



Advance in genetics of migraine

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Purpose of review

Migraine is a primary headache disorder and one of the most common and disabling neurological diseases worldwide. Genome-wide association studies have identified ≈ 40 genetic loci associated with migraine. How these and other genetic findings are used to expand our knowledge on the pathophysiological mechanism of common migraine and rare migraine variants will be discussed.

Recent findings

The genetic load, based on common polygenic variation, is higher in familial migraine cases than in nonfamilial cases, and higher for migraine with aura and hemiplegic migraine. Migraine shares common genetic variant risks with depression. Specific clinical features of common migraine seem to be determined by genetic factors. A stronger family history of migraine is associated with lower age-at-onset, higher frequency and number of medication days and the migraine with aura subtype. Mild hemiplegic migraine is likely caused by complex polygenic interaction of multiple gene variants and environmental factors, like in common migraine subtypes. Phenotypical features in hemiplegic migraine patients may guide physicians in providing adequate genetic counseling.

Summary

Integration of genetic, phenotypic and epigenetic data will help to identify the biological mechanisms by which genetic factors contribute to migraine pathogenesis. Recent studies show the impact of genetics on clinical features and comorbidities in migraine and may guide clinicians to an adequate genetic advice for patients.

Keywords

depression, genetics, genome-wide association study, hemiplegic migraine, migraine

INTRODUCTION

Migraine is a disabling episodic brain disorder characterized by headache attacks associated with photophobia and phonophobia and/or nausea or vomiting [1]. In approximately one-third of patients, headaches are preceded by transient focal neurological symptoms, so-called auras. Hemiplegic migraine is a rare subtype of migraine with aura in which the aura phase includes motor weakness [2]. Migraine is rated as the second most disabling disorder [3] and is often associated with other neurological or psychiatric disorders, such as stroke, epilepsy and depressive disorder [4–6]. A study in a genetic isolate suggested that the bidirectional association between depression and migraine, in particular, migraine with aura, can be partly explained by shared genetic factors [7].

Over the past decade, genome-wide association studies (GWAS) have made important contributions to identifying genetic components involved in migraine. These studies provided further evidence that common types of migraine are genetically complex in the sense that multiple genetic variants, with

small effect sizes, together with environmental factors confer migraine susceptibility. Epidemiological studies suggested that familial occurrence is most profound with an early disease onset and the aura subtype, indicating a possibly higher genetic susceptibility in migraine with aura [8,9]. Therefore, it seemed paradoxical that for migraine without aura, more robust associations with genetic loci were

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KEY POINTS

- Integration of genetic, phenotypic and epigenetic data will help to identify the biological mechanism by which common variants can regulate genes and contribute to the pathogenesis of migraine.
- The genetic load, based on common polygenic variation, is higher in familial migraine cases than in nonfamilial cases, and higher for migraine with aura and hemiplegic migraine.
- Specific clinical features of migraine seem to be determined by genetic factors. A stronger family history of migraine is associated with lower age-at-onset, higher frequency and number of medication days and the migraine with aura subtype.
- Migraine shares common genetic variant risks with psychiatric diseases among which depression. These results highlight the importance of common genetic variation as a risk factor for brain disorders and the value of heritability-based methods in understanding their etiology.
- Most patients with hemiplegic migraine without a mutation in the three known HM genes (*CACNA1A*, *ATP1A2*, or *SCN1A*) display a mild phenotype that is more akin to that of common migraine with aura. A major fourth gene for hemiplegic migraine might be unlikely. Thus, not all offspring of hemiplegic migraine cases seem to have an a priori 50% chance, in case of autosomal dominant inheritance, to get the disease. Mild hemiplegic migraine is likely to be caused by complex polygenic interaction of multiple gene variants with small effect and environmental factors, like in common migraine subtypes. Phenotypical features in hemiplegic migraine patients may guide physicians in selecting patients for mutation screening and in providing adequate genetic counseling.

discovered in the migraine GWAS [10]. It was hypothesized that this suggests that medium/high-risk alleles with rare(r) prevalence, not captured in GWAS, confer susceptibility to migraine with aura instead. This was further supported by the fact that hemiplegic migraine, a rare monogenic syndrome at the end of the spectrum of the aura subtype, is caused by missense mutations in the *CACNA1A* (FHM1), *ATP1A2* (FHM2) and *SCN1A* (FHM3) genes [1,11]. Recent reports suggested that the *PRRT2* gene might be the fourth hemiplegic migraine gene. There is, however, reasonable doubt, already because *PRRT2* was typically shown to be associated with paroxysmal kinesigenic dyskinesia, benign familial infantile seizures, or infantile convulsion choreoathetosis syndrome in hundreds of patients [12]. Only in a few typical *PRRT2* families, hemiplegic migraine was reported in some mutation carriers, most of which also had the typical

phenotype. Vice versa, *PRRT2* mutations were found in less than 5% of index cases with hemiplegic migraine who often also displayed the typical phenotypes [13]. The most logical conclusion is that a *PRRT2* mutation is not sufficient to cause hemiplegic migraine. Likely, in those few *PRRT2* mutation carriers who displayed hemiplegic migraine, additional gene variants interacting with the *PRRT2* mutation may be involved. This would, thus, imply that in part of the hemiplegic migraine families a complex genetic rather than a monogenic mechanism causes the disorder [13].

The present review aims to highlight the most recent advances in migraine genetics, focusing on studies that have used GWAS data to explore pathophysiological mechanisms, and on studies that investigated to what extent (endo)phenotypes, individual features of migraine, familial occurrence of migraine and comorbid neuropsychiatric conditions are determined by genetic susceptibility. Additionally, the clinical spectrum of hemiplegic migraine and chances of finding a pathogenic mutation will be discussed.

FROM GENOME-WIDE ASSOCIATION STUDIES TO INCREASING INSIGHT IN MIGRAINE PATHOGENESIS

Several GWAS have been performed in migraine [10,14–18]. In a GWAS several million common DNA variants, so called single-nucleotide polymorphisms (SNPs), that are dispersed over the genome are tested in large cohorts for association with a trait. By identifying different allele frequencies between patients and controls that survive rigorous multiple testing correction genomic regions that associate with a disease are identified. GWAS have been undertaken that focus on migraine without aura [15], migraine with aura [17], clinic-based samples [15,17] and population-based samples [16]. The most recent meta-analysis GWAS included 59 674 cases and 316 078 controls and identified 38 distinct genomic regions associated with migraine (Table 1) [14]. The likely implicated genes related to these SNPs are involved in neuronal, vascular, metalloproteinases, pain and metal-iron-related pathways [10,14,19^{*}]. This GWAS also employed pathway analysis, which indicated typical enrichment of genes from the vascular pathway, highlighting a possible vascular cause of migraine [14]. However, the analysis was limited as only the genes closest to the respective significant index SNP were considered and the gene nearest to the associated SNP may not always be the causal gene [14]. Hence, further analyses are needed for each SNP to clarify the exact relationship to migraine. A study by Gupta *et al.* [20]

Table 1. Loci associated with common migraine and headache and their association with clinic-based samples and migraine with and without aura

Index SNP ^a	Chromosome	Gene nearest index SNP	Gene prioritized with DEPICT ^b	Clinic-based migraine sample ^c	Migraine ^d	Migraine without aura ^e	Migraine with aura ^f	Headache ^g
Migraine loci found in Gormley <i>et al.</i> , 2016.								
rs10218452	1	<i>PRDM16</i>	<i>PRDM16</i>		X	X		X
rs1572668	1	<i>LRRIG3</i>			X			
rs2078371	1	<i>TSPAN2</i>	<i>NGF</i>		X			X
rs6693567	1	<i>ADAMTSL4</i>	<i>ECM1</i>		X			X
rs1925950	1	<i>MEF2D</i>		X	X	X		X
rs138556413	2	<i>CARF</i>	<i>NBEAL1</i>		X			
rs10166942	2	<i>TRPM8</i>		X	X	X	X ^h	X
rs6791480	3	<i>TGFBR2</i>	<i>TGFBR2</i>	X	X	X		
rs13078967	3	<i>GPR149</i>	<i>ARHGEF26</i>		X			X
rs7684253	4	<i>SPINK2</i>	<i>REST</i>		X			
rs9349379	6	<i>PHACTR1</i>		X	X	X		X
rs140002913	6	<i>NOTCH4</i>			X			
rs10456100	6	<i>KCNK5</i>			X			
rs67338227	6	<i>FHL5/UFL1</i>		X	X	X	X ^h	X
rs28455731	6	<i>GJA1</i>	<i>GJA1</i>		X			X
rs1268083	6	<i>HEY2</i>	<i>HEY2</i>		X			
rs186166891	7	<i>SUGCT</i>		X	X			
rs10155855	7	<i>DOCK4</i>			X			
rs6478241	9	<i>ASTN2</i>		X	X	X		X
rs2506142	10	<i>NRP1</i>	<i>NRP1</i>		X			
rs10786156	10	<i>PLCE1</i>	<i>PLCE1</i>		X			
rs12260159	10	<i>HPSE2</i>	<i>HPSE2</i>		X			
rs2223089	10	<i>ARMS2</i>	<i>HTRA1</i>		X			X
rs4910165	11	<i>MRV11</i>	<i>MRV11</i>		X			X
rs11031122	11	<i>MPPED2</i>			X			
rs10895275	11	<i>YAP1</i>	<i>YAP1</i>		X			
rs561561	11	<i>IGSF9B</i>			X			
rs1024905	12	<i>FGF6</i>	<i>FGF6</i>		X			X ⁱ
rs11172113	12	<i>LRP1</i>	<i>LRP1</i>	X	X	X	X ^h	X
rs11624776	14	<i>ITPK1</i>			X			
rs77505915	16	<i>CFDP1</i>			X			X
rs4081947	16	<i>ZCCHC14</i>	<i>ZCCHC14</i>		X			
rs75213074	17	<i>WSCD1</i>			X			
rs17857135	17	<i>RNF213</i>			X			
rs111404218	20	<i>JAG1</i>	<i>JAG1</i>		X			
rs4814864	20	<i>SLC24A3</i>			X			
rs144017103	20	<i>CCM2L</i>	<i>CCM2L</i>		X			
rs12845494	X	<i>MED14</i>			X			
Additional migraine loci identified in previous GWAS								
rs10915437	1	<i>AJAP1</i>	-	X				
rs1835740	8	<i>MTDH</i>	-	X			X	
rs10504861	8	<i>MMP16</i>	-			X		
rs11172113	12	<i>TARBP2/NPFF</i>	-			X ^h	X ^h	
Additional headache loci identified by Meng <i>et al.</i> , 2018								
rs2036465	1	<i>MACF1</i>	-					X

Table 1 (Continued)

Index SNP ^a	Chromosome	Gene nearest index SNP	Gene prioritized with DEPICT ^b	Clinic-based migraine sample ^c	Migraine ^d	Migraine without aura ^e	Migraine with aura ^f	Headache ^g
rs7555006	1	<i>CDKN2C</i>	-					X
rs3748784	1	<i>PTBP2</i>	-					X
rs2072806	6	<i>BTN2A2</i>	-					X
rs4596713	9	<i>FXN</i>	-					X
rs2895526	10	<i>CAMK1D</i>	-					X
rs56349329	11	<i>ATG13</i>	-					X
rs6606710	12	<i>MYO1H</i>	-					X
rs7300001	12	<i>IFT81</i>	-					X
rs8614	17	<i>NUFIP2</i>	-					X
rs77804065	17	<i>LINC02210-CRHR1-MAPT</i>	-					X
rs4941139	18	<i>ZCCHC2</i>	-					X
rs1555132	20	<i>NOL4L</i>	-					X

GWAS, genome-wide association studies; SNPs, single-nucleotide polymorphisms.

^aSNPs found in migraine GWAS [14] and Headache GWAS [29].

^bGene-prioritization function used to identify likely causal gene at each GWAS locus with DEPICT, data-driven expression-prioritized integration for complex traits.

^cData from previous GWAS [10,15,17].

^dData from previous GWAS [14].

^eData from previous GWAS [15].

^fData from previous GWAS [17].

^gData from previous GWAS [29].

^hIdentified by using a gene-based pleiotropy approach across migraine with and without aura patient groups [25].

ⁱLoci not found in top 28 SNPs, however, SNP present in list of 3343 significant SNPs.

nicely illustrates how integration of genetic, phenotypic and epigenetic data led to the identification of the biologic mechanism. The common, noncoding, GWAS hit implied the *PHACTR1* as the locus for no less than five vascular diseases, including migraine. Through genetic fine-mapping and epigenomic analysis, the disease-associated SNP *rs9349379* in the third intron of the *PHACTR1* gene, was demonstrated to regulate expression of endothelin 1 (*EDN1*), a gene with a clear vascular function, that is located 600 kb upstream of *PHACTR1*. The known physiologic effects of *EDN1* on the vasculature may explain the pattern of risk for the five associated diseases including migraine. Furthermore, current evidence indicates that endothelin 1 may have a role in migraine attack induction [21].

Shared genetic architecture for migraine with and without aura

There has been continuous debate whether migraine with and without aura are distinct disorders or whether these subtypes are genetically related. Previous observations supported that the migraine subtypes are a continuum of severity, with migraine with aura being more severe but not etiologically distinct from migraine without aura [11,22–24]. Clinical and epidemiological studies showed that in many

patients, the prevailing form of migraine changes over time [24]. Moreover, the same prophylactic and acute migraine drugs may be effective in both migraine subtypes. Family studies demonstrated that subtypes of migraine co-occur within families [11,24]. Initially, GWAS focused on migraine with aura or without aura and found different genomic loci for both migraine subtypes [15,17]. These studies, however, had relative small sample sizes and only focused on the top SNP hits, so only on SNPs with *P* values below the genome-wide significance threshold (5×10^{-8}). Recently, significant overlap was found in the portion of shared genes associated with migraine with and without aura, which led to the conclusion that genetically the two migraine subtypes are more alike than different [25].

GENETIC LOAD OF MIGRAINE AND ITS ENDOPHENOTYPES

Family and twin studies estimated the heritability for migraine to be ~42% (95%CI: 36–47%) [26]. This is in line with the observation that migraine aggregates in families. A recent study, using a novel approach, used results of the most recent migraine GWAS [14] to create polygenic risk scores to see if the genetic load of these common variants contribute to the aggregation of migraine in families (1589

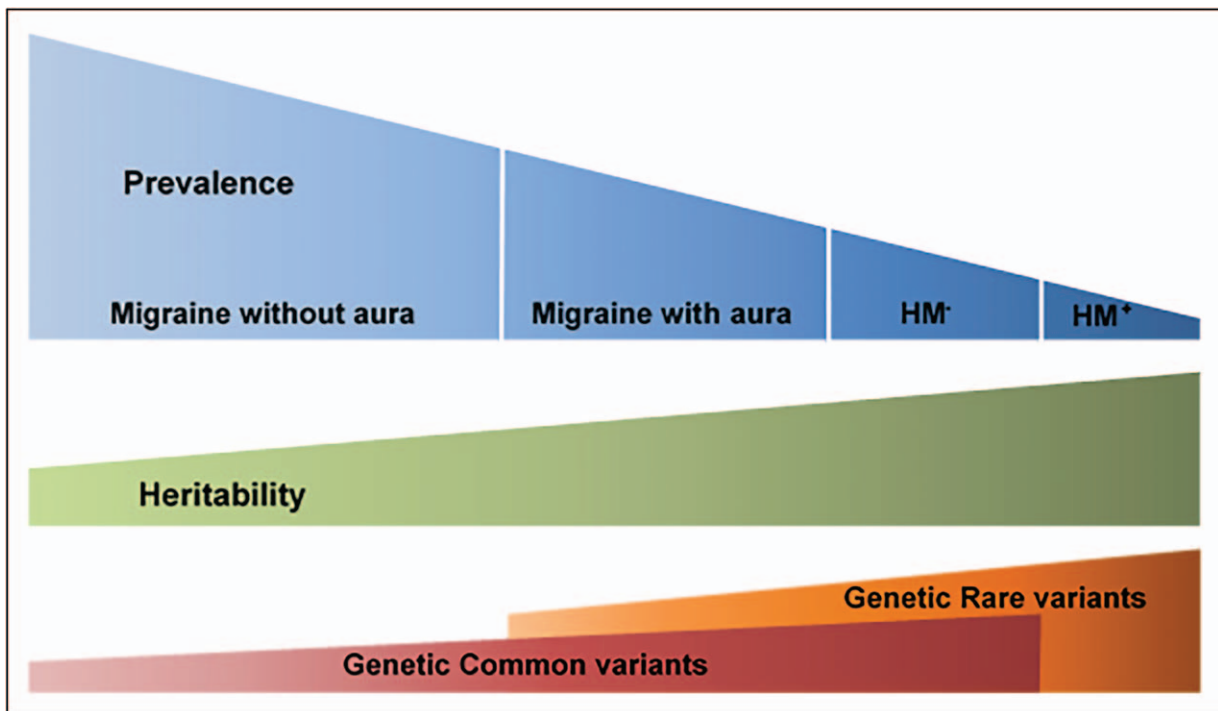


FIGURE 1. Migraine spectrum. As the prevalence of migraine decreases, common variant load appears to increase. Data from [27[■]]. HM^- hemiplegic migraine without mutation in one of the hemiplegic genes; HM^+ , hemiplegic migraine with a mutation in one of the hemiplegic migraine genes.

Finnish families were included) [27[■]]. Indeed, the aggregation of migraine in families can at least partly be explained by the contribution of common polygenic variations. Familial cases carried higher common variant burden compared with nonfamilial cases.

Migraine features determined by genetic predisposition

In this polygenic risk score study, the genetic load was higher in migraine with aura and hemiplegic migraine cases compared with migraine without aura (Fig. 1) [27[■]]. This could partially explain the lower prevalence of migraine with aura and hemiplegic migraine, as conceivably a higher genetic burden is required for developing these subtypes. There were no differences found between genetic common variant burden in migraine with aura and hemiplegic migraine (sporadic or familial) [27[■]]. This may be because of a lack of power as there were fewer hemiplegic migraine patients included. Another likely explanation is that rare genetic variants (not captured in GWAS), in combination with common variants, contribute to hemiplegic migraine. Importantly, the involvement of common variants in hemiplegic migraine is further indicated by the observation that 41% of the familial cases were in the highest quartile of polygenic risk (Fig. 1) [27[■]]. These findings provide compelling evidence that not all hemiplegic

migraine cases seem to be caused by single-gene mutations (see also paragraph predictors of finding a pathological mutation in hemiplegic migraine).

The Finnish study also showed that higher polygenic risk scores were associated with stronger family history of migraine, lower age-at-onset and the migraine with aura subtype [27[■]]. This is in accordance with a large Dutch clinical study in which a stronger family history of migraine, defined as one or both parents being affected, was associated with lower age-at-onset, higher frequency and higher number of medication days and the migraine with aura subtype [28[■]].

Overlap between genetic loci causing migraine and headache

A recent study from UK Biobank that had 74 461 cases and 149 312 controls identified 28 genomic loci associated with a broadly defined ‘headache’ phenotype (Table 1) [29]. Of note, ‘only’ 14 of the found loci were previously identified in a migraine GWAS (Table 1) [14]. There are three possible explanations for this finding. Firstly, these loci are involved in a broader headache pathway, as part of the cases may in fact be patients with tension type headache. Epidemiological studies showed co-occurrence of migraine and tension type headache previously [30]. Secondly, not all migraine patients

in the migraine GWAS may be true migraine patients and may have been misdiagnosed patients with another headache phenotype. Given the robustness of the associated SNPs in the migraine GWAS and the fact that six of the loci identified in the headache GWAS were also identified in clinical-based migraine GWAS, this scenario seems unlikely [10,14]. Thirdly, part of the headache cases suffered from migraine.

GENETIC RELATION BETWEEN MIGRAINE AND OTHER BRAIN DISORDERS

Substantial epidemiological comorbidity is found between neuropsychiatric disorders, including migraine [31,32^{*}]. To quantify the degree of genetic overlap between different brain disorders, the Brainstorm Consortium was formed. This consortium used GWAS summary statistics of a staggering 265 218 cases and 784 643 controls to assess the genetic risk factor overlap of 25 common brain disorders [32^{*}].

Genetic relation between migraine and psychiatric disorders, especially depression

Of note, the Brainstorm Consortium study indicated that migraine was correlated to several psychiatric disorders, including attention deficit hyperactivity disorder and major depressive disorder (Fig. 2) [32^{*}]. This is in agreement with a recent Australian study specifically searching for a shared genetic background for depression and migraine. In that meta-analysis in the combined 8 045 569 SNPs of the migraine GWAS

and the top 10 000 SNPs from a major depressive disorder GWAS, three novel risk loci were identified that were associated with both disorders [33]. Of the putative candidate genes, *CDCA2* is especially interesting, as it has been shown to be involved in a pathway linked to both migraine with and without aura [25]. Furthermore, gene-based association analyses revealed significant enrichment of genes associated with both migraine and major depressive disorder. Pathway analyses suggested several important pathways, especially neural-related pathways of signaling and ion channel regulation to be involved in this shared etiology [33]. This study shows that valuable genetic information can be found when considering all SNPs, more than only the significant (top) SNPs.

Genetic correlation between migraine and neurological disorders

The Brainstorm Consortium found no significant genetic risk overlap across neurological disorders. However, their results may indicate a possible genetic sharing between epilepsy and migraine, albeit not significant (Fig. 2) [32^{*}]. Not reaching significance may be explained by several factors including the relative small epilepsy cohort that was used, the heterogeneity of the epilepsy phenotype, and the fact that only summary statistics were used for the analyses [32^{*}]. The correlation between migraine and epilepsy is not surprising. For instance, in patients with hemiplegic migraine, there is often co-occurrence of epileptic and

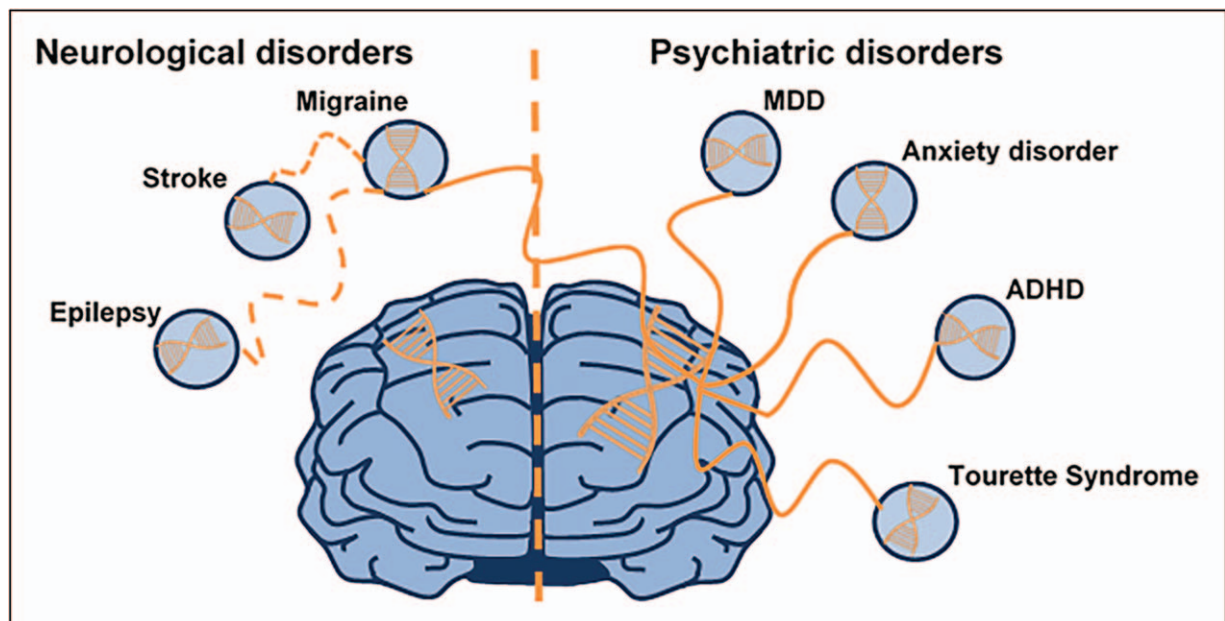


FIGURE 2. Shared genetic heritability between migraine and common brain disorders. Adapted from Anttila *et al.* [32^{*}]. MDD, major depressive disorder.

(hemiplegic) migraine attacks [34], and comorbidity between common migraine and epilepsy was also seen in epidemiological studies [31]. The Brainstorm Consortium also failed to find a significant genetic risk between ischemic stroke and migraine, despite the fact that an earlier GWAS had revealed substantial genetic overlap between both disorders [35] and epidemiological studies demonstrated increased risk of ischemic stroke in migraine patients [5,36]. Future studies with larger cohorts and more detailed data may be able to show genetic correlation for migraine and comorbid neurological disorders, such as epilepsy and stroke.

PREDICTORS OF FINDING A PATHOLOGICAL MUTATION IN HEMIPLEGIC MIGRAINE

Genetic and neurological counseling of patients with hemiplegic migraine is not only of value for themselves, but also for their offspring. Pelzer and coworkers investigated whether the clinical characteristics of patients with hemiplegic migraine with and without

autosomal dominant mutations in *CACNA1A*, *ATP1A2* or *SCN1A* differ, and whether disease in the latter may be caused by mutations in other genes. The clinical characteristics of 208 patients with familial ($n=199$) or sporadic ($n=9$) hemiplegic migraine because of a mutation in *CACNA1A*, *ATP1A2*, or *SCN1A* were compared with those of 73 patients with familial ($n=49$) or sporadic ($n=24$) hemiplegic migraine without a mutation in these genes [37^{*}]. In addition, 47 patients (familial: $n=33$; sporadic: $n=14$) without mutations in *CACNA1A*, *ATP1A2*, or *SCN1A* were scanned for mutations in novel genes by using whole exome sequencing (WES). The study showed that the chance of finding a mutation in one of the three FHM genes in a hemiplegic migraine patient is higher if attacks are characterized by more extensive motor weakness, associated with brainstem manifestations, confusion, or brain edema, or are triggered by mild head trauma (Fig. 3). Moreover, only mutation carriers have mental retardation, progressive ataxia or both [37^{*}]. Additionally, patients with mutations often have a younger age of disease onset and more affected family members [37^{*}].

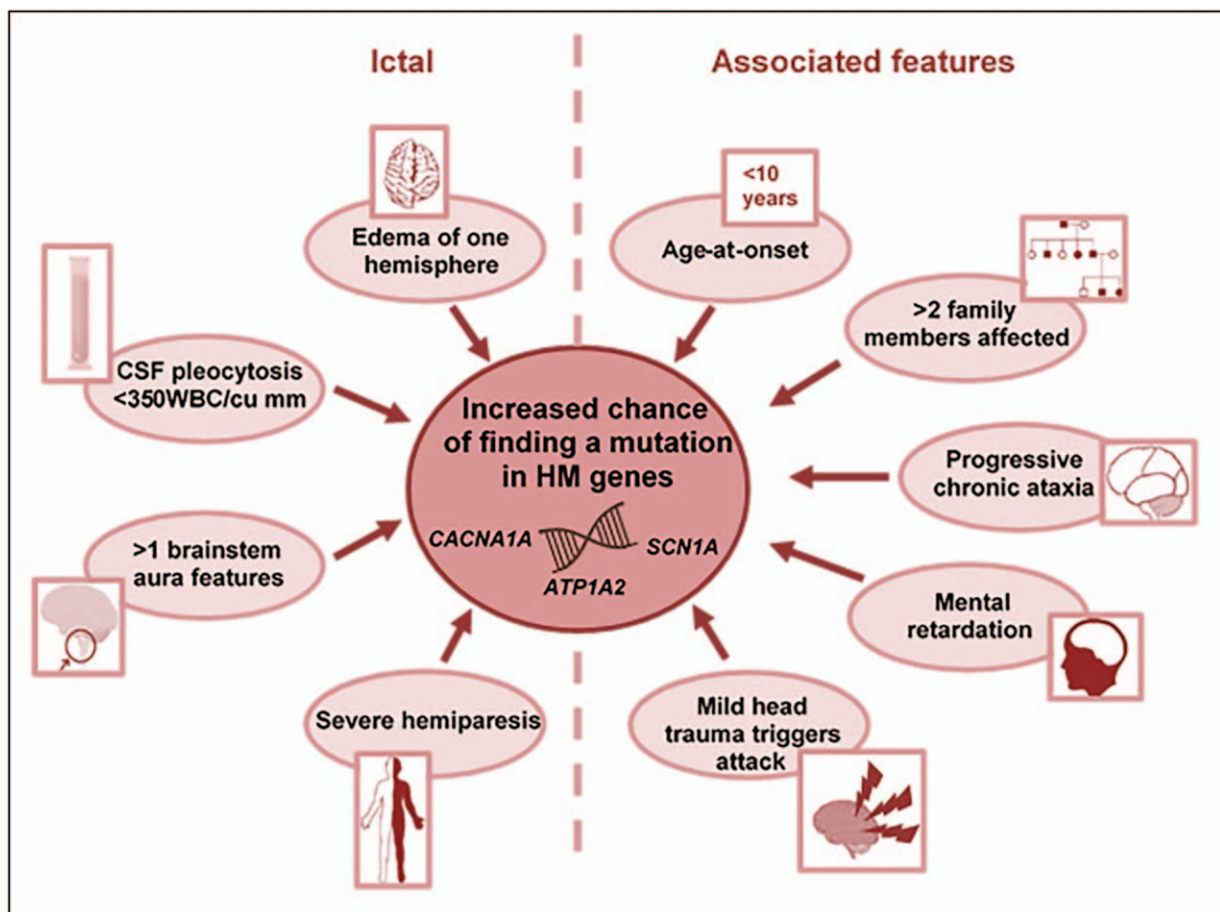


FIGURE 3. Predictors of finding a mutation in hemiplegic migraine. HM, hemiplegic migraine; WBC, white blood cell count. Adapted from Pelzer *et al.* [37^{*}].

Most patients with hemiplegic migraine without a mutation in *CACNA1A*, *ATP1A2* or *SCN1A* display a mild phenotype that is more akin to that of common (nonhemiplegic) migraine. This seems reflected by the fact that WES failed to identify pathogenic mutations in new genes that fit a Mendelian inheritance. A major fourth autosomal dominant gene for hemiplegic migraine may be unlikely, although this cannot be fully excluded. As a consequence, not all offspring of hemiplegic migraine cases have an a priori 50% chance to inherit hemiplegic migraine. Mild hemiplegic migraine is more likely caused by complex polygenic interaction of multiple gene variants with small effect, like in common migraine subtypes [27[■],37[■]]. Phenotypical features in hemiplegic migraine patients may guide physicians in selecting patients for mutation screening and in providing adequate genetic counseling [37[■]].

CONCLUSION

A new era in the genetics of migraine has begun with the identification of an increasing number of common genetic variants using the GWAS approach. Recent studies showed that the genetic load, based on common polygenic variation, is higher in familial migraine cases than in nonfamilial cases, and higher for migraine with aura and hemiplegic migraine. Mild hemiplegic migraine is likely caused by complex polygenic interaction of multiple gene variants, like in common migraine subtypes. Phenotypical features in hemiplegic migraine patients may guide physicians in providing adequate genetic counseling. Specific clinical features of common migraine seem to be determined by genetic factors. A stronger family history of migraine is associated with lower age-at-onset, higher frequency and number of medication days and the migraine with aura subtype. Migraine shares common genetic variant risks with depression.

Integration of genetic, phenotypic and epigenetic data will help to identify the biological mechanisms by which genetic factors contribute to migraine pathogenesis. It also shows the impact of genetics on clinical features and comorbidities in migraine and may guide clinicians to an adequate genetic advice for patients.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

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This article will help guide physicians in selecting hemiplegic migraine patients for mutation screening and will also help with providing adequate genetic counseling.