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A Comprehensive Review on the Role of Genetic Factors in the Pathogenesis of Migraine

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Abstract

Migraine is a common neurovascular condition. This disorder has a complex genetic background. Several single-nucleotide polymorphisms (SNPs) or mutations within genes regulating glutamatergic neurotransmission, cortical excitability, ion channels, and solute carriers have been associated with polygenic and monogenic forms of migraine. SNPs within *ACE*, *DBH*, *TRPM8*, *COMT*, *GABRQ*, *CALCA*, *TRPV1*, and other genes have been reported to affect the risk of migraine or the associated clinical parameters. The distribution of some HLA alleles within the HLA-DRB1, HLA-DR2, HLA-B, and HLA-C regions have also been found to differ between migraineurs and healthy subjects. In addition, certain mitochondrial DNA changes and polymorphisms in this region have been shown to increase the risk of migraine. A few functional studies have investigated the molecular mechanisms contributing to these genetic factors in the development of migraine. Here we review studies evaluating the role of genetic polymorphisms and mRNA/miRNA dysregulation in migraine.

Keywords Migraine · Polymorphism · miRNA · Expression

Introduction

As a neurovascular condition, migraine is classified into two main subtypes based on the presence or absence of aura, defined as visual, sensory, or neurological symptoms occurring prior to the headache (Zhang et al. 2016). Migraine attacks have a number of clinical phases. The headache is associated with trigeminal activation. However, before this phase, patients might experience symptoms such as fatigue, mood alterations, photophobia, and other symptoms (Dodick 2018). Some affected persons also have an aura phase, characterized by optical, sensory, speech, and motor defects, in addition to disturbances in higher cortical activity shortly before or concurrently with the headache (Dodick 2018). Migraine has a complicated genetic background. According to family and twin studies, the heritability of migraine is expected to be 30–60% (Honkasalo et al. 1995; Mulder et al. 2003; Polderman et al. 2015). However, at least a monogenic form of migraine has been described which is caused by mutations in the *CACNA1A*, *ATP1A2*, and *SCN1A* genes and is associated with hemiplegia (Sutherland et al. 2019). Generally, abnormalities in glutamatergic neurotransmission and cortical excitability have been reported to be associated with aura. In addition, a number of genetic variations within genes coding ion channels and solute carriers, or those implicated in the modulation of neurotransmitters at synaptic regions, are associated with monogenic migraine and similar conditions (Sutherland et al. 2019). Apart from these monogenic forms, migraine has also been associated with several single-nucleotide polymorphisms (SNPs) and other types of genetic variants in different genes. A number of studies have also reported aberrant expression of mRNA or microRNA (miRNA) coding genes in patients with migraine. Here we review studies evaluating the role of genetic polymorphisms and mRNA/miRNA dysregulation in migraine.

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Genetic Polymorphisms in Migraine

Palmirotta et al. genotyped the insertion/deletion (I/D) polymorphism within the angiotensin-converting enzyme (*ACE*) gene in a cohort of Caucasian migraineurs and healthy subjects. They reported a significant association between the I/I genotype and a lower rate of preventive medication use in migraineurs with aura and also in patients with chronic migraine. Furthermore, the I/I genotype was suggestively more frequent in migraineurs with aura who did not have a family history of migraine. Collectively, the authors stated that the I/D variation in the *ACE* gene is not a direct susceptibility parameter in migraine, but it might affect the clinical characteristics of this disorder (Palmirotta et al. 2014). Abedin-Do et al. investigated the association between rs4343 in the *ACE* gene and vulnerability to migraine in an Iranian cohort. They demonstrated an association between rs4343 and migraine. They also reported over-representation of the GG genotype in patients with aura relative to those without aura (Abedin-Do et al. 2017). Fernandez et al. genotyped two possibly functional SNPs within the dopamine beta-hydroxylase (*DBH*) gene in two cohorts of migraineurs. They demonstrated a substantial association between the promoter marker −1021C > T and migraine in both cohorts. However, the polymorphism located in exon 11 (+1603C > T) was not associated with risk of migraine in any set of patients (Fernandez et al. 2009). Notably, the SNP located in the promoter region was previously demonstrated to explain half of the DBH activity in plasma (Zabetian et al. 2001). The association between these two SNPs and an additional SNP within this gene, namely +444G > A (rs1108580), was also assessed in a Turkish cohort. The study showed a significant association between the +1603C > T SNP but no other SNPs and migraine (Sezer et al. 2016). *DBH* has another genetic variant, i.e. the 19-bp I/D polymorphism. This variation has not been associated with risk of migraine or the majority of clinical parameters. However, in a subgroup of chronic migraine, patients having the D allele were more susceptible to misuse of analgesics (Barbanti et al. 2019). The rs4680 (Val158Met) SNP within the *COMT* gene has not been associated with migraine in female subjects. However, female subjects with the Met/Met genotype had greater levels of migraine-associated debility compared with other genotypes. Moreover, within the subgroup of female subjects with chronic migraine, the Met/Met genotype was associated with higher levels of depression and anxiety (Fernández-de-Las-Peñas et al. 2019). The association between several SNPs within the GABAergic system and susceptibility to migraine has also been assessed. Among the assessed SNPs, the GABRE rs1139916 AA genotype has tended to have a protective role in the female gender, but the differences did not remain significant after correction for multiple comparisons. It was found that the GABRQ rs3810651 might affect the age of migraine onset. Moreover, GABRA4 rs2229940 and GABRQ rs3810651 tended to be associated with the impact of ethanol on the migraine attacks, although the differences were not significant after correction for multiple comparisons (García-Martín et al. 2018). Ling et al. reported an association between the T allele of the *TRPM8* rs10166942 and chronic migraine. The T allele of this SNP has also been associated with allodynic symptoms in migraineurs (Tang et al. 2019). *MTHFR* C677T is another polymorphism whose contribution to the risk of migraine has been assessed by numerous researchers (Fig. 1).

Table 1 shows the results of investigations assessing the association between genetic polymorphisms and migraine.

HLA Alleles and Risk of Migraine

The association between HLA alleles and different types of migraine has been assessed by a number of researchers. For instance, Coelho et al. demonstrated no significant difference in HLA-DQB1*0602 allele frequency between migraineurs with aura and those without aura (Coelho et al. 2007). Martelletti et al. reported a similar distribution of HLA-A, HLA-B, and HLA-C antigens in migraine patients compared to healthy subjects. However, the HLA-DR2 antigen was less frequent in patients with aura than in those without aura and in healthy controls (Martelletti et al. 1999). Another study of HLA-DRB1 allele frequencies among Italian individuals revealed a lower frequency of the DRB1*12 allele in migraineurs, in spite of the higher frequency of the DRB1*16 allele in these patients as compared with healthy controls. Notably, the HLA-DRB1**16 allele frequency was higher only in the subgroup of migraineurs without aura (Rainero et al. 2005). O'Neill et al. compared the distribution of HLA-A and HLA-B alleles among different subtypes of migraineurs (classical/common migraine and migraineurs with/without a family history of this disorder). They demonstrated no significant association between these alleles and risk of migraine (O'Neill et al. 1979). Finally, Huang et al. reported a remarkable association between HLA-B and HLA-C alleles and clinic-based migraine. HLA-B*39:01, HLA-B*51:01, HLA-B*58:01, and HLA-C*03:02 were identified as risk factors for migraine. Clinic-based migraineurs who had HLA-B*58:01 or HLA-C*03:02 were more prone to chronic migraine with drug-abuse headache compared to episodic migraine. However, no HLA allele was associated with self-reported headache or migraine in the community (Huang et al. 2020). Table 2 reviews the studies assessing the contribution of HLA alleles in the development of migraine.

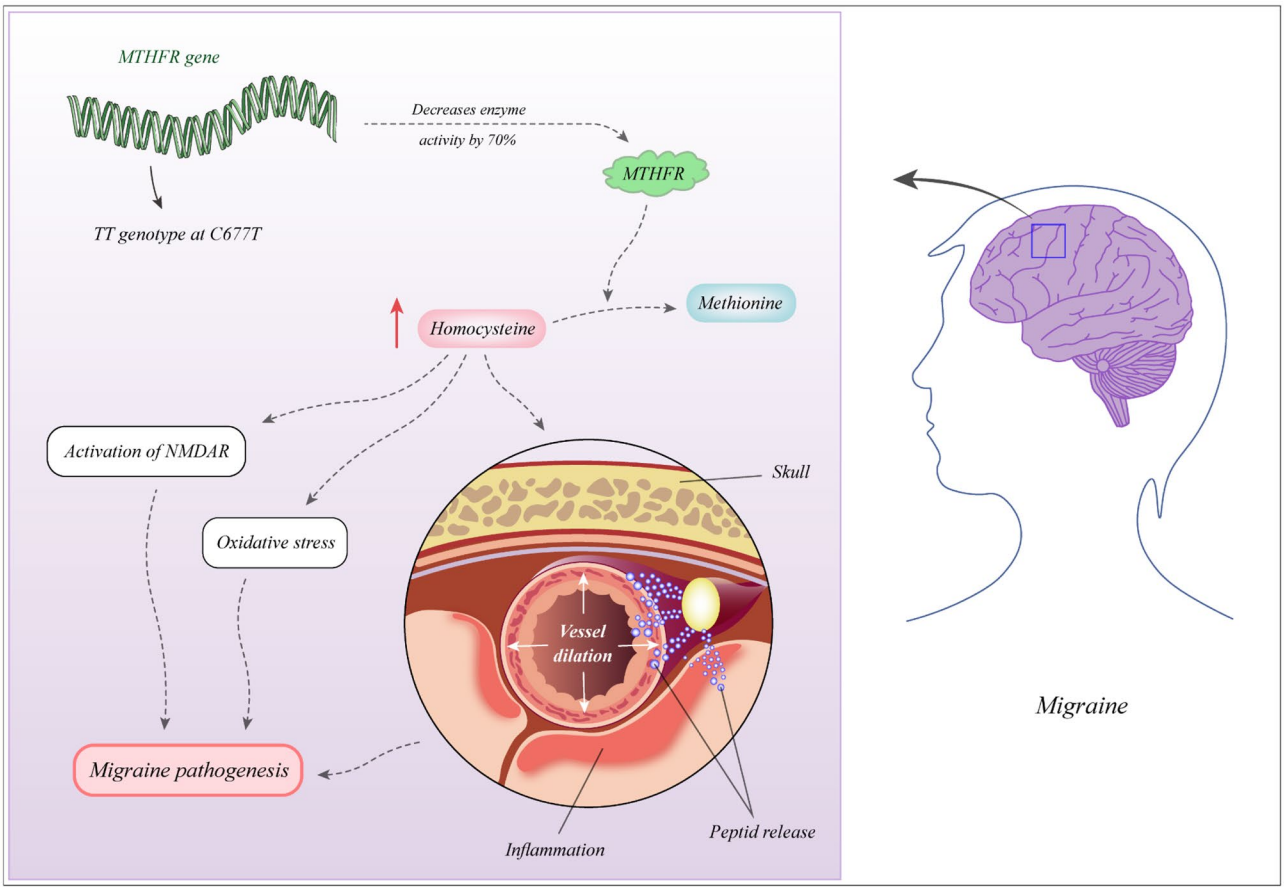

Fig. 1 Homozygosity for the T allele of *MTHFR* C677T results in 70% reduction in the activity of this enzyme and a significant increase in homocysteine levels. An increase in this factor leads to vasodilation, enhances NMDAR activity, and increases oxidative stress, all of which increase susceptibility to migraine (Cacciapuoti 2017; Orsini et al. 2018)

Mitochondrial DNA Changes and Polymorphisms in Migraine

The role of mitochondrial genome alterations in the development of migraine has been assessed in a few studies. Fachal et al. investigated 15 SNPs in the mitochondrial genome in patients with diverse disorders, namely Alzheimer disease, Parkinson disease, and migraine, versus controls. The authors detected no substantial association for any SNPs or haplogroup in Alzheimer disease and Parkinson patients. However, T4216C, G13708A, and haplogroup J were associated with risk of migraine, although this association was not verified in another cohort of patients (Fachal et al. 2015). Wang et al. reported a higher frequency of homoplasmic sequence variants in the nt 16040–16188 region among migraineurs without aura compared with controls (Wang et al. 2004). Guo et al. showed a higher prevalence of migraine in individuals having the 3243A > G mutation compared with controls. This observation was confirmed in both genders and both subtypes of migraine (with/without aura) (Guo et al. 2016). Zaki et al. demonstrated an association between the 16519C > T polymorphism and migraine, and the 3010G > A polymorphism was also associated with risk of migraine in persons with 16519 T (Zaki et al. 2009). A summary of studies assessing the role of mitochondrial DNA changes in migraine is presented in Table 3.

Altered Expression of Genes in Migraine

A few high-throughput sequencing experiments have assessed the transcriptome of migraineurs. Greco et al. measured expression levels of endocannabinoid system elements in the peripheral blood mononuclear cells of patients with episodic migraine, those with chronic migraine and drug overuse, and healthy subjects. Expression of cannabinoid receptor 1 and cannabinoid receptor 2 were higher in both groups of migraineurs compared with controls. On the other hand, expression of fatty acid amide hydrolase was downregulated in migraineurs. There were other dysregulated genes in the endocannabinoid system

Table 1 The role of genetic polymorphisms in migraine

Gene	Polymorphism	Samples	Population	Assay method	Association	Reference
ACE	Insertion/deletion (I/D) (rs1799752)	Blood samples from 502 patients with migraine and 323 healthy controls	Caucasian	PCR	ACE I/I genotype cannot be considered as a risk factor for migraine but is associated with low consumption of preventive agents in migraine patients with aura	(Palmirotta et al. 2014)
ACE	SNP (rs4343)	148 patients with migraine and 149 age- and gender-matched healthy controls	Iranian	TP-ARMS-PCR	This SNP was associated with augmented risk of migraine. rs4343 GG genotype has high frequency in migraine patients with aura in comparison to migraine patients without aura	(Abedin-Do et al. 2017)
DBH	SNP (rs1611115)	Blood samples from 2 cohorts including 200 migraine patients and 200 controls in one cohort, and 300 migraine patients and 300 controls in other cohort	Australian Caucasians	PCR–RFLP	rs1611115 alleles and genotypes were significantly correlated with migraine risk	(Fernandez et al. 2009)
DBH	SNP (rs1611115, rs6271, rs1108580)	Blood samples from 200 patients with migraine and 267 healthy volunteers	Turkish	PCR–RFLP	Genotypic and allelic frequencies of rs6271 were associated with migraine risk	(Sezer et al. 2016)
DBH	19-bp insertion/deletion (I/D) (rs72393728/ rs141116007)	Blood samples from 400 migraine patients and 204 healthy subjects	Caucasian (Italy)	PCR	In the chronic migraine patient subgroup, deleted (D) allele carriers were significantly more susceptible to analgesics abuse, but there was no association between genotypic frequency and migraine risk	(Barbanti et al. 2019)
TRPM8	SNP (rs10166942)	1904 migraine patients	Taiwanese	Sequenom MassARRAY iPLEX platform	Carriers of T allele had increased risk of chronic migraine compared to non-T carriers. Also, carriers of T allele were more prone to allodynic symptoms	(Tang et al. 2019)

Table 1 (continued)

Gene	Polymorphism	Samples	Population	Assay method	Association	Reference
COMT	SNP (rs4680 Val158Met)	Nonstimulated whole-saliva samples from 50 female patients with episodic migraine, 50 with chronic migraine, and 50 matched female healthy volunteers	Spanish	TaqMan real-time PCR	Genotype distribution was not correlated with migraine susceptibility, but women with the Met/Met genotype exhibited more migraine-related complications than women with the other two genotypes	(Fernández-de-Las-(Peñas et al. 2019)
GABRQ	SNP (rs3810651)	Blood samples from 197 migraine patients and 394 age- and gender-matched subjects as controls	Spanish	TaqMan Assays	Migraine age of onset in patients with rs3810651AA genotype is significantly lower than carriers of other two genotypes	(García-Martín et al. 2018)
CALCA TRPV1	SNP (CALCA rs3781719, TRPV1 rs222749)	156 female patients with migraine treated with onabotulinumtoxinA	Spanish	KASP method	CALCA rs3781719 C allele frequency and TRPV1 rs222749 A allele frequency were lower in responders to onabotulinumtoxinA compared with non-responders	(Moreno-Mayordomo et al. 2019)
TRPV1	SNP (Ile585Val rs8065080)	Blood samples from 27 episodic migraine patients, 19 chronic migraine patients, and 50 healthy controls	Russian Caucasians	Allele-specific PCR	Genotype distribution differed significantly between episodic migraine patients and chronic migraine patients	Yakubova et al. 2020)
NNMT	SNP (rs694539)	Blood samples from patients with migraine and 229 healthy controls	Turkish	PCR–RFLP	Female subjects with AA genotype exhibited increased risk of migraine. In contrast, GG genotype was correlated with lowered risk of migraine in females. There was no correlation between male patients and this polymorphism	(Sazci et al. 2016)
Near TSPAN2 MEF2D PHACTR1 FHL5 LRP1	SNP (Near TSPAN2 rs12134493, MEF2D rs2274316, PHACTR1 rs9349379, FHL5 rs11759769, LRP1 rs11172113)	Blood samples from 1806 unrelated patients with migraine and 6415 controls	Danish	Centaurus assays	These polymorphisms were associated with migraine risk	(Esserlind et al. 2016)

Table 1 (continued)

Gene	Polymorphism	Samples	Population	Assay method	Association	Reference
TSPAN2	SNP (rs12134493, rs2078371)	Blood samples from 425 migraine patients and 425 healthy subjects	Han Chinese	-	rs2078371 was significantly associated with migraine risk, especially migraine with aura in female patients	(Fang et al. 2018)
MEF2D ASTN2	SNP (MEF2D rs2274316, ASTN2 rs6478241	581 migraine patients and 533 ethnically matched volunteers as controls	Chinese	Sequenom MALDI-TOF mass spectrometry iPLEX platform	Allelic and genotypic frequencies of theses polymorphisms were associated with migraine risk	(An et al. 2017a)
Near NRP1	SNP (rs2506142)	Biological samples from 235 women with menstrual migraine and 140 controls	English	Agena MassARRAY platform	This polymorphism was significantly associated with menstrual migraine risk	(Pollock et al. 2018)
MTHFR	SNP (C667T; rs1801133, A1298C; rs1801131)	Blood samples from 100 patients with migraine and 100 healthy controls	North Indian population	PCR–RFLP	CC genotype in A1298C was associated with migraine risk, and CT genotype and T allele in C667T affected predisposition to migraine with aura.	(Kaur et al. 2018)
MTHFR	SNP (C677T)	324 patients and 103 controls	Italian	-	T/T genotype was associated with an elevated risk of all migraine types	(Orsini et al. 2018)
MTHFR	SNP (rs4846049, C677T)	Blood samples from 223 migraine patients and 275 normal subjects	Iranian	TP-ARMS-PCR, PCR–RFLP	rs4846049 and C677T variants were associated with migraine risk	(Salehi et al. 2018)
PRDM16	SNP (rs2651899)	150 patients with migraine and 150 healthy volunteers	North Indian population	PCR–RFLP	CT and TT genotypes were associated with increased migraine risk. Also, rs2651899 was a factor for migraine predisposition in migraine patients without aura and a female subgroup	(Kaur et al. 2019)
PRDM16	SNP (rs2651899)	Blood samples from 1806 unrelated migraine patients	Danish	Centaurus assays	rs2651899 was associated with efficacy of triptans treatment in migraine patients	(Christensen et al. 2016)
UTS2	SNP (Thr21Met rs228648, Ser89Asn rs2890565)	Blood samples from 186 migraine patients without aura and 171 healthy subjects	Turkish	TaqMan SNP Genotyping Assay	Thr21Met polymorphism but not Ser89Asn polymorphism was associated with migraine risk	(Geyik et al. 2016)

Table 1 (continued)

Gene	Polymorphism	Samples	Population	Assay method	Association	Reference
CD40	SNP (rs1883832)	Blood samples from 190 migraine patients with and 200 healthy volunteers as controls	Iranian	PCR–RFLP	TC genotype was associated with migraine risk and also was associated with higher levels of soluble CD40L	(Ramroodi et al. 2018)
GWAS	SNP (rs72793414)	380 African-American children and 2129 ancestry-matched volunteers as controls, another 233 African-American patients and 4038 controls without migraine	African-American	Illumina Infinium II HumanHap550 and Human Quad610 BeadChips	rs72793414 was correlated with risk of migraine in African-American children. Also, genotypes of this SNP were associated with NMUR2 mRNA expression level	(Chang et al. 2018)
MDR1	C3435T	Blood samples from 251 migraine patients	Turkish	RPC-RFLP	MDR1 3435TT genotype was associated with favorable response to prophylactic migraine treatment with topiramate	(Atasayar et al. 2016)
CYP19A1 NRIP1 ESR1	SNP (CYP19A1 rs10046, NRIP1 rs2229741, ESR1 rs726281)	Blood samples from 142 migraine patients and 141 nonmigraine subjects	Turkish	BioMark 96.96 dynamic array system	rs10046 TT genotype was correlated with migraine risk. rs2229741 GG genotype was correlated with migraine risk in female patients, and the rs726281 GG genotype was associated with migraine related to menstruation in female patients	(Coşkun et al. 2016c)
ESR1	SNP (rs2234693, rs9340799)	494 migraine patients and 533 controls	Chinese	Sequenom MALDI-TOF mass spectrometry iPLEX platform	rs2234693 was associated with migraine risk and rs2234693-rs9340799 TA haplotype was correlated with migraine risk	(An et al. 2017b)
MEIS1	SNP (rs2300478)	211 migraine patients with restless leg syndrome (RLS) and 781 patients with migraine without RLS	Taiwanese	iPLEX Gold primer extension assays	Associated with elevated risk of RLS in migraine patients	(Fuh et al. 2016)
DLG2 GFRA1	SNP (DLG2 rs655484, GFRA1 rs3781545)	1120 migraine patients and 604 gender-matched healthy controls	Han Chinese	Sequenom MassARRAY iPLEX platform	Both rs655484 and rs3781545 were associated with migraine risk	(Chen et al. 2018)

Table 1 (continued)

Gene	Polymorphism	Samples	Population	Assay method	Association	Reference
Lp-PLA2	SNP (rs1051931 or Ala-379Val)	Blood samples from 103 migraine patients and 100 healthy volunteers	Iranian	HRM PCR	The V allele had lower frequency in migraine patients in comparison to controls and this polymorphism was associated with decreased risk of migraine	(Haghdoost et al. 2016)
DRD2	SNP (rs1800497)	Blood samples from 250 migraine patients and 250 age- and gender-matched volunteers as controls	Han Chinese	TaqMan-based qPCR	rs1800497 was correlated with migraine risk in female patients, and its genotypes were associated with different plasma levels of DRD2	(Deng et al. 2018)
HCRTR1	SNP (G1222A rs2271933, *G29A rs41263963)	Blood samples from 123 patients with migraine and 123 control subjects	Polish	PCR, HRMA and sequencing	G1222A and *G29A may be associated with different subtypes of migraine comprising migraine with aura and migraine without aura	(Kowalska et al. 2018)
COX-2	SNP (rs20417, rs689466)	Blood samples from 100 patients with migraine and 100 non-migraine subjects	Iranian	PCR–RFLP	CC and CG genotypes of rs20417 and GG and AG genotypes of rs689466 were correlated with increased risk of migraine	(Mozaffari et al. 2016)
COX-2	SNP (Gly587Arg rs3218625)	Blood samples from 110 unrelated migraine patients and 108 healthy controls	Han Chinese	LDR-PCR	GG genotype of rs3218625 was associated with increased risk of migraine	(Guan et al. 2020)
5-HTR2C	SNP (rs3813929)	Blood samples from 135 migraine patients and 139 controls	Turkish	96.96 dynamic array	rs3813929 was associated with migraine risk in a Turkish population	(Yücel et al. 2016)
5-HTR6	SNP (rs770963777)	Blood samples from 92 vestibular migraine patients and 100 healthy volunteers	Chinese	TaqMan SNP assay	Genotypic and allelic frequencies were different between vestibular migraine (VM) patients and control group, and rs770963777 was correlated with VM onset	(Wu et al. 2020)

Table 1 (continued)

Gene	Polymorphism	Samples	Population	Assay method	Association	Reference
MEFV	SNP (M694V, M694I, M680I, V726A, R761H, K695R, P369S, E148Q)	220 patients with migraine and 228 healthy subjects	Turkish	TaqMan real-time PCR	Heterozygotes of E148Q had significantly high frequency in the control group, but homozygotes and the compound heterozygotes for other mutations were higher in the patient group	(Coşkun et al. 2016b)
NGF	SNP (rs6330)	288 migraine patients and 288 healthy controls	Turkish	TaqMan 5′-exonuclease allelic discrimination assays	TT genotype was higher in migraine patients with aura and may be a potential risk factor for developing aura in migraine disease	(Coşkun et al. 2016a)
-	SNP (rs4379368, rs10504861, rs12134493)	Blood samples from 201 patients with migraine and 200 healthy volunteers as controls	Han Chinese	PCR–RFLP and direct sequencing	CT genotype of rs4379368 and TT genotype of rs10504861 have high frequency in patients with migraine with aura and can be considered as potential factors for predisposition to migraine with aura. rs12134493 can be a potential factor for the risk of migraine without aura	(Lin et al. 2017)
SYN1 SNAP25 STXBP5 UNC13B	SNP (SYN1 rs5906435, SNAP25 rs363039, STXBP5 rs1765028, UNC13B rs7851161)	Blood samples from 188 unrelated headache patients and 286 healthy subjects	Population from northern Portugal	SNaPshot	C allele of rs5906435 was accompanied with increased risk of migraine in females. CT genotype of rs363039, rs1765028 T allele and TT genotype of rs7851161 were significant risk factors for migraine	(Quintas et al. 2020)
LGR6	SNP (LGR6 rs77234324, rs79004933 in the intergenic region	Blood samples from 53 migraine patients with RLS and 180 migraine patients without RLS	Taiwanese	Affymetrix array	rs77234324 and rs79004933 were correlated with elevated risk of RLS in migraine patients	(Lin et al. 2020)
RORA	SNP (rs4774388)	Blood samples from 200 patients with migraine and 200 healthy subjects	Iranian	TP-ARMS-PCR	There was a significant association between the rs4774388 polymorphism and migraine risk	(Farahani et al. 2020)

Table 2 The role of HLA alleles in conferring risk of migraine

HLA region	Samples	Population	Assay method	Association	Reference
HLA-DQB1	52 migraine patients with aura, 53 migraine patients without aura, and 50 healthy volunteers	Brazilians	PCR-ASA	HLA DQB1*0602 allele frequency did not differ between migraine patients and controls	(Coelho et al. 2007)
HLA-DRB1	Blood samples from 255 migraine patients and 325 healthy subjects	Italians	PCR amplification using specific probes and primers	Frequency of the DRB1*12 allele was significantly decreased and the DRB1*16 allele was significantly augmented in migraine patients in comparison to controls	(Rainero et al. 2005)
HLA-DR2	Blood samples from 45 migraine patients and 53 healthy volunteers as controls	Italians	PCR-SSP	The HLA-DR2 allele frequency was decreased in migraine patients with aura in comparison to migraine patients without aura and control subjects	(Martelletti et al. 1999)
HLA-B	Blood samples from 50 migraine patients and 80 control volunteers	Caucasians	Microlymphocytotoxicity assay	HLA-B8 and HLA-B27 frequencies were increased in migraine patients but this was not statistically significant	(O'Neill et al. 1979)
HLA-B HLA-C	2999 subjects with migraine or headache history and 6055 subjects	Taiwanese	Axiom Genome-Wide Single Nucleotide Polymorphism Arrays	HLA-B*39:01, HLA-B*51:01, HLA-B*58:01, and HLA-C*03:02 alleles were significantly correlated with migraine risk	(Huang et al. 2020)

Table 3 Mitochondrial DNA changes and polymorphisms in migraine

mtDNA variant	Samples	Population	Assay method	Association	Reference
T4216C G13708A	Two cohorts including 248 migraine patients and 310 controls in one cohort and 458 migraine patients and 384 controls in another cohort	Spanish	MALDI-TOF MS using Sequenom MassArray System and iPLEX Gold genotyping chemistry	These polymorphisms were associated with migraine in second cohort but the results were not replicated in the other cohort	(Fachal et al. 2015)
hypervariable region 1	30 cyclic vomiting syndrome (CVS) patients, 30 randomly ascertained CVS (rCVS), 18 migraine patients with aura (MA), 32 migraine patients without aura (MO) and 35 control haplogroup H cases	North American population	Temporal temperature gradient gel electrophoresis (TTGE)	Homoplasmic sequence variants, within the nt 16040–16188 segment, were threefold more common in CVS groups and MO patients in comparison to control subjects and were associated with CVS and migraine without aura	(Wang et al. 2004)
3243A > G	Blood samples from 57 mDNA 3243A > G carriers and 3471 controls	Danish	Allele-specific PCR	Prevalence of migraine in carriers of this mutation was significantly higher including both migraine with aura and without aura and both genders	(Guo et al. 2016)
3243A > G	Blood samples from 25 migraine patients with aura who have affected mothers	Italian	PCR–RFLP	This polymorphism was not detected in any of the subjects	(Gennaro et al. 2000)
16519C > T 3010G > A	112 haplogroup-H migraine patients without aura, 30 patients with CVS, and 231 controls	European-American, British, American, Italian, Finnish, German	PCR–RFLP	These two polymorphisms were highly associated with migraine risk	(Zaki et al. 2009)
ND4 11084A > G	Blood samples from 30 migraine patients with aura, 30 migraine patients without aura and 30 non-migraineurs	Danish	PCR–RFLP	This mutation was not detected in Danes	(Russell et al. 1997)
11084A > G	Blood samples from 164 migraine patients and 64 controls	Korean	PCR–RFLP	There was no association between this polymorphism and migraine risk	(Kang et al. 2007)
11084A > G	Blood samples from 166 migraine patients and 483 controls	Japanese	C,D3D!C	This polymorphism was not associated with migraine risk	(Takeshima et al. 2001)
MELAS mutations (A3243G, C3256T, T3271C, T3291C, A5814G, T8356C, T9957C, G13513A, and A13514G) LHON mutations (T4216C, A4917G, and G13708A)	Blood samples from samples from 10 migraine patients with prolonged aura	-	PCR–RFLP	None of these mutations was found in migraine patients with prolonged aura	(Rozen et al. 2004)
Mitochondrial GWAS	Blood samples from 71,860 participants	Nord-Trøndelag (Norwegian county)	Illumina HumanCoreExome microarray	None of the mtDNA polymorphisms and haplogroups were correlated with migraine	(Børte et al. 2020)

among migraineurs as well (Greco et al. 2020). Vgontzas et al. used single-cell RNA sequencing data obtained from different parts of the nervous system to investigate the signature of possible migraine-related genes in various cell types in these tissues. Their experiments revealed broad expression of most of migraine-associated genes. However, they also identified numerous cell-type-specific migraine-related genes as well (Vgontzas and Renthal 2020). Through a comprehensive transcriptome analysis, Kogelman et al. identified the differential expression of *NMNAT2* and *RETN* genes between migraineurs with aura and healthy subjects; however, they could not verify these results in an independent set of patients (Kogelman et al. 2019). Table 4 reviews the results of high-throughput studies assessing RNA signatures in migraine.

Expression of miRNAs in Migraine

miRNAs are small non-coding RNAs which are created via a multi-step procedure in two distinct cellular compartments, i.e. cytoplasmic and nuclear spaces. They principally attach to the 3′-UTR of complementary targets via their seeding region and degrade the transcript or suppress its translation (O'Brien et al. 2018). miRNA profiles have also been assessed in the peripheral blood of migraineurs. Andersen et al. measured serum miRNA signatures in these patients throughout migraine episodes and pain-free intervals compared with healthy subjects. The authors reported differential expression of 32 miRNAs and demonstrated a significant increase in miR-34a-5p and miR-382-5p levels during headache attacks. The former miRNA was also suggested as a biomarker for migraine based on the significant difference in its expression in the pain-free interval compared with healthy status (Andersen et al. 2016). Cheng et al. reported upregulation of miR-155, miR-126, and let-7 g in migraineurs compared with controls. Notably, expression levels of miR-155 and miR-126 in migraineurs were correlated with syncope rate in the previous year (Cheng et al. 2018). Tafuri et al. demonstrated upregulation of miR-27b and downregulation of miR-181a, let-7b, and miR-22 in migraineurs without aura compared with controls. The MiRNA signature accurately distinguished migraineurs from controls. Notably, these miRNAs were functionally related to atherosclerosis and stroke (Tafuri et al. 2015). Gallelli et al. quantified expression levels of hsa-miR-34a-5p and hsa-miR-375 in the serum and saliva of migraineurs without aura versus controls. They reported upregulation of hsa-miR-34a-5p and hsa-miR-375 in saliva samples of untreated migraineurs compared with controls. In addition, levels of these miRNAs were lower in treated migraineurs than in untreated persons (Gallelli et al. 2019). Finally, peripheral transcript levels of miR-30a were decreased in the peripheral blood of migraineurs compared with controls in association with hypermethylation of its promoter region. In addition, its expression was downregulated in subjects with bilateral seizures, insistent pain, and high pain index. miR-30a has been shown to target CALCA. Taken together, these results indicate that reduced expression of miR-30a in migraineurs could relieve migraine via suppression of CALCA (Zhai and Zhu 2018). Table 5 reviews the altered expression of miRNAs in migraine.

In Vivo Studies

Based on the acknowledged role of inflammatory substances and vascular inflammatory agents in the pathogenesis of migraine, Abdollahi et al. assessed IL-6 and CRP levels in migraineurs following administration of curcumin and ω-3 fatty acids. They demonstrated downregulation of both substances following treatment with ω-3 and nano-curcumin. Thus, they suggested ω-3 fatty acids and curcumin supplementation as a therapeutic modality for prevention of migraine (Abdolahi et al. 2019). These two substances had synergic effects in decreasing expression of COX-2/iNOS transcripts in the serum samples of migraineurs. In addition, the combined administration of these agents significantly decreased the rate, severity, and length of headaches (Abdolahi et al. 2018). An animal study demonstrated the effects of long-term and recurrent administration of systemic nitroglycerin in inducing the expression of CGRP in central areas and its possible role in the process of pain perception and its association with the GABAergic system (Greco et al. 2018). Another animal study revealed the role of microglial NLRP3 inflammasome stimulation in the mediation of IL-1β production and central sensitization in an animal model of migraine (He et al. 2019). In a mouse model of nitroglycerin-induced migraine, 109 genes showed nitroglycerin treatment-by-region interaction. The solute carrier family 32 member 1 (Slc32a1) and preproenkephalin (Penk) were two of these genes with reversal of expression profiles between the nitroglycerin and control groups. Erbb4 and Slc1a2 displayed constant differential expression between treatments. Notably, numerous transcription factors were found to be among the nitroglycerin-disturbed target genes (Jeong et al. 2018). Table 6 summarizes the results of in vivo studies in migraine which reported altered gene expression.

In Vitro Studies

CGRP is a neuropeptide with strong vasoactive properties and is a biomarker of trigeminal inflammation. This molecule has essential roles in diverse kinds of migraine

Table 4 Altered expression of genes in migraine

Gene	Samples	Source of samples	Population	Results	Reference
Gene expression of endocannabinoid system components	25 patients with episodic migraine, 26 patients with chronic migraine. and 24 age-matched healthy controls	PBMCs of participants	Italian	Expression of CB1, CB2, MAGL, and DAGL genes were elevated in both episodic and chronic migraine subjects. FAAH expression was lower in migraineurs	(Greco et al. 2020)
Single-cell RNA sequencing data	-	-	-	54 migraine-associated genes were expressed in central and peripheral nervous system. Six genes were expressed in central nervous system cell types, 3 genes in neurovascular cells, and 2 genes in peripheral nervous system cells	(Vgontzas and Renthal 2020)
RNA sequencing	17 female migraine patients without aura, 9 female migraine patients with aura, and 20 age-matched female controls Replication cohort included 2407 females, among which 21 were diagnosed with migraine with aura	Cubital venous blood	Danish and Icelandic	Only NMNAT2 and RETN had differential expression between migraine with aura and control group, but these results were not reproduced in a replication cohort	(Kogelman et al. 2019)
Cytokine-coding genes	120 migraine patients (66 patients with migraine with aura and 54 patients with migraine without aura) and 40 healthy subjects as controls	Blood samples from participants	Iranian	Expression of INF-γ was upregulated in migraine patients compared with controls (it also had lower expression in female than in male patients) Also IL-4, TGF-β, and TNF-α were overexpressed in patients compared with controls CXCL8 was downregulated in patients compared with controls	(Taheri et al. 2020)

Table 5 Altered expression of miRNAs in migraine

microRNA	Samples	Source of samples	Population	Results	Reference
Serum microRNA profiling	Two cohorts of 24 migraine patients, and age- and gender-matched healthy subjects	Serum	Danish	32 microRNAs were differentially expressed. miR-34a-5p and miR-382-5p were upregulated in migraine attack miR-382-5p can be considered as diagnostic marker for migraine in pain-free period	(Andersen et al. 2016)
miR-155 miR-126 miR-21 Let-7 g	30 migraine patients without overt vascular risk factors and 30 gender- and age-matched healthy volunteers as controls	Plasma	Taiwanese	Expression of miR-155, miR-126, and let-7 g were elevated in migraine patients in comparison to controls There was a significant association between expression levels of miR-155 and miR-126 and syncope frequency in migraine patients in the past year	(Cheng et al. 2018)
MicroRNA profiling	15 female patients with migraine without aura and 13 matched healthy subjects	Exosomes and monocytic cells	-	miR-181a, let-7b, and miR-22 were significantly underexpressed and miR-27b was significantly overexpressed in migraine patients miR-22 and let-7b downregulation may be a potential diagnostic biomarker for migraine (AUC = 0.956)	(Tafuri et al. 2015)
hsa-miR-34a-5p hsa-miR-375	12 treated migraine patients without aura, 12 untreated migraine patients without aura, and 12 healthy volunteers as controls	Blood samples and saliva samples	Italian	hsa-miR-34a-5p and hsa-miR-375 were upregulated in untreated patients hsa-miR-34a-5p and of hsa-miR-375 significantly downregulated in treated patients in comparison to untreated patients	(Gallelli et al. 2019)
miR-30a	Migraine patients and healthy controls	Serum	-	miR-30a was significantly downregulated in migraine patients miR-30a can relieve migraine by targeting CALCA and degrading it	(Zhai and Zhu 2018)

Table 6 The results of in vivo studies in migraine

Gene	Samples	Population	Animal model	Results	Reference
IL-6	80 patients with episodic migraine	Iranian	-	ω-3 fatty acids and nano-curcumin alone and in combination decreased IL-6 gene expression in blood PBMCs, so these compounds may have therapeutic effects in prevention of migraine	(Abdolahi et al. 2018)
COX-2 iNOS	74 episodic migraine patients	Iranian	-	ω-3 fatty acids and nano-curcumin either alone or in combination downregulated COX-2 and iNOS mRNA expression in PBMCs isolated from patients	(Abdolahi et al. 2019)
PTX3	38 episodic migraine patients	Iranian	-	Nano-curcumin caused a decrease in PTX3 gene expression and serum levels in patients with migraine. Thus curcumin may be a potential treatment for migraine management	(Djalali et al. 2020)
CGRP c-Fos	-	-	Male Sprague Dawley rats were administered nitroglycerin (NTG) or vehicle (saline, alcohol 6% and propylene glycol) every 2 days over a 9-day period; another group of animals was injected with saline or topiramate every day for 9 days	Nitroglycerin caused spinal hyperalgesia and orofacial allodynia, in addition to elevation of CGRP and c-Fos gene expression in trigeminal ganglia and central areas, but topiramate reversed nitroglycerin effects	(Greco et al. 2018)
NLRP3 IL-1β	-	-	Mouse model of chronic migraine was established from male C57BL6/J mice through repeated intraperitoneal injection of nitroglycerin	Nitroglycerin injection augmented expression of NLRP3 and IL-1β and caused acute and chronic mechanical hyperalgesia. Inhibition of NLRP3 or IL-1β reversed these effects	(He et al. 2019)
RNA sequencing of trigeminal ganglia and the nucleus accumbens regions	-	-	Male C57BL6/J mice established as chronic migraine models by NTG administration Male C57BL6/J mice without administration of NTG as control group	Slc32a1 and Penk expression patterns had reversal profile between NTG and control groups. Erbb4 and Slc1a2 showed steady differential expression between treatments at different magnitudes	(Jeong et al. 2018)
CGRP A2aR A1R	-	-	Electrical stimulation of the trigeminal ganglion (ESTG) rat models	The expression of CGRP, A2aR and A1R was regulated by Tianshu capsule, and these proteins were implicated in pain transmission and regulation	(Lu et al. 2016)

Table 6 (continued)

Gene	Samples	Population	Animal model	Results	Reference
CGRP preproPACAP	-	-	Male Sprague Dawley rats were injected with Complete Freund's Adjuvant (CFA) or saline	Expression of CGRP and preproPACAP were enhanced concurrently in central region of activated trigeminovascular system and affected mechanical hyperalgesia formation	(Körtési et al. 2019)
CGRP	-	-	Male 6-week-old, specific-pathogen-free Sprague Dawley rats established as migraine model by repeated electrical stimulation of the superior sagittal sinus	Electroacupuncture at Fengchi (GB20) suppressed expression of CGRP in the trigeminovascular system of rat models and relieved migraine pain	(Zhao et al. 2017)
COX-2 CB1R CGRP CCK	-	-	60 mice and 48 Wistar rats	Hejie Zhitong prescription downregulated COX-2, CGRP, and CCK expression in midbrain but upregulated CB1R expression. Thus Hejie Zhitong prescription has anti-migraine effects	(Wang et al. 2020)

including the pure menstrual one. Ansari et al. assessed the anti-inflammatory impact of melatonin on CGRP transcript levels, levels of inducible nitric oxide synthase (iNOS), NO, and IL-1β production in an in vitro assay. They reported the role of melatonin treatment in reducing CGRP and NO synthesis as well as iNOS activity in the peripheral blood mononuclear cells of migraineurs (Ansari et al. 2017). Another in vitro study demonstrated the role of NO in the stimulation of trigeminal ganglion neurons for production of CGRP and other migraine-associated substances, possibly through induction of GSK-3β (Yao et al. 2020). Table 7 summarizes the results of in vitro studies in this regard.

Discussion

Migraine is a disorder with a complex genetic background. Numerous genome-wide association studies (GWAS) and single-gene association studies have reported an association between migraine and variants within neuronal and vascular related genes (Sutherland et al. 2019). Genetic variants might also influence the age of migraine onset or other clinical parameters. Although the frequency of alleles of some of these polymorphisms were not different among subgroups of migraineurs, a number of polymorphisms such as HLA-DR2 antigens were differently distributed among different subtypes of migraineurs. Therefore, these genes may signify different pathogenic events among migraine subtypes.

Although the numbers of HLA genotyping studies in migraine are few and the results are not consistent, they point to the presence of a putative immunologic background for migraine. Replicated studies in different ethnic groups are needed to verify the contribution of HLA loci in the pathophysiology of migraine.

Expression profiles of several mRNAs and miRNAs have been found to differ between migraineurs and healthy subjects. Notably, a specific miRNA signature was able to differentiate migraineurs in pain-free intervals from healthy controls, implying its role as a biomarker for migraine. Other miRNAs were also correlated with the occurrence of certain comorbid conditions in the migraineurs. There was a functional overlap between migraine-associated miRNAs and those related to atherosclerotic events, further supporting the role of vascular events in the pathogenesis of migraine.

The data presented above support dysregulation of several types of transcripts in the peripheral blood of migraineurs. However, few studies have explored the functional annotation of these genes and pathway-based analysis. A simultaneous analysis of mRNA and miRNA profiles would help in determining the functional links between dysregulated members of these transcripts and

Table 7 In vitro studies in migraine

Gene	Samples	Population	Assessed cells	Results	Reference
CGRP	12 patients with pure menstrual migraine and 12 age-and gender-matched healthy controls	Iranian	PBMCs were isolated from each group and treated with melatonin	Melatonin treatment significantly decreased CGRP mRNA expression in the patient group. In addition, nitric oxide production and iNOS activity were decreased in the patient group. Thus melatonin can decrease inflammation in migraine patients	(Ansari et al. 2017)
CGRP	Postnatal 3-day-old Wistar rats	-	Trigeminal ganglia cells were removed from rats	Nitric oxide (NO) caused upregulation of CGRP by activating the Akt/GSK-3β/NF-κB signaling pathway in trigeminal ganglion neurons	(Yao et al. 2020)

better identification of the molecular events in the pathologic course of migraine. Moreover, assessment of the functional link between migraine-associated SNPs and genes with altered expression would further facilitate the understanding of the pathology of migraine. For instance, *CALCA* is regarded as a risk locus for migraine, while this gene has been shown to be targeted by miR-30a, a miRNA which is dysregulated in migraineurs through epigenetic mechanisms.

Collectively, migraine is a disorder with several genetic loci, each explaining a small portion of migraine heritability. Epigenetic factors such as DNA marks can also change expression patterns of migraine-associated genes, thus participating in the pathogenesis of this condition. Future studies should focus on identifying the interplay between environmental factors and genetic/epigenetic factors in the context of migraine. The signature of all classes of non-coding RNAs should be recognized during the migraine attack and in response to environmental risk factors.

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Author Contributions MT and SGF wrote the draft and revised it. KE, MGH and MS collected the data, and designed the tables and figures. All authors contributed equally and read the submission.

Data Availability The data sets generated and analyzed during the study are available from the corresponding author on reasonable request.

Compliance with Ethical Standards

Competing Interests The authors declare that they have nothing to report.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent forms were obtained from all study participants. The study protocol was approved by the ethical committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.RETECH.REC.1398.304). All methods were performed in accordance with the relevant guidelines and regulations.

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