, MWOA = 214), nC = 325. Italy.	The frequency of DRB1*12 allele is significantly decreased (P = 0.02) in patients with migraine, while that of DRB1*16 allele is significantly increased ($P = 0.04$) as compared to the control group. The frequency of HLA-DRB1** 16 allele is significantly increased (P < 0.05) in MWOA. [60,61]
HRH3 (histamine receptor H3)	Histamine H3 receptor activation blocks the release of peptides responsible for headache	p.Ala280Val	nP = 147, nC = 186. Mexico.	Frequencies of VV and VA genotypes is higher in patients with migraine, as compared to the control group (P = 0.001). VV and VA are risk genotypes. [62]
HTR1A (5-hydroxytryptamine (serotonin) receptor 1A, G protein-coupled)	Involved in 5-HT-induced vasoconstriction	1019C>G	nP = 197 (MWA = 98, MWOA = 99), nC = 117. Germany.	GG genotype is associated with avoidance of physical activity during a migraine attack (P = 0.008). [63]
HTR1B (5-hydroxytryptamine (serotonin) receptor 1B, G protein-coupled)		861G>C	nP = 197 (MWA = 98, MWOA = 99), nC = 117. Germany.	CC genotype is associated with the intensity of headache attacks (P < 0.05). [63]
			nP = 91 (MWA = 24, MWOA = 67), nC = 119. Japan.	Genotypic distribution of G861C (P = 0.040) differed in the MWA group and controls. [8]
HTR2A (5-hydroxytryptamine (serotonin) receptor 2A, G protein-coupled)		rs2070040	nP = 82 (MWA = 20. MWOA = 62), nC = 115. Japan.	Genotype AA is more common in MWA, than in MWOA. [64]
		102 T > C	nP = 61, nC = 44. Turkey.	It may be involved in the formation of aura —C/C genotype prevailed in MWA (P = 0.02), while C/T and T/T genotypes prevailed in MWOA (P < 0.01). [65]
ICAM1 (intercellular adhesion molecule 1)	Association of cytokines with neurogenic inflammation in the pathogenesis of migraine; a central role in enhancing the inflammatory cascade	rs5498	nP = 114 (MWOA = 80. MWA = 34), nC = 125. China.	The frequencies of EE genotype and E alleles are higher in patients with migraine, in particular with MWOA, as compared to the control group (P < 0.01). Serum ICAM1 level is significantly increased in patients with migraine as compared to the control group (P < 0.01). [66]
IL1A (interleukin 1, alpha)		889C > T	nP = 269. Italy.	In patients with TT genotype, migraine attacks begin about 10 years earlier. [67]
IL1B (interleukin 1, beta)		rs1143634	nP = 67 c MWOA, nC = 96. Turkey.	+3953T allele is more common in patients with MWOA, than in controls (P = 0.004). [68]

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Table 1 (*continued*)

Official symbol	Probable reasons for association with migraine	Markers	Sample parameters	Comments/reference
INSR (insulin receptor)	It affects the brain metabolism and cerebral blood flow	rs2860172, rs2860174, rs1799817, rs2860183, SNP265	Populations of North America: nP = 827, nC = 765. Australian populations: nP = 275, nC = 275. Great Britain.	A significant association of 5 substitutions with migraine. Minor alleles rs2860172 (=SNP84), rs2860174 (=SNP90), rs1799817 (=SNP274), rs2860183 (=SNP81) are associated with migraine. Minor allele SNP265 is protective. [69]
KCNAB3 (potassium voltage-gated channel, shaker-related subfamily, beta member 3)	Involved in ion homeostasis, plays an important role in neuronal excitability	p.Arg187Cys	nP = 110. nC = 250. Canada.	Found only in migraine patients. [70]
KCNB2 (potassium voltage-gated channel, Shab-related subfamily, member 2)		rs13276133, interaction of rs1431656 and rs7076100 (CACNB2)	1) nP = 841 MWA, nC = 884. Finland. 2) nP = 2835, nC = 2740. Netherlands, Germany, Australia.	rs13276133 – association with MWA (P = 0.00041). Interaction between rs1431656 (KCNB2) and rs7076100 (CACNB2) increases the risk of migraine development. [24]
KCNG4 (potassium voltage-gated channel, subfamily G, member 4)		p.Leu360Pro	nP = 110. nC = 250. Canada.	Found only in migraine patients. [70]
KCNJ10 (potassium inwardly-rectifying channel, subfamily J, member 10)		rs1130183	nP = 243 (MWA = 85%, MWOA = 15%), nC = 243 Australia.	Association with migraine (P = 0.02). [71]
KCNK18 (potassium channel, subfamily K, member 18) TRESK		p.F139WfsX24	nP = 110	Frameshift mutation (F139WfsX24) is associated with familial MWA. [72]
		p.Phe139TrpfsX24	nP = 110, nC = 250. Canada.	Found only in migraine patients. [70]
KCNN3 (potassium intermediate/small conductance calcium-activated channel, subfamily N, member 3)	Regulates neuronal hyperpolarization after an action potential; calcium-activated	rs4845663, rs7532286, rs6426929, rs1218551	285 subjects, of them 76 with migraine. Norfolk Island.	rs4845663, rs7532286, rs6426929 and rs1218551 substitutions are associated with migraine (P < 0.05). [73]
		polyglutamine site	nP = 190 (MWA = 93, MWOA = 97), nC = 232. Germany	Allele 15 of polyglutamine site increases the risk 12-fold (P = 0.025). [74]
LDLR (low density lipoprotein receptor)	Is involved in the binding and internalization of cholesterol	G142A in exon 10, (TA)n in the 3′ UTR in exon 18	nP = 360, nC = 200. Italy.	Significant differences in the distribution of the LDLR (TA)n alleles (allele 4), in MO patients versus both controls and the MA subgroup. [75]
LRP1 (low density lipoprotein receptor-related protein 1)	Is involved in the proliferation of vascular smooth muscle cells, modulates synaptic transmission	rs11172113	nP = 340, nC = 200. India.	Allele C is protective (P = 0.009). [76]
			1) nP = 2326 c MWOA, nC = 4580. Germany and Netherlands. 2) nP = 2508 c MWOA, nC = 2652. Europe.	Association with MWOA (P < 0.05). [21]
			nP = 5122, nC = 18,108. USA.	Associated with migraine. [77,78]
			nP = 2328, nC = 95,425. Europe. IHGC GWA meta-analysis.	Association of allele T with MWA and MWOA. [53]
LTA (lymphotoxin alpha)	Cytokines play an important role in the modulation of pain threshold	TNFB*2	nP = 79 (MWA = 32, MWOA = 47). nC = 101. Italy.	TNFB * 2 allele produces a high risk of MWOA development. [79]
		rs2844482, rs2071590, rs2239704, rs909253, rs3889157	nP = 439, nC = 382. Korea.	CC genotype (rs2844482) is associated with migraine (P = 0.005). TGAAC haplotype (rs2844482, rs2071590, rs2239704, rs909253, rs3889157) is protective (P = 0.0005). [80]
MAOA (monoamine oxidase A)	Metabolizes triptans	VNTR (30 bp in promoter region)	nP = 110 (MWA = 30. MWOA = 80), nC = 150. Croatia.	Weak association of short allele with MWOA in men (P = 0.0423). [81]
			nP = 104. Italy.	Long allele is associated with chronic migraine. [33]
		941T>G, VNTR (30 bp)	nP = 91 (MWA = 24, MWOA = 67), nC = 119. Japan.	Distribution of T941G genotypes (P = 0.048) differed in patients with migraine and controls. Genotypic distribution of MAOA-VNTR (P = 0.077) differed in the MWA group and controls. The distribution of genotypes T941G (P = 0.068) differed in the group with MWOA and controls. Multivariate analysis showed that MAOA T941G (P = 0.010), MTHFR C677T (P = 0.034), TNF-b G252 A (P = 0.027), the neurotism (P = 0.001) and conscientiousness scale (P = 0.004) were identified as important factors in the pathogenesis of migraine. [8]
MEF2D (myocyte enhancer factor 2D)	Regulates neuronal differentiation while maintaining the survival of newly formed neurons; neural MEF2D activation limits the number of	rs1050316, rs3790455	1) nP = 2326 c MWOA, nC = 4580. Germany and Netherlands. 2) nP = 2508 with MWOA, nC = 2652. Europe.	Association with MWOA (P < 0.05). [21]

Table 1 (*continued*)

Official symbol	Probable reasons for association with migraine	Markers	Sample parameters	Comments/reference
	excitatory synapses			
MEP1A (meprin A, alpha (PABA peptide hydrolase))	Hydrolyzes substance P involved in pain signal transduction	Ex4-20A>T	nP = 178, nC = 224. Sweden.	Polymorphism Ex4-20A>T is discovered, possibly associated with migraine. [82]
MMP2 (matrix metallopeptidase 2 (gelatinase A, 72 kDa gelatinase, 72 kDa type IV collagenase))	Alter the permeability of cerebral blood vessels and disrupt the blood-brain barrier (BBB)	-735C>T	nP = 204 (MWA = 51, MWOA = 153), nC = 148. Brazil.	CC genotype (C (-735) T) is associated with high MMP-2 concentrations in plasma of patients with MWA ($P < 0.05$). [83]
MMP3 (matrix metallopeptidase 3 (stromelysin 1, progelatinase))		interaction between MMP3 (-1171 5A>6A) and ACE (rs1799752)	nP = 180 (MWOA = 109, MWA = 59, basilar type = 10, complicated = 2), nC = 210. Turkey.	Interaction between ACE (287bP ID) and MMP3 (-1171 5A>6A) is associated with migraine. Combined DD/5A5A and ID/5A5A genotypes increase the risk of migraine. Protector genotypes - II and/or 6A6A. [13]
MMP9 (matrix metallopeptidase 9 (gelatinase B, 92 kDa gelatinase, 92 kDa type IV collagenase))		rs3918242, rs2234681, rs17576	Women. nP = 187 (46 MWA и 141 MWOA), nC = 102. Brazil.	CLQ haplotype was associated with high MMP9 concentrations in plasma of patients with migraine. [84]
MTDH (metadherin)	Involved in the glutamate homeostasis	rs1835740	nP = 5950 (MWA = 25,6%, MWOA = 41%, MAO = 33,8%), nC = 50,809. Denmark, Iceland, Netherlands and Germany.	Allele A is associated with migraine ($P < 0.05$) and a high level of MTDH expression. [85]
MTHFD1 (methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 1, methenyltetrahydrofolate cyclohydrolase, formyltetrahydrofolate synthetase)	Correlation with the level of homocysteine that acts on the trigeminal vascular system	rs2236225, interaction with MTHFR (rs1801133)	nP = 329 (MWA = 138, MWOA = 191), nC = 237. Spain.	QQ and TT genotypes (MTHFR, C677T) together increase the risk of migraine in general ($P = 0.01$). [86]
MTHFR (methylenetetrahydrofolate reductase (NAD(P)H))		rs1801133	17 studies: nP = 8903, nC = 27637.	T allele is associated with a significantly increased risk of common migraine, particularly with MWA in Asians. [87]
			nP = 74 with migraine (MWA = 22, MWOA = 52). nP = 47 with TH , nC = 261. Japan.	T allele and TT genotype are associated with migraine, particularly with MWA. [88]
			1) MWA = 100. MWOA = 106. nC = 105. 2) nP = 106 with spontaneous cervical artery dissection (no migraine =49, MWOA =44, MWA = 13), nP = 227 with ischemic stroke, without cervical artery dissection (no migraine =169, MWOA = 31, MWA = 24), and, nC = 187 (no migraine =153, MWOA = 25, MWA = 9). Italy.	1) Association of TT genotype with MWA as compared to the control group and patients with MWOA. 2) Migraine and TT genotype are associated with spontaneous cervical artery dissection. [89]
			nP = 267. Australia.	TT genotype is significantly associated with MWA ($P < 0.0001$) and unilateral headache ($P = 0.002$). CT genotype is associated with the discomfort of physical activity ($P < 0.001$) and stress as a trigger of migraine ($P = 0.002$). [90]
			nP = 413 (MWA = 187, MWOA = 226), nC = 1212. USA.	TT genotype is associated with an increased risk of MWA ($P < 0.006$). [91]
			nP = 2961 (MWA = 2170, MWOA = 791), nC = 2319. Italy.	TT genotype is associated with an increased risk of MWA. [92]
			nP = 270, nC = 270. Australia.	TT genotype is associated with an increased risk of MWA. [93]
			nP = 151 (MWOA = 130. MWA = 21), nC = 137. China.	High frequency of T allele in patients with migraine ($P = 0.004$), in particular MWOA ($P = 0.003$ compared to the control group). [94]
			nP = 35, nC = 50. Italy	677T allele increases the risk of migraine. [52]
			nP = 83 (MWA = 19, MWOA = 64), nC = 50. Russia.	TT genotype is associated with accompanying symptoms (photophobia), but is also more sensitive to triggers of migraine attacks. [95]
			15 studies. Canada.	Associated with MWA. [96]

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Table 1 (*continued*)

Official symbol	Probable reasons for association with migraine	Markers	Sample parameters	Comments/reference
			nP = 230 (MWOA = 152, MWA = 78), nC = 204. Spain.	Association of T allele with MWA (P = 0.006). [97]
			nP = 6446 (MWA = 3645, MWOA = 2899), nC = 24,578.	TT genotype is associated with MWA. [6]
			nP = 91 (MWA = 24, MWOA = 67), nC = 119. Japan.	The distribution of C677T genotypes (P = 0.026) differed in patients with migraine and controls. The distribution of C677T genotypes (P = 0.008) differed in the group with MWOA and controls. Multivariate analysis showed that MAOA T941G (P = 0.010), MTHFR C677T (P = 0.034), TNF-b G252A (P = 0.027), the neurotism (P = 0.001) and conscientiousness scale (P = 0.004) were identified as important factors in the pathogenesis of migraine. [8]
		rs1801133, rs1801131	nP = 74 (MWA = 22, MWOA = 52). nP = 47 c TH , nC = 261. Turkey.	T677 and 1298C alleles are associated with migraine. C1298C, C677C / C1298C, T677T genotypes have a greater susceptibility to migraine with aura and without aura. [98]
		interaction with ACE	nP = 103 (MWOA = 81, MWA = 9, MAO = 13), nC = 336 (cardiovascular diseases). Italy.	MTHFR and ACE polymorphisms are associated with migraine. [9]
		rs1801133, interaction with ACE (rs4646994)	nP = 150, nC1 = 220 patients with non-migraine headache (disease control), nC2 = 150 normotensive patients. India.	DD (ACE, rs4646994)/CT (MTHFR, rs1801133) positive association in patients with common MWA, women with MWA, as compared to the control. [11]
			nP = 270 (MWA = 63%, MWOA = 37%), nC = 270. Australia.	The combination of TT (rs1801133) and ID/DD (ACE, rs4646994) genotypes increases the risk of migraine (P = 0.018), in particular MWA (P = 0.002). [12]
		rs1801133, interaction with ACE and vWF	MWA = 61, MWOA = 64. USA.	Patients with combined ACE DD and MTHFR TT genotypes had a high level of vWF activity (179%). TT genotype is associated with MWA. [10]
		rs1801133, interaction with TS (2R/3R) and MTHFD1 (rs2236225)	nP = 329 (MWA = 138, MWOA = 191), nC = 237. Spain.	The interaction between 3R3R (TS) and TT (MTHFR) genotypes increases the risk of MWA. QQ (MTHFD1) and TT (MTHFR) genotypes together increase the risk of migraine in general (P = 0.01). [86]
NGFR (nerve growth factor receptor)	neurons grow and proliferation	rs9908234	nP = 2446, nC = 8534. Six population-based European.	GWAS results. The SNP rs9908234 had a P-value of 8.00 × 10(−8). [99]
NOS2 (nitric oxide synthase 2, inducible)	synthesis of nitric oxide - a powerful vasodilator	rs3833912	nP = 504, nC = 512. China.	Association with migraine. Carrier status of 9- and 10-repeat alleles is significantly more common in the control group, while 11-repeat alleles are more common in patients. [100]
		rs2297518, rs2779249	Women. nP = 200 (MWA = 52, MWOA = 148), nC = 142. Brazil.	Allele A (rs2297518) and AA haplotype (rs2297518, rs2779249) are associated with MWA (P < 0.05). [101]
		rs2297518, interaction with eNOS (rs743506)	Women. nP = 150 (MWA = 43, MWOA = 107), nC = 99. Brazil.	The combination of rs2297518 and rs743506 (NOS3) affects migraine susceptibility (P = 0.0120). [102]
NOS3 (nitric oxide synthase 3 (endothelial cell))		rs3918166	nP = 312 (MWA = 243, MWOA = 69), nC = 407. USA.	The minor allele A is more common in patients with MWA, than those with MWOA (P = 0.03). [44]
		rs743506, interaction with NOS2 (rs2297518)	Women. nP = 150 (MWA = 43, MWOA = 107), nC = 99. Brazil.	The combination of rs743506 (NOS3) and rs2297518 (NOS2) affects the migraine susceptibility (P = 0.0120). [102]
		rs743506; rs2070744, rs1799983, VNTR (27 bp) in intron 4, rs3918226 and rs743506.	Women. nP = 178 (MWA = 44, MWOA = 134), nC = 117. Brazil.	GA genotype (rs743506) is more common in controls than in migraine patients (P < 0.01). "CC a Glu G" and "CC b Glu G" haplotypes were reported in patients with MWA more often than in those with MWOA (P < 0.0015625). [103]
		rs1799983	nP = 156, nC = 125. Italy.	AspAsp genotype is 3-fold more common in patients with MWA than in those with MWOA, and 2-fold more common than in the control group. [104]
NOTCH3 (notch 3)	Involved in vascular endothelial damage	rs1043994	1) nP = 275, nC = 275. 2) nP = 300, nC = 300. Australia.	G684A substitution is associated with migraine, in particular with MWA. [105]
NOTCH4 (notch 4)		rs422951, rs9267835, rs8192573	nP = 239 (MWA = 49, MWOA = 190), nC = 264. Italy.	Allele T (rs9267835) is associated with vomiting (P = 0.034), allele C (rs8192573) is associated with an increased duration of attacks (P = 0.02), allele A (rs422951) is associated with the severity of menstrual migraine symptoms (*P* = 0.016). [106]

Table 1 (*continued*)

Official symbol	Probable reasons for association with migraine	Markers	Sample parameters	Comments/reference
NPFF (neuropeptide FF-amide peptide precursor)	Regulation of heart rate and blood pressure and the modulation of morphine-induced antinociception	rs11170566	nP = 2328, nC = 95,425. Europe. IHGC GWA meta-analysis.	Association of allele T with MWA and MWOA. [53]
OPRM1 (opioid receptor, mu 1)	Involved in analgesia, response to drug therapy, and pain relief	118A>G	nP = 153 women with MWA. Australia.	G118 allele carriers had more severe pain compared with homozygous carriers of allele A118 (P = 0.0037). A118G substitution is related to migraine severity. [107]
PGR (progesterone receptor)	Associated with the hormonal system	rs1042838	nP = 217 (MWA = 84, MWOA = 133), nP = 179 TH. nC = 217. India.	A1A2 genotype and allele A2 are protective. [46]
PHACTR1 (phosphatase and actin regulator 1)	Controls synaptic activity and synapse morphology	rs9349379	1) nP = 2326 c MWOA, nC = 4580. Germany and Netherlands. 2) nP = 2508 c MWOA, nC = 2652. Europe.	Association with MWOA (P < 0.05). [21]
PLAUR (plasminogen activator, urokinase receptor)	Involved in inflammatory processes by facilitating the migration of inflammatory cells into different tissues	rs344781	nP = 103. nC = 100. Iran.	Association with MWOA (P = 0.001). [108]
PON1 (paraoxonase 1)	Involved in oxidative stress	p.Gln192Arg	nP = 197, nC = 220. Spain.	192QQ genotype and 192Q allele are significantly more common in patients with early onset of migraine. [109,110]
PRDM16 (PR domain containing 16)	Its functional role is not yet clear	rs2651899	nP = 5122, nC = 18,108. USA.	Associated with migraine. [77,78]
			nP = 340, nC = 200. India.	The protective effect of T allele against migraine and MWOA (P < 0.05). [76]
		rs2651899	nP = 749, nC = 4018. Sweden.	Minor C allele was more common in patients with migraine than in controls (P = 0.0019). [111]
PTGS2 (prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase))	Inhibition of COX-1 and COX-2 inhibits neurogenic inflammation in migraine	765G>C, 1195A>G	nP = 144, nC = 123. Turkey.	The frequency of GG and GC (765G>C) genotypes is higher in patients than in controls (P < 0.0001). The AG genotype (1195A>G) frequency also significantly differed in patients (P < 0.05). [112]
RAMP1 (receptor (G protein-coupled) activity modifying protein 1)	Association with CGRP; cause photophobia and mechanical allodynia	rs3754701	nP = 284, nC = 284. Australia.	Insignificantly associated with migraine in men (P = 0.031). [113]
RHAG (Rh-associated glycoprotein)	Association with ion channels	507G>T	nP = 178, nC = 177. Sweden.	RHAG (507G>T) polymorphism discovered, possibly related to migraine. [82]
PTX3 (pentraxin 3, long)	May be involved in inflammation by activation of cytokines production.	rs3816527	nP = 103, nC = 148. Iran.	C allele was significantly associated with susceptibility to migraine only in men (*P* = 0.003). [114]
SLC1A2 (solute carrier family 1 (glial high affinity glutamate transporter), member 2), EAAT2	Regulation of glutamate levels in CNS	SNP (A>C)	74 patients with episodic migraine attacks (M–E); 59 migraine patients with chronic daily headaches (M–CDH). Caucasian Spanish.	The frequency of use of analgesics is significantly higher in patients with migraine with the A allele (*P* = 0.019). EEAT2 polymorphism promotes the tendency to frequent use of analgesics in patients with migraine. [115]
SLC6A3 (solute carrier family 6 (neurotransmitter transporter, dopamine), member 3)	Mediates reuptake of dopamine from the synapses and is the major regulator of dopaminergic neurotransmission	rs40184	nP = 270 + 380 (MWA), nC = 272 + 378. Germany.	Association with MWA (*P* = 0.032). [38]
SLC6A4 (solute carrier family 6 (neurotransmitter transporter), member 4) HTT; 5HTT; OCD1; SERT; 5-HTT; SERT1; hSERT; 5-HTTLPR	Responsible for the reuptake of serotonin from the synaptic cleft, thereby regulating the serotonin transmission	VNTR STin2	Children. nP = 87 (MWA = 38, MWOA = 49). nC = 464. Hungary.	STin2 – association with MWA (genotype 12.12 – risk of MWA is increased 2-fold) with excessive vomiting and abdominal pain during attacks. [116]
			nP = 52, nC = 80. Turkey.	Allele 10 prevailed in the group with migraine (P = 0.01), allele 12 was more common in controls (P = 0.02). [117]
			5 samples: nP = 557 (MWA = 257, MWOA = 289). nC = 849. Denmark, Australia, Turkey, Italy, Hungary.	Genotype 10/12 reduces the risk of migraine by 25%. [118]
			15 studies: nP = 2368 with migraine. nC = 2661.	Allele 12 and genotype 12/12 increase the risk of migraine (P = 0.006; P = 0.002). [119]
			nP = 285 (MWA = 94, MWOA = 173, MAO = 18). nC = 133. Great Britain.	Genotype 12/12 increases the risk of MWA and MWOA, genotype 9/9 only increases the risk of MWA. Allele 10 is protective. [120]
		rs1979572, rs2066713	nP = 251 (MWA = 32, MWOA = 178, MAO = 41). nC = 192. Germany.	Association of rs1979572 A allele with MWA in women, low prevalence of rs2066713 A allele in women with MWA. [121]

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Table 1 (*continued*)

Official symbol	Probable reasons for association with migraine	Markers	Sample parameters	Comments/reference
		5-HTTLPR	nP = 197 with migraine (MWA = 96, MWOA = 101). nC = 115. Germany.	S allele frequency is increased in patients with MWA ($P < 0.001$). [122]
			nP = 144 with migraine (MWA = 52, MWOA = 92). nC = 105. Italy.	SS genotype is associated with MWA ($P < 0.05$). [123]
		5-HTTLPR, 5-HTTVNTR	nP = 91 (MWA = 24, MWOA = 67), nC = 119. Japan.	Genotypic distribution of 5-HTTLPR ($P = 0.004$), 5-HTTVNTR ($P = 0.029$) differed between the group with MWA and controls. [8]
SLC20A2 (solute carrier family 20 (phosphate transporter), member 2)	Plays an important role in phosphate homeostasis	p.Val507Glufs*2	48 y. o. woman with episodic migraine.	A frameshift mutation P·Val507Glufs*2 was found. [124]
STX1A (syntaxin 1A (brain))	Interacts with different presynaptic K + channels, modulating their ability to determine the presynaptic action potentials	rs941298, rs6951030	nP = 188 (MWOA = 111, MWA = 77). nC = 287. Portugal.	TT genotype (rs941298) is associated with an increased risk of migraine and MWOA. The GG and GT (rs6951030) genotypes are associated with migraine. [125]
		rs4363087, rs941298, rs6951030. rs2293489	nP = 567, nC = 720. Great Britain.	rs4363087, rs941298 substitutions are associated with migraine and MWOA. A-G (rs6951030-rs4363087) and A-C (rs4363087-rs2293489) haplotypes are associated with migraine and MWOA. [126]
		rs941298, rs6951030, rs941298, rs4363087	nP = 210 with migraine (MWA = 86, MWOA = 102, HM = 22), nC = 210. Spain.	A-T-G (rs6951030-rs941298-rs4363087) is the risk haplotype for migraine. T allele (rs941298) is associated with migraine. [127]
SYNE1 (spectrin repeat containing, nuclear envelope 1)	Expressed in smooth muscle, and localized on the nuclear membrane	rs9371601	nP = 282 (MM, PMM = 68, MRM = 214), nC = 155. UK.	Allele T is associated with MM (P = 0.009), particularly MRM (P = 0.002). [128]
TARBP2 (TAR (HIV-1) RNA binding protein 2)	Involved in processing of RNA or pre-miRNA and RNA gene silencing	rs11170566	nP = 2328, nC = 95,425. Europe. IHGC GWA meta-analysis.	Association of allele T with MWA and MWOA. [53]
TDO2 (tryptophan 2,3-dioxygenase) TPH2	Brain serotonin biosynthesis	rs1487275, rs1386486, rs4448731, rs17110477, rs12229394, s4760820, rs1352250	nP = 503 (MWA = 214, MWOA = 289), nC = 515. Germany.	TTGGG (rs4448731-rs17110477-rs12229394-rs4760820-rs1352250) haplotype is associated with MWOA (P = 0.006). CC genotype (rs1487275) and AA genotype (rs1386486) reduce the risk of migraine. [129]
TGFB1 (transforming growth factor beta 1)	Regulate proliferation, differentiation, adhesion, migration, and other functions in many cell types	-800G/A, -509C/T, 869 T/C, 915G/C	nP = 100, nC = 88 (children and adolescents). Turkey.	509C/T was significantly different between control and migraine without aura patients (P = 0.04). For SNP 869 T/C genotypic (CC) and C allelic frequency were significantly higher in migraine patients versus healthy controls (P = 0.00). [130]
TGFBR2 (transforming growth factor, beta receptor II (70/80 kDa))	Involved in the regulation of cell proliferation and differentiation, as well as production of extracellular matrix	rs7640543	1) nP = 2326 c MWOA, nC = 4580. Germany and Netherlands. 2) nP = 2508 with MWOA, nC = 2652. Europe.	Association with MWOA ($P < 0.05$). [21]
TLR4 (toll-like receptor 4)	Signaling receptor of innate immunity	896 A > G	nP = 170, nC = 170. Iran.	The frequency of G allele ($P < 0.0001$) and AG genotype (P = 0.00002) is higher in patients with migraine as compared with the control group. [131]
TNF (tumor necrosis factor)	A central role in enhancing the inflammatory cascade	rs1800629	nP = 203, nC = 202. Turkey.	Association with migraine ($P < 0.0001$). [132]
			nP = 985, nC = 958. China.	A meta-analysis of 5 studies. Association with the risk of migraine in Asians. [133]
			nP = 376 (M = 216, TH = 160), nC = 216. India.	Allele A is associated with MWA, particularly in women ($P < 0.05$). [134]
			nP = 221 with MWOA. nC = 183. Iran.	The allele A frequency was higher in the MWOA group than in the controls ($P < 0.0001$). [135]
			nP = 299, nC = 306. Italy.	GG genotype (-308G>A) is associated with migraine, particularly MWOA ($P < 0.001$). [136]
			nP = 67 with MWOA, nC = 96. Turkey.	Allele A is more common in patients with MWOA, than in controls (P = 0.012). [68]
		252A>G	nP = 91 (MWA = 24, MWOA = 67), nC = 119. Japan.	The distribution of G252A genotypes (P = 0.074) differed in patients with migraine and controls. Genotypic distribution of G252A (P = 0.007) differed in the group with MWA and controls. Multivariate analysis showed that MAOA T941G (P = 0.010), MTHFR C677T (P = 0.034), TNF-b G252A (P = 0.027), the neurotism (P = 0.001) and conscientiousness scale (P = 0.004) were identified as important factors in the pathogenesis of migraine. [8]
		rs3093664	nP = 282 (MM, PMM = 68, MRM = 214), nC = 155. UK.	Allele G is associated with MM (P = 0.008), particularly MRM (P = 0.006). [128]
TNFRSF1B (tumor necrosis factor	Neutralizes	rs5745946	nP = 416, nC = 415.	15 bp insertion allele is associated with an increased risk of

Table 1 (*continued*)

Official symbol	Probable reasons for association with migraine	Markers	Sample parameters	Comments/reference
receptor superfamily, member 1B)	TNF-α-induced hyperalgesia during migraine attacks		China.	migraine (P = 0.04). [137]
TPH1 (tryptophan hydroxylase 1)	Involved in the synthesis of serotonin and melatonin	218C > A	nP = 59, nC = 62. Turkey	AA genotype was more common in controls than in patients with migraine (P = 0.02). [138]
TRPM8 (transient receptor potential cation channel, subfamily M, member 8)	May be involved in the mechanism of development of cutaneous allodynia (pain in response to non-painful stimuli) that is present in most patients with migraine	rs17862920, rs10166942	1) nP = 2326 with MWOA, nC = 4580. Germany and Netherlands. 2) nP = 2508 with MWOA, nC = 2652. Europe.	Association with MWOA (P < 0.05). [21]
		rs17863838, rs10187654	nP = 2328, nC = 95,425. Europe. IHGC GWA meta-analysis.	Association of allele G of rs17863838 with MWOA. Association of allele C of rs10187654 with MWA. [53]
		rs10166942	nP = 5122, nC = 18,108. USA.	Associated with migraine. [77]
TYMS (thymidylate synthetase)	Correlation with the level of homocysteine that acts on the trigeminal vascular system	Polymorphism 2R/3R, interaction with MTHFR (rs1801133)	nP = 329 (MWA = 138, MWOA = 191), nC = 237. Spain.	Interaction between 3R3R and TT (MTHFR) genotypes increases the risk of MWA. [86]
UFL1 (UFM1 specific ligase 1)	Neuroglia specific, involved in cell proliferation	rs4598081, rs11153058	nP = 2328, nC = 95,425. Europe. IHGC GWA meta-analysis.	Association of allele A of rs11153058 with MWOA. Association of allele T of rs4598081 with MWA. [53]
VDR (vitamin D (1,25-dihydroxyvitamin D3) receptor)	Vitamin D plays a role in the release of serotonin and dopamine	rs2228570, rs731236	nP = 103 with MWOA, nC = 100. Iran.	Ff (rs2228570) and Tt (rs731236) genotypes were more common in patients with migraine than in the control group (P = 0.001; P = 0.018). An increase in the frequency of f and t alleles was observed in patients with migraine. An overall HIT-6 (headache imPact test-6) score was significantly different between patients with Ff and FF (P = 0.004). [139]
VEGFA (vascular endothelial growth factor A)	Regulates growth factors and cytokines	rs699947, rs1570360, rs2010963	Women. nP = 175 (MWA = 46, MWOA = 129), nC = 114. Brazil.	CAC (rs699947, rs1570360. rs2010963) haplotype prevailed in the control group; AGC haplotype prevailed in patients with MWA (P < 0.05). [140]

Next, we analyzed referenced articles in detail. Original research papers with statistically significant results were taken into consideration (positive association of certain gene modification or one of its variants with the disease, symptom, or group of symptoms; interaction with another gene; association of genotypes or alleles of different genes; presence of mutation in families with high occurrence of the disease; cosegregation of genetic alteration with manifestations of the disease). The reviews were excluded from analysis. In case of insufficient information about a gene (three references or less), less reliable results might be considered (for instance, probable association). The results are provided in Table 1.

The familial hemiplegic migraine genes of types I, II, and III were excluded from the analysis (*CACNA1A*, *ATP1A2*, and *SCN1A* genes, respectively).

2. Table description

Official symbol – the name of gene considered official according to NCBI database. A symbol, which is used more often in the literature, is placed after comma.

Probable reasons for association with migraine – participation in cellular and physiologic processes involved in migraine pathogenesis.

Markers – one or more conditions may be met: 1) an association with the mutation was found (in this case, the type of mutation is mentioned: SNP, deletion, insertion, STR, or VNT); 2) an association with another gene proved to have an association with migraine; 3) result of polygenomic study.

Sample parameters – 1) number of patients (nP) along with the information about migraine type or inclusion of patients with other headache disorders: migraine without aura (MWOA), migraine with aura (MWA), tension headache (TH); 2) control sample volume (nC) along with information about concomitant diseases, if any; 3) sample ethnicity (if not indicated, then country where the original research had been held).

Comments/references – detailed description indicating which genetic alteration is associated with the disease or its clinical characteristics and reference.

For each article, the type of association with migraine, sample volume, and reference are put on the same row. The exclusion is *MTHFR* gene: in order not to overload the table, probable types of association and comments for them are listed without article binding.

As the result of the analysis, 98 genes were left out of the original gene list. Total 175 SNP (including insertion/deletion), 10 repeats (STR or VNT), and 26 cases of gene-gene interactions (associated with migraine complex genotypes). The genes associated with migraine could be classified into 8 major groups: homeostasis of blood vessels - 26.5%, metabolism of neurotransmitters - 11.2%, transport and reception of neurotransmitters - 24.5%, neurogenesis - 5.1%, inflammation - 8.2%, sex hormones - 5.1%, ion channels and membrane potential - 11.2%, other - 8.2%.

3. Conclusion

These findings parallel the range of mechanisms implicated in migraine pathogenesis.

Conflicts of interest

The authors declare that they have no conflict of interest.

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