REVIEW

Exploring the Hereditary Nature of Migraine

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Abstract: Migraine is a common neurological disorder which affects 15–20% of the population; it has a high socioeconomic impact through treatment and loss of productivity. Current forms of diagnosis are primarily clinical and can be difficult owing to comorbidity and symptom overlap with other neurological disorders. As such, there is a need for better diagnostic tools in the form of genetic testing. Migraine is a complex disorder, encompassing various subtypes, and has a large genetic component. Genetic studies conducted on rare monogenic subtypes, including familial hemiplegic migraine, have led to insights into its pathogenesis via identification of causal mutations in three genes (*CACNA1A*, *ATP1A2* and *SCN1A*) that are involved in transport of ions at synapses and glutamatergic transmission. Study of familial migraine with aura pedigrees has also revealed other causal genes for monogenic forms of migraine. With respect to the more common polygenic form of migraine, large genome-wide association studies have increased our understanding of the genes, pathways and mechanisms involved in susceptibility, which are largely involved in neuronal and vascular functions. Given the preponderance of female migraineurs (3:1), there is evidence to suggest that hormonal or X-linked components can also contribute to migraine, and the role of genetic variants in mitochondrial DNA in migraine has been another avenue of exploration. Epigenetic studies of migraine have shown links between hormonal variation and alterations in DNA methylation and gene expression. While there is an abundance of preliminary studies identifying many potentially causative migraine genes and pathways, more comprehensive genomic and functional analysis to better understand mechanisms may aid in better diagnostic and treatment outcomes.

Keywords: migraine, migraine without aura, migraine with aura, familial hemiplegic migraine, X-linked, mitochondrial variants, epigenetics

Introduction

Migraine is a common neurovascular disorder which affects 15–20% of the population.[1–5] Given the prevalence of the disorder, migraine has a large socio-economic impact through treatment costs and loss of productivity, estimated at USD $19.6 billion, €27 billion and AUD$35.7 billion per annum in America, Europe and Australia, respectively.[4–6] Migraine is characterised by severe headache, typically including unilateral throbbing, nausea, vomiting, photophobia and/or phonophobia.[1–5,7,8] There are two common subtypes of migraine, which are determined by the presence or absence of aura.[9] Migraine without aura (MO) is the most common, affecting around 70% of migraineurs, while approximately 30% suffer migraine with aura (MA).[10,11] In MA, the migraine is accompanied by aura symptoms, largely manifested as visual disturbances, but can also include sensory and speech-related symptoms, muscle weakness and motor disturbances in some cases.[7,12]

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The Hereditary Nature of Migraine

It has long been established that there is a significant genetic component to migraine.[13,14] Studies have in addition shown an increased familial risk for common migraine, which is considered to be polygenic, with heritability estimates of 34–64%.[8,12,15] Investigations into migraine families and twin studies have shown that a first-degree relative of an MO proband is twice as likely to have MO and 1.4 times as likely to have MA.[12] However, a first-degree relative of an MA proband is four times more likely to have MA, but has no increased risk of MO.[12] Furthermore, there are some rare subtypes of migraine which are considered to be monogenic, predominantly caused by autosomal dominant mutations in genes encoding ion channels. Owing to the complex nature of common migraine, determining all genes and their interaction with environmental factors that contribute to the disorder remains a challenge.[16] Initial studies focused on genes involved in neuronal, vascular and hormonal functions using candidate gene association studies (CGAS), testing for differences in frequency of genetic polymorphisms across particular genes between migraine cases and controls to determine whether they influence susceptibility to the disorder.[17–20] An extensive study of 155 ion transporter genes in 841 migraineurs and 884 controls[21] identified 21 promising genes associated with migraine; however, these results failed to be replicated in a larger cohort of thousands, suggesting that the majority were potentially false positives.[22] This could be for several reasons: CGAS tend to have modest sample sizes which are underpowered to detect genetic variants that have small effects; they also use a hypothesis-driven set of genes and polymorphisms for testing,[23,24] and while the genes selected may have a likely role in the disease pathway, they may not present a genetic risk, or only be a cofactor of the cause. Many of these issues have been tackled through advances in technology which allow for fast and cost-effective genotyping. Genome-wide association studies (GWAS) use microarray platforms to test up to millions of single-nucleotide polymorphisms (SNPs) in one experiment. As GWAS are not hypothesis driven, they can identify novel genes and pathways, and with large sample sizes and statistical correction for multiple testing are less likely to produce the false positives of CGAS. The largest GWAS performed to date included 59,674 migraineurs and 316,078 healthy controls to identify 44 SNPs mapped to 38 loci associated with common

polygenic migraine.[25,26] This study largely supported previous GWAS performed by Anttila et al[25] and Chasman et al[27] identifying neuronal variants (Figure 1). Freilinger et al[28] added a number of genes associated with vascular pathways and, finally, the Gormley study introduced a number of genes related to ion homeostasis.[26]

Monogenic Forms of Migraine

An alternative approach used to study the complex genetic pathways of this neurological disorder is to examine monogenic subtypes of migraine,[12,27] and there have been a number of multigenerational studies performed on MA pedigrees[29] and unrelated hemiplegic migraine probands.[30,31]

Familial Migraine with Aura

A study of particular families which show strong inheritance of MA showed that a frameshift mutation of the *KCNK18/TRESK* gene segregated with migraine diagnosis, suggesting that it was causal.[29] This was further corroborated in a study by Pettingill et al, which demonstrated through the use of CRISPR-Cas9 that frameshift mutations of TRESK are associated with migraine phenotypes.[32] The *TRESK* gene is part of a two-pore domain family of potassium channels that regulate cellular excitability, and are themselves regulated by calcium-dependent phosphatase calcineurin.[29,33] A study by Rainero et al has also shown that mutations in TRESK can be found in non-related probands in both MO and MA populations.[34] In addition, mouse models have shown that knocking out *TRESK* modifies nociceptive afferentation.[35] While some variants have been found in this gene that are causal of MA, other studies have shown loss of function variants in both migraine and control populations.[33,36] This complex relationship may be explained by the findings that some *TRESK* frameshift mutations produce altered protein fragments which can affect the function of other ion channels.[37]

Rasmussen et al used an approach where they first identified migraine-associated modules through analysis of RNAseq from brain and vascular tissues, and then performed analysis of the genes from these modules in whole genome sequencing (WGS) data from migraine families with Mendelian-like segregating patterns. They found that rare variants in genes involved in five pathways were over-represented: thyrotropin-releasing hormone receptor signalling, oxytocin receptor-mediated signalling, Alzheimer's disease amyloid secretase, serotonin receptor
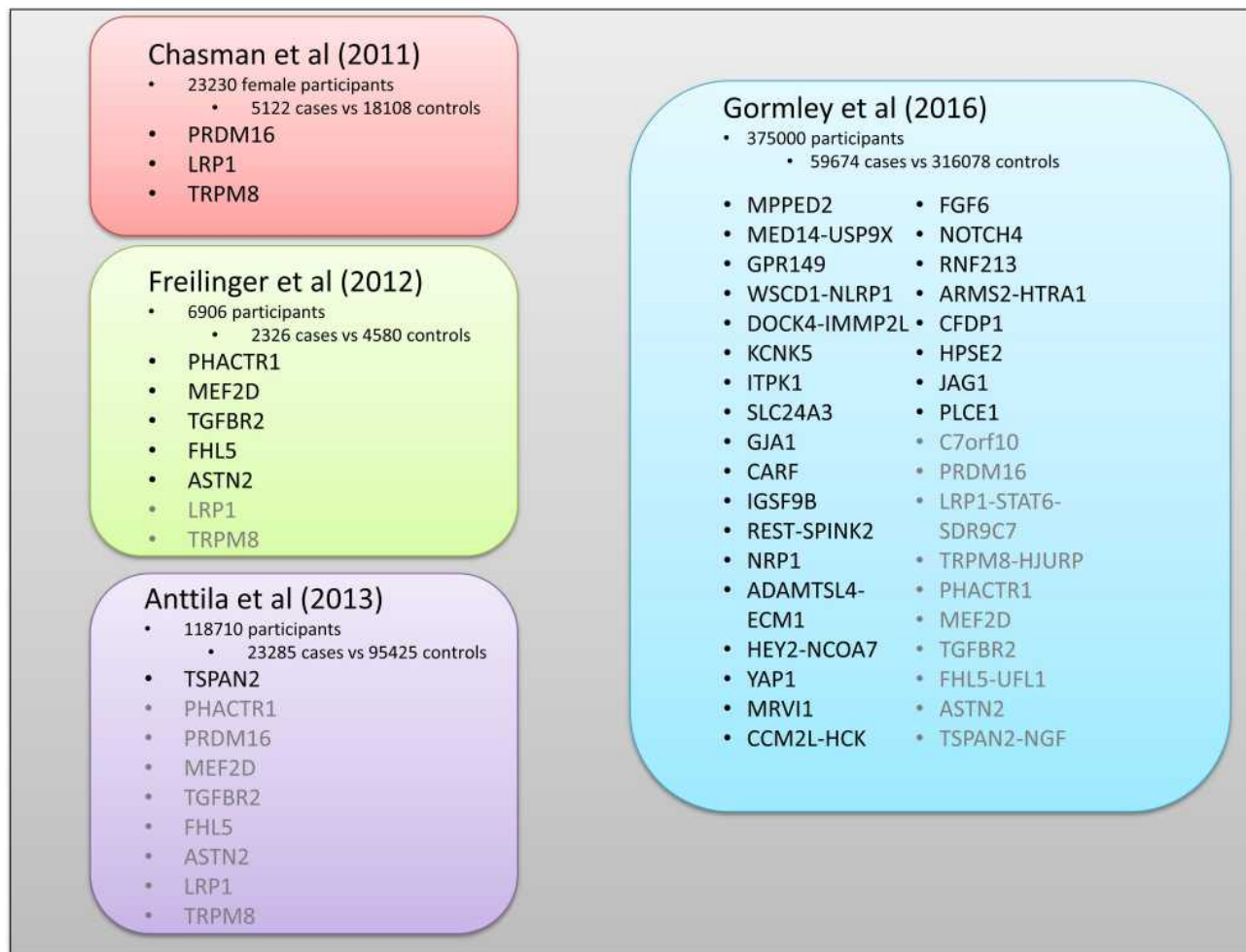
Figure 1 GWAS-identified genes associated with migraine. The figure shows the major studies identifying the genes associated with polygenic forms of migraine, which largely fall into either neuronal or vascular function. Genes displayed in black text were new discoveries of each study, while the grey text highlights those that have been replicated for existing studies.[25–28]

signalling, and heterotrimeric G-protein signalling pathway-Gq alpha and Go alpha-mediated pathways, and furthermore identified the *ATXN1*, *FAM153B* and *CACNA1B* genes as being the most frequently mutated among migraine families.[38]

Hemiplegic Migraine

Hemiplegic migraine (HM) is a rare and severe MA subtype, with patients also having symptoms of hemiparalysis accompanying the migraine or motor disturbances.[12] A typical aura attack can last anywhere from 10 minutes to a few hours, with paraesthesia and speech disturbances.[39] In addition to this, 66% of HM patients report that they suffer from normal MO (without paralysis) on occasion.[40] There is variability within cases; some with symptoms that last days or weeks, and some with increased severity that can result in coma or

seizures.[41–43] HM has both sporadic (SHM) and familial forms (FHM), with the latter typically inherited in an autosomal dominant fashion with a 70–90% penetrance.[44] To date, three main genes have been implicated in the cause of FHM, all of which encode for ion channels (Table 1). FHM1 is caused by mutations in the *CACNA1A* gene on chromosome 19p13, which encodes for the α1A subunit of P/Q-type voltage-gated calcium channels.[45] These particular channels are responsible for the control of calcium in the neuron as a response to membrane depolarisation.[46] The second gene associated with FHM is the *ATP1A2* gene (FHM2) on chromosome 1q23, which encodes for a glial sodium/potassium pump.[47] The third FHM gene is *SCN1A* (FHM3) located on chromosome 2q24, which encodes a neuronal voltage-gated sodium channel.[48] The symptoms of the three FHM subtypes are similar, although the functional effect and

Table 1 Known FHM Causal Genes and Functional Effects of Mutations Identified in FHM

Gene	Location	Function	Mechanism
CACNA1A (FHM1)	19q13	Gain of function	Results in excessive Ca^{2+} influx, resulting in increased glutamatergic neurotransmission
ATP1A2 (FHM2)	1q23	Loss of function	Results in decreased Na^+/K^+ exchange, increasing extracellular K^+ and neuronal excitability
SCN1A (FHM3)	2q24	Gain or loss of function*	Increased firing of inhibitory GABAergic neurons, higher extracellular potassium, leading to enhanced glutamate release[58]

Note: *Some mutations result in a loss of function,[59] some gain and loss of function,[60] and others a gain of function through rescue mechanisms.[58]

mechanism of FHM-causing mutations for each gene vary (Table 1). A fourth causal gene for FHM, the proline-rich transmembrane protein 2 (PRRT2), was suggested by Riant et al.[49] PRRT2 is located on chromosome 16p11.2 and encodes for a type II transmembrane protein which interacts with SNARE complexes to regulate voltage-gated calcium channels in glutamatergic neurons.[50–53] Various studies have suggested that PRRT2 could be considered a fourth FHM gene,[49,54–56] although there is some controversy on that front, and Riant et al suggested that PRRT2 may only act as a modifier because of complex heterogeneity and pleiotropy of phenotypes.[49] Suzuki et al have also shown that homozygous mutations in the SLC4A4 gene can cause syndromic HM, but as yet it has not been included as a known FHM gene.[57]

Aside from their role as the three FHM genes, these genes have also been implicated in many other disorders. Specific types of mutations in CACNA1A have been linked to spino-cerebellar ataxia type 6, episodic ataxia, progressive cerebellar ataxia and epilepsy; ATP1A2 has been linked with cerebellar ataxia and epilepsy, but also confusion, coma and mental retardation; and finally, SCN1A is associated with more severe epilepsy syndromes, such as myoclonic epilepsy in infants and epilepsy with febrile seizures.[2] Currently, migraine and FHM are diagnosed through extensive patient interview, family history and pedigrees.[7,61] Patients are diagnosed based on the specifications of the International Classification of Headache Disorders (ICHD), which outlines the age of disorder onset, the severity and frequency of the attacks, and the presence of aura symptoms.[7] However, this form of diagnosis is complicated owing to the variability between patients and symptoms.[41–43] This has also contributed to the difficulty in identifying genes associated with classical migraine for diagnosis. The common genetic mechanisms behind these disorders often lead to clinical presentation with similar symptoms, making molecular diagnosis through limited gene sequencing difficult. In recent years, the advent of next generation sequencing (NGS) technologies has allowed for better screening for neurological diseases, which has, in turn, increased diagnostic rates. NGS allows for millions of small fragments of DNA to be sequenced at once, allowing for entire gene sets or even the whole genome to be investigated, rather than targeted exons or regions.[15,62,63] Several research groups have reported increased diagnostic rates for several neurological diseases, through the use of whole exome sequencing (WES)[64–66] and targeted gene panels.[67–69] WES analysis has shown that not all suspected HM cases have exonic mutations in the known FHM genes,[30,31] or genes that cause overlapping disorders, which suggests that additional genes or other factors as yet unknown are causative of HM,[12] some of which may be revealed through WES or whole genome sequencing and structural analysis.

Migraine and Circadian Rhythms

Environmental factors such as sleep and stress have been cited as leading triggers for migraine attacks.[70,71] This can be attributed to the fact that there are several hormones and neurotransmitters that play a role in both sleep disruption and migraine;[71] there is evidence to show that dopamine, serotonin, gamma-aminobutyric acid and gonadotropin-releasing hormone changes are involved in both disorders.[71–73] There are also studies showing that migraine and sleep disorders tend to co-segregate within family pedigrees.[74,75] Brennan et al showed that a mutation in CSNK1D, which has been shown to cause familial advanced sleep phase syndrome, was found in two large independent migraine pedigrees. The study also demonstrated that mice with a transgene CKIδ-T44A mutation display increased sensitisation to nitroglycerin infusions, particularly in female mice. In addition, they showed that the CKIδ-T44A mice have reduced thresholds for cortical spreading depression (CSD) compared to the wild type.[74]

Farahani et al have also shown a link between the circadian clock and migraine; genotyping of 200 migraineurs and 200 healthy controls showed that a variant in the RAR-related orphan receptor (RORA), which regulates

both inflammation and circadian rhythm, was associated with circadian rhythm dysfunction and migraine.[76] Further research by Baksa et al suggests that variations in the circadian locomotor output cycles kaput (*CLOCK*) gene may influence the risk of migraine in response to financial stress.[77] In addition to circadian rhythm, Kim et al posited that various sleep disorders can be linked to migraine; subjects with insomnia, for example, have significantly higher prevalence of migraine compared to those without.[78] Kilic et al similarly showed that insufficient glycogen-derived energy (or lack of sleep) can cause synaptic stress and lower the threshold for CSD, suggesting that this lack of synaptic energy may predispose subjects to migraine attack.[79] Thus, genes related to sleep disorders may be a promising target for migraine diagnosis and treatment, although further investigations with larger cohorts are required.

Role of X-Chromosome Loci in Migraine

While studies have shown that there are genetic components to all forms of migraine, there is also evidence to suggest that gender plays a fundamental role in the disorder. Numerous migraine studies demonstrate a preponderance of migraine in females.[12,16,27,80–82] A population study by Stewart et al[83] showed that in 1992, 18% of women suffered from migraine compared to 6% of men, setting the incidence rate at 3:1. This unequal distribution of gender in migraine sufferers is common to both MO and MA,[81,83–87] suggesting either a hormonal link to migraine or possibly an X-chromosomal link if there is a dominant inheritance pattern. The presence of X-linked migraine loci is supported by results from linkage analysis by Nyholt et al[81,85,88] in several studies showing localisation of migraine susceptibility to the X chromosome. Further refinement through haplotype analysis suggested that a migraine susceptibility locus may be localised to the Xq24-28 region.[89] In addition, a study by Maher et al[90] using the genetically isolated Norfolk Island population showed evidence of migraine susceptibility loci at Xq27 and Xq12. However, genes and variants within these regions that may contribute to migraine risk are yet to be identified. Another study of a migraine family and the X chromosome conducted by Weiser et al[82] suggests that a migraine susceptibility locus resides at Xp22. A case–control study performed by Quintas et al reported a link between migraine and the synapsin I (*SYN1*) gene, which is on the X chromosome.[91] Utilising a cohort of 188 migraine patients and 286 healthy controls, and genotyping 119 SNPs in genes related to pathways involving synaptic vesicle molecular machinery or

neurotransmission, the study determined that in females the rs5906437 GC genotype acts as a protective factor for migraine, while the rs5906435 G allele conferred increased migraine susceptibility,[91] but the same effect was not observed in males. A larger sample size may be necessary to determine whether this is a true reflection of a gender-specific effect.[91]

Role of the Mitochondrial Genome in Migraine

Another avenue of exploration of migraine susceptibility is through the genetic analysis of mitochondrial DNA (mtDNA). As mtDNA does not undergo recombination and it is passed exclusively through the maternal line, it allows mutations in the mtDNA sequence to be tracked across multiple generations. Through the use of family studies, researchers have been able to find clear causal variants in various mitochondrial diseases.[92,93] There are various justifications for an investigation into the mitochondrial genome in relation to migraine. The primary role of the mitochondria is to create ATP via the electron transport chain, providing all the energy required for cellular processes.[94] Mitochondrial disorders result in decreased ATP production which, in turn, causes oxidative stress. Given that the muscles and brain are highly dependent on oxidative metabolism, it stands to reason that these tissues will be the most adversely affected by any variations in mtDNA.[94] It has also been shown that decreased ATP resulting from mitochondrial disease can decrease the threshold for CSD, which has been extensively linked to migraine (Figure 2).[95–97] Furthermore, mitochondria play an essential role in calcium ion homeostasis, which is a necessary requirement for normal neuronal function.[98] There is also an abundance of studies showing that migraine is often a by-product or comorbidity of many mitochondrial disorders.[99,100] Imaging techniques have been used to show that migraine patients show disturbances in mitochondrial metabolism in specific regions of the brain.[101] There are also various studies linking mitochondrial dysfunction with other neurological disorders, such as Alzheimer's disease,[102] Parkinson's disease[103] and amyotrophic lateral sclerosis.[104] Given the role of mitochondria in these and other disorders, it is reasonable to explore potential genetic aspects in relation to migraine. A systematic review by Smeitink et al[105] suggested a tentative genetic link between migraine and several mitochondrial disorders, such as mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) and maternally inherited diabetes and deafness (MIDD). More
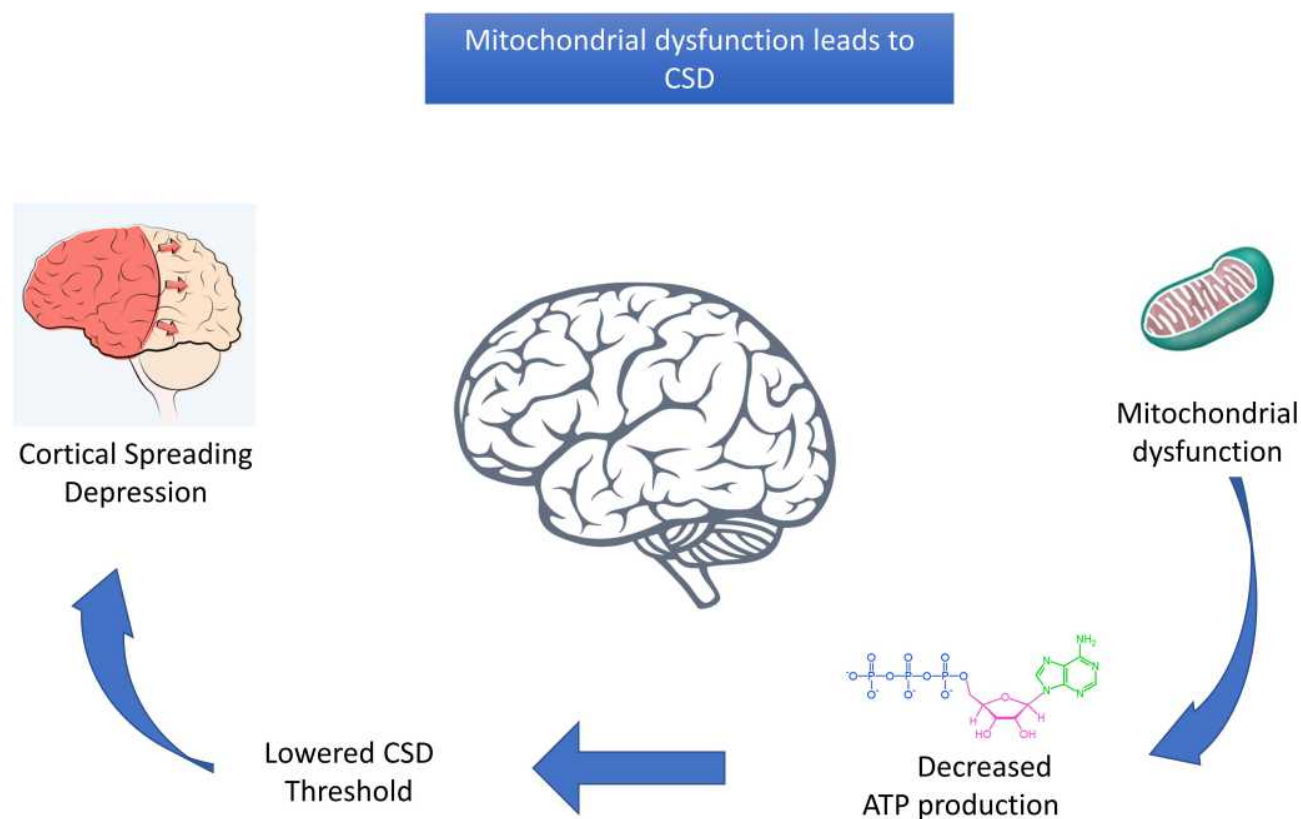
Figure 2 Mitochondrial dysfunction leads to CSD. The image demonstrates how mechanical disruptions to the mitochondrion's energy production could cause migraine by lowering the threshold for propagation of CSD.

specifically, these mitochondrial diseases have a particular mutation in the mitochondrial transfer of RNA leucine; patients with the m.3243A>G mutation seem to have a significantly higher prevalence of migraine than the general population.[106] Cohort studies showed that in the general population there was an 18–29% prevalence of migraine.[107–109] However, similar research using the m.3243A>G mutation population showed migraine prevalence to be 38–89%, with migraine being the only visible symptom in some patients.[110,111] These studies suggest that there may be a link between mitochondrial dysfunction and migraine prevalence, even just as a starting point of the neurological cascade of events that cause migraine. Conversely, a GWAS of mitochondrial migraine using the HUNT study cohort did not find any common genetic variants associated with migraine.[112] The study used a cohort of 18,309 participants, with 4021 migraine cases and 14,288 healthy controls, examining 775 variants, but none was significant after correction for multiple testing.[112] This was also reflected in the haplogroups, which showed no significant association with migraine.[112] The study acknowledges that there may be a limitation based on the questionnaire used for selection

criteria, and only focused on current migraine participants (the last 12 months); this may have introduced past migraineurs into the control group, which would skew the results.[112] Several aspects require further study, for example, distant maternal relatives will share mtDNA but will not necessarily share other genetic risk factors, such as nuclear variants or environmental factors.[113] At this stage, there are no known methods to adjust for close maternal relatedness in mitochondrial association studies, and this may have an impact on the results.[112] Another aspect to consider is the presence of heteroplasmy, as most mitochondrial diseases can be impacted by the presence of heteroplasmy. While mitochondrial dysfunction in migraine patients merits investigation, the role of rare variants, nuclear-encoded mitochondrial variants and environmental factors needs further exploration.

Migraine Epigenetics

While there is clearly a genetic component to migraine susceptibility, there is also significant evidence to suggest that environmental factors also contribute to the disorder.[12,114,115] Monozygotic twin studies have shown that MO heritability is

up to 60% genetic, while 40% can be attributed to environmental factors.[114,115] Commonly held environmental contributors to migraine range from stress, lack of sleep and eating habits, to the changes in hormones during menstruation, pregnancy and menopause.[116] The hormonal theory has received great traction in the field given that migraines are three times more common in women than men.[117] Furthermore, many women experience migraines more often during menstruation and pregnancy, but have significantly fewer migraines when not influenced by the hormonal changes associated with these conditions,[118] and the changes in hormones during menopause have been linked with decreased migraine frequency.[116] These variations in hormones can lead to changes in neuronal activity and inflammation; these can result in remodelling of the chromatin, which then affects gene expression.[119] Alternatively, rat studies have shown that hormonal treatments can alter the activity of the trigeminal nociceptive pathway via nuclear receptors, which adjust the epigenetic programming of targeted genes.[120,121] Glucose transport Glut4 is regulated by oestrogen receptor β through maintaining low levels of DNA methylation at the promoter.[122] Using oestrogen receptor-β agonists in mice increased GABA synthesis,[123] while oestrogen receptor-α activation enhanced expression of *SLC1a3* and *Eaat1*, changing the balance between inhibitory and excitatory neurotransmission;[124] all of which has been linked to FHM1 through transgenic mouse models.[125] Animal studies have also shown that female mice with an FHM mutation are more susceptible to CSD.[126,127] There is also the comorbidity factor; migraine has been shown to have comorbidity with depression, epilepsy and stroke, all of which have been shown to have an epigenetic component.[128,129] Further evidence suggests that epigenetics may contribute to CSD by changing neuronal plasticity and neuroprotection.[130–132] Stress is a common modulator for migraine attack, which is highly sensitive to epigenetic programming. Rat models have shown that early life stress can have lasting effects on behaviour, as a result of increased DNA methylation of Nr4a3.[133] Research in humans as also shown that stress during early life and adulthood can be linked to a variety of epigenetic alterations at stress effector genes such as *BDNF*, *NR3C1* and *CRH*, all of which affect structural and functional aspects of synaptic plasticity and stress reactivity.[134] Some of the genetic factors linked to migraine have also been linked to epigenetic mechanisms; for example, functional polymorphisms in *MTHFR* (a gene involved in the pathway for generating the methyl donor required for DNA methylation) have been found to be associated with migraine in some studies.[135,136] *MTHFR* is not the only gene related to epigenetic processes that has

been linked to migraine pathophysiology; genes such as *MTDH*, *MEF2D* and *PRDM16* have also been implicated in the disorder.[25,27,28] Winsvold et al showed that changes in episodic to chronic migraine can be associated with changes in the DNA methylation profile compared to healthy controls; they further showed that the most strongly associated CpG site was at the *SH2D5* gene, which is involved in the regulation of synaptic plasticity.[137] Terlizzi et al show changes in methylation for catechol-O-methyltransferase (*COMT*), zinc finger protein 234 (*ZNF234*) and suppressor of cytokine signalling 1 (*SOCS1*) in chronic migraine.[138] Gerring et al identified 63 differentially methylated regions in genes largely involved in solute transport and cellular homeostasis (*SLC2A9*, *SLC38A4* and *SLC6A5*).[139] Each of these studies has various limitations and weaknesses, such as small sample sizes and the lack of consideration of medication regimes, as many drugs can influence the epigenetic profile of the subjects. Thus, while several genes have been implicated in relation to epigenetics and migraine, research is still required to fully understand the impact of environmental factors on migraine risk.

Conclusions

Migraine is a complex neurological disorder with a genetic basis, although we do not fully understand all the genes and the mechanisms behind the disorder. Genetic studies of migraine are further complicated by variation in patient symptoms and comorbidity with other complex neurological diseases. Linkage studies and sequencing in family pedigrees, as well as GWAS to identify common variants associated with migraine, have shed light on some of the suspected genes and pathways involved in migraine, although there is still a need for further research using larger participant numbers. The advent of more cost-effective NGS approaches has allowed researchers to more readily explore population cohorts and family pedigrees for rare variants. Migraine is genetically complex and is likely to have a combination of factors contributing to risk and cause; unravelling these will lead to better diagnosis and treatment for the disorder.

Abbreviations

MO, migraine without aura; MA, migraine with aura; CGAS, candidate gene association studies; GWAS, genome-wide association studies; SNP, single-nucleotide polymorphism; WGS,whole genome sequencing; HM, hemiplegic migraine; SHM, sporadic hemiplegic migraine; FHM, familial hemiplegic migraine; NGS, next generation sequencing; WES, whole exome sequencing; CSD,

cortical spreading depression; mtDNA, mitochondrial DNA; MELAS, mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes; MIDD, maternally inherited diabetes and deafness.

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