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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]