Genetics of migraine: complexity, implications, and potential clinical applications

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Migraine is a common neurological disorder with large burden in terms of disability for individuals and costs for society. Accurate diagnosis and effective treatments remain priorities. Understanding the genetic factors that contribute to migraine risk and symptom manifestation could improve individual management. Migraine has a strong genetic basis that includes both monogenic and polygenic forms. Some distinct, rare, familial migraine subtypes are caused by pathogenic variants in genes involved in ion transport and neurotransmitter release, suggesting an underlying vulnerability of the excitatory–inhibitory balance in the brain, which might be exacerbated by disruption of homoeostasis and lead to migraine. For more prevalent migraine subtypes, genetic studies have identified many susceptibility loci, implicating genes involved in both neuronal and vascular pathways. Genetic factors can also reveal the nature of relationships between migraine and its associated biomarkers and comorbidities and could potentially be used to identify new therapeutic targets and predict treatment response.

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Introduction

Migraine is a complex neurobiological disorder. Diagnosis relies on the clinical features of the headache and on associated features during attacks, which can occur with or without aura, as defined by the International Classification of Headache Disorders, 3rd edition (ICHD-3),[1] although the symptoms, timing, and duration of migraines can vary widely. Environmental, metabolic, hormonal, medicinal, sleep, stress, and other factors can lead to disruption of homoeostatic functions and precipitate a migraine attack.[2,3] Migraine generation involves changes in the activity and connectivity of the hypothalamus and brain stem, changes in thalamic and thalamocortical activity, release of vasoactive neuropeptides such as calcitonin gene-related peptide (CGRP), and triggering of pain via activation of the trigeminovascular system.[4,5] Approximately a third of people with migraines experience aura shortly before or during the headache phase, which is thought to be propagated by cortical spreading depression (CSD). Predisposing genetic factors, interacting with other internal and external factors, underlie both susceptibility and heterogeneity in migraine-related disorders.[2,4,5]

The heritability of migraine has been estimated at 30–60% from twin and family studies.[6–8] Migraine with aura appears to have higher heritability than migraine without aura,[9] and there are rare monogenic subtypes of migraine with aura, such as familial hemiplegic migraine (FHM), which show Mendelian inheritance. Some rare single-gene cerebrovascular disorders also often feature migraine. Nevertheless, most migraine is considered to be polygenic, with variation in many genes contributing to susceptibility. Genome-wide association studies (GWAS) have identified numerous common genetic variants associated with migraine risk, which support the notion that both neurological and vascular elements have a role in the disorder.

Although some migraine pathways are shared across subgroups, diversity at the genetic level has an influence on the different causes and subgroups of migraine, as well as varied response to treatments. A broad understanding of the genetic factors involved in individuals and families, and across the general population, will be crucial for improving clinical outcomes. In this Review, we outline current knowledge of the genetics of both Mendelian and common migraine forms, with a focus on advances made since 2018 that have accompanied the increased availability of next-generation sequencing and GWAS data. We also discuss how genomic information could be used from a clinical perspective in migraine disorders in the future: in diagnosis, in identifying biomarkers and potential drug targets, in understanding comorbidities and causal factors, and in improving targeting of therapies.

Identifying the genetic factors involved in migraine

Discovering the genetic factors in migraine has traditionally been approached either by studying suspected monogenic forms of the disorder to find pathogenic variants in causal genes in affected probands and families, or by testing single nucleotide polymorphisms (SNPs) for association with migraine susceptibility in case–control cohorts (figure 1). Technologies used for genetic discovery have reflected this dichotomy, with either DNA sequencing or genotyping methods (eg, SNP arrays) commonly used. Emerging data suggest that migraine probably spans a spectrum between monogenic and polygenic causes. However, until more complete genomic data are available, considering findings from each approach in turn is useful, while highlighting their commonalities.

Mendelian forms of migraine considered to be primarily monogenic

Familial hemiplegic migraine

Hemiplegic migraine is characterised by severe attacks of migraine accompanied by hemiplegia or motor aura symptoms.[1] Although hemiplegic migraine can occur sporadically, FHM usually shows autosomal-dominant

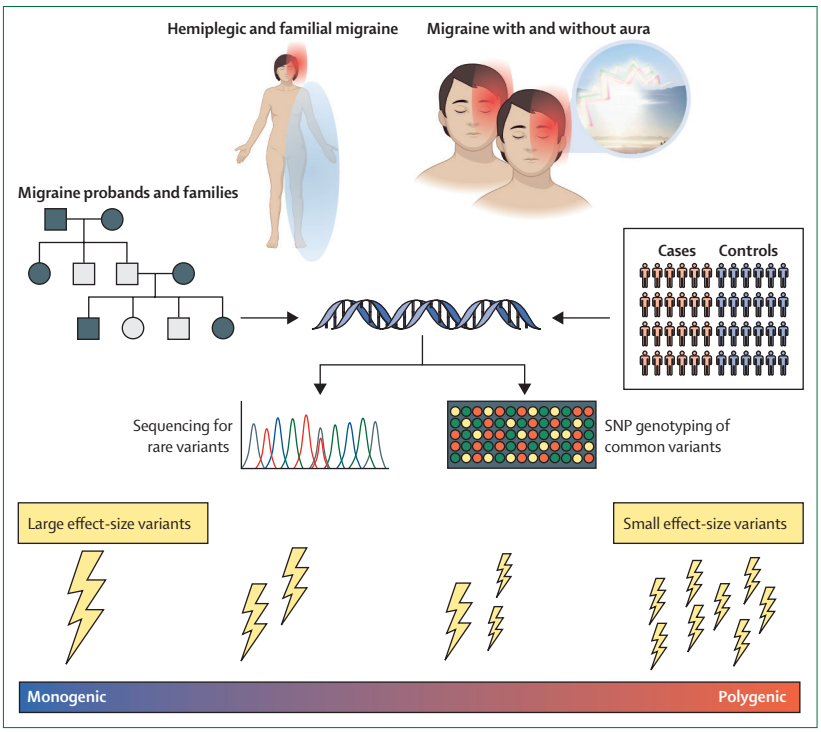

Figure 1: **Complex genetic spectrum of migraine disorders**
Knowledge of genetic factors involved in migraine disorders has traditionally come from two approaches: the study of Mendelian forms, such as familial hemiplegic and familial non-hemiplegic migraine, which are assumed to be caused by pathogenic variants with large effects in single genes; and case–control association studies of common polygenic migraine, which results from combinatorial effects of variants across many genetic loci, each with small effect. Discovering potentially causal variants in Mendelian types of migraine mainly uses sequencing-based technologies (eg, Sanger sequencing and now next-generation sequencing methods). Finding SNPs associated with common migraine has relied on genotyping methods, with SNP arrays being used for most genome-wide association studies. The genetic architecture of migraine probably spans a spectrum from monogenic to polygenic forms, with contributions from both deleterious variants with large effects and accumulation of small-effect susceptibility variants. Figure created with BioRender.com. SNP=single-nucleotide polymorphism.

inheritance.[10] Studying genes and specific pathogenic variants that cause FHM has provided insights into how brain function might be affected in migraine. We only briefly outline the mechanisms involved (table 1; figure 2) as they have been reviewed extensively.[10,12] Large families with FHM enabled linked genetic loci to be mapped and sequenced, identifying causal missense mutations in three genes: *CACNA1A*, *ATP1A2*, and *SCN1A* (table 1).[11,15,41] Each gene encodes either voltage-gated ion channels or an ion-transport protein with neuronal or astrocytic functions that influence excitability or neurotransmission at glutamatergic synapses in the CNS (figure 2). Numerous FHM pathogenic variants have been reported, some recurrent, but many have been only found to occur in one individual or their family members. Functional assays of mutations in cellular and mouse models suggest effects on channel activity, properties, or localisation,[13,16,19] and mouse models with knock-in of human FHM type 1 (FHM1), FHM type 2 (FHM2), and FHM type 3 (FHM3) mutations display enhanced susceptibility to CSD and behaviours suggesting migraine features, such as unilateral head pain.[13,14,17,20,21] FHM1 and FHM2 genes converge on glutamatergic signalling and neurotransmission pathways; mutations result in increased concentrations of glutamate in the extracellular space (and have been visualised as glutamate plumes in FHM2 mice),[18] which could cause underlying dysregulation of the cortical excitatory–inhibitory balance in the brain and increased CSD initiation and propogation.[12,13,17,18] FHM phenotypes are not specifically distinguishable by which gene is mutated, but treatments in patients might be targeted to the nature of the molecular lesion if it is known (eg, by use of appropriate channel blockers).[10,42]

PRRT2 has been suggested as a fourth FHM gene,[24] although whether it is causal or a modifier is debated.[43] *PRRT2* mutations, in particular recurrent frameshifts resulting in haploinsufficiency (table 1), can cause paroxysmal movement disorders and account for a large proportion of cases of paroxysmal kinesigenic dyskinesia (PKD).[27] However, individuals with *PRRT2* mutations can present with a range of symptoms, including migraine, hemiplegic migraine, ataxia, and epilepsy.[25,27] An important study published in 2022 interrogating *PRRT2* in a large cohort further highlighted its role in hemiplegic migraine and FHM; mutations (ie, frameshifts, missense, or whole-gene deletions) were detected in 30 of 860 probands, and in affected family members in 11 pedigrees.[26] In some of these instances of hemiplegic migraine, the deletion involved additional genes and appeared to be the recurrent 16p11.2 microdeletion commonly associated with neurodevelopmental disorders and autism.[29] Questions therefore remain around the variable phenotypes observed for *PRRT2* variants and interactions with other gene variants.[28] Proline rich transmembrane protein 2 (PRRT2) localises to glutamatergic synapses, where it interacts with glutamate ionotropic receptor AMPA type subunit 1 (GRIA1) and a synaptic t-SNARE protein synaptosomal-associated protein 25kDa (SNAP25), suggesting it influences synaptic vesicle docking and neurotransmitter release.[30] Furthermore, PRRT2 can regulate neuronal excitability via modulation of sodium voltage-gated channel α subunit 2 (Nav1.2) and sodium voltage-gated channel α subunit 6 (Nav1.6),[22] as well as the cell-surface density of calcium voltage-gated channel subunit α1 A (Cav2.1; *CACNA1A*).[23] The paroxysmal non-kinesiogenic dyskinesia (PNKD) protein, which is mutated in some patients with hemiplegic migraine, also localises to synapses, where it interacts with PRRT2 (table 1).[27] The migraine prophylactic onabotulinum toxin A targets this pathway, cleaving SNAP25 to inhibit SNARE-dependent regulated exocytosis of pro-inflammatory and excitatory neurotransmitters and neuropeptides.[44]

Increasing the diagnostic rate for hemiplegic migraine

Next-generation sequencing approaches with whole-exome sequencing or targeted panels covering all the

coding regions of *CACNA1A*, *ATP1A2*, and *SCN1A* have revealed that protein-altering mutations (eg, missense, splicing, or frameshift) in these genes are detected in only a minority of patients with hemiplegic migraine.[26,45,46] Some patients presenting with hemiplegia or hemiplegic migraine actually have mutations in ion or solute-carrier genes usually associated with other disorders (eg, *ATP1A3*, *SLC1A3*, *SLC2A1*, and *SLC4A4*; table 1).[27,31–34,47] This finding suggests either symptom overlap or converging phenotypes for mutations in genes with

	Encoded protein	Function	Migraine-related disorder in which gene is implicated (OMIM number), inheritance mode	Other disorders in which gene is implicated (OMIM number), inheritance mode	Pathogenic variant effects
Causal genes for familial hemiplegic migraine					
CACNA1A	Cav2·1	Pore-forming α1 subunit of the neuronal voltage-gated calcium channel, found in membranes of excitable cells in the brain, where it mediates Ca^{2+} influx in response to depolarisation; Cav2·1 is particularly highly expressed in the cerebellum, localising to the presynaptic terminals of neurons, where it is important in controlling the release of neurotransmitters	Hemiplegic migraine and familial hemiplegic migraine type 1 (141500), autosomal dominant	Episodic ataxia type 2 (108500), autosomal dominant; developmental and epileptic encephalopathy 42 (617106), autosomal dominant; spinocerebellar ataxia type 6 (183086), autosomal dominant	Familial hemiplegic migraine type 1 variants are mostly missense, gain of function,[11] and lead to an increased Ca^{2+} influx into the presynaptic terminal; in knock-in mouse models, enhanced glutamatergic neurotransmission and increased susceptibility to and propagation of cortical spreading depression;[12–14] episodic ataxia type 2 and developmental and epileptic encephalopathy 42 variants are commonly truncations or missense loss-of mutations that result in decreased channel function and intracellular Ca^{2+}; spinocerebellar ataxia type 6 is caused by expansion of polyglutamine repeats in the C-terminal tail of Cav2·1, which have a toxic gain of function, altering channel function and resulting in selective cerebellar Purkinje cells degeneration
ATP1A2	ATP1A2	α2 catalytic subunit of the Na^+–K^+-ATPase ion transport pump that maintains physiological gradients of Na^+ and K^+; highly expressed in astrocytes, Na^+–K^+-ATPase α2 is important for regulating neurotransmitter uptake and neuronal excitability	Hemiplegic migraine and familial hemiplegic migraine type 2 (602481), autosomal dominant	Alternating hemiplegia of childhood 1 (104290), autosomal dominant; FARIMPD (619602), autosomal recessive	FHM2 and alternating hemiplegia of childhood 1 variants are mostly missense, partial-to-complete loss of function;[15,16] familial hemiplegic migraine type 2 variants result in impaired clearance of extracellular K^+ by astrocytes leading to increased synaptic K^+ and glutamate;[12,16,17] α2 Na^+–K^+-ATPase also interacts with the glutamate transporters *SLC1A3* and *SLC1A2* and its loss results in reduced density of glutamate transporters at astrocytic processes and leads to impaired glutamate clearance;[17] dysregulated glutamate release and uptake triggers neuronal hyperexcitability and cortical spreading depression susceptibility and propagation;[17,18] FARIMPD variants are usually nonsense or frameshift loss of function
SCN1A	Nav1·1	Mediates voltage-dependent Na^+ permeability of excitable membranes; expressed in and functionally important for the generation and propagation of action potentials in neurons (mainly inhibitory GABAergic interneurons)	Hemiplegic migraine and familial hemiplegic migraine type 3 (609634), autosomal dominant	Dravet syndrome (607208), autosomal dominant; GEFSP2 (604403), autosomal dominant	Complex spectrum of pathogenic variants leading to a range of phenotypes and severity of symptoms. FHM3 variants are typically gain of function and can result in fast recovery from fast inactivation,[19] which predicts interneuron hyperactivity and increased extracellular K^+, which might facilitate initiation of cortical spreading depression;[12,20,21] Dravet syndrome and GEFSP2 variants are usually loss of function and result in impaired GABAergic transmission of inhibitory neurons and hyperexcitable neuronal networks
Genes with mutations in some patients with hemiplegic migraine, but mainly associated with other disorders					
PRRT2	PRRT2	Interacts with synaptic proteins, including SNARE complex, with a role in the Ca^{2+}-sensing machinery that regulates neurotransmission at the synapse; *PRRT2* also regulates the density of P-type and Q-type channels, including Cav2·1, and is a negative modulator of Nav1·2 and Nav1·6 voltage-gated sodium channels in excitatory neurons[22,23]	Hemiplegic migraine and familial hemiplegic migraine, autosomal dominant	Paroxysmal kinesigenic dyskinesia or episodic kinesigenic dyskinesia 1 (128200), autosomal dominant; infantile convulsion and choreoathetosis syndrome (602066), autosomal dominant; benign familial infantile seizures 2 (605751), autosomal dominant	Mostly missense or frameshift variants (most common are 649dupC or 649delC) that result in nonsense mediated decay and loss of function;[24–26] the same variants have been found in individuals with different disorders, suggesting presence of modifying genetic factors;[25,27,28] whole-gene deletions also occur in some individuals and larger deletions can encompass approximately 546 kb regions on chromosome 16 and chromosome 29, including *PRRT2*, and might be associated with developmental and neuropsychiatric symptoms;[26,28,29] impaired interaction with SNARE complexes[30] and voltage-gated ion channels[22] affects control of neuronal excitability and synaptic transmission

(Table 1 continues on next page)

	Encoded protein	Function	Migraine-related disorder in which gene is implicated (OMIM number), inheritance mode	Other disorders in which gene is implicated (OMIM number), inheritance mode	Pathogenic variant effects
(Continued from previous page)					
PNKD	Paroxysmal nonkinesiogenic dyskinesia metallo-β-lactamase domain containing protein	Probable role in modulating neurotransmitter release in neuronal synapses as paroxysmal nonkinesiogenic dyskinesia long isoform interacts with pre-synaptic RIM proteins to inhibit synaptic exocytosis	Hemiplegic migraine	Paroxysmal non-kinesiogenic dyskinesia	N-terminal missense variants that alter protein cleavage and stability, or deletion variants, lead to reduced inhibition of exocytosis and thus excessive neurotransmitter release[27]
ATP1A3	ATP1A3	α3 catalytic subunit of the Na^+–K^+-ATPase ion transport pump, which maintains physiological gradients of Na^+ and K^+; important for clearing high intraneuronal Na^+ concentrations that occur after intense neuronal firing	Autosomal dominant	Alternating hemiplegia of childhood 2 (614820), autosomal dominant; CAPOS (601338); rapid-onset dystonia-parkinsonism or dystonia 12 (128235), autosomal dominant; developmental and epileptic encephalopathy 99 (619606)	*ATP1A3* disorder causal variants are mostly missense and might affect pump activity, ion affinity, ion leakage, or biosynthesis;[31] symptoms and severity might reflect variant location and effect; two main recurrent pathogenic variants for alternating hemiplegia of childhood 2 are Asp801Asn and Glu815Lys; CAPOS is caused by a Glu818Lys variant; rapid-onset dystonia-parkinsonism is caused by missense (eg, Thr613Met) or small indel variants
SLC1A3	SLC1A3 or EAAT1	Transporter in the CNS that recaptures released glutamate from the synaptic cleft into glia via coupled Na^+-K^+-H^+-glutamate transport to restrict neurotransmitter levels within synapses and prevent spillover outside active synapses; also mediates a Cl^- flux	Hemiplegic migraine, autosomal dominant	Episodic ataxia type 6 (612656), autosomal dominant	Episodic ataxia type 6 and hemiplegic migraine variants are usually missense and result in decreased glutamate uptake;[32] for some variants, this reduced uptake might occur via altered anion channel function, which then affects glutamate transport; impaired glutamate reuptake could lead to activation of extrasynaptic NMDA receptors or receptors located in neighbouring synapses,[33] and might be involved in triggering cortical spreading depression[17,18]
SLC2A1	SLC2A1 or GLUT1	Major glucose transporter at the mammalian blood–brain barrier; mediates energy-independent, facilitative transport of glucose into the brain	Hemiplegic migraine, autosomal dominant	GLUT1 deficiency syndrome 1 (606777), autosomal dominant; GLUT1 deficiency syndrome 2 (612126), autosomal dominant; paroxysmal exercise-induced dyskinesia or dystonia 9 (601042), autosomal dominant	SLC2A1 disorders are caused by missense, nonsense, or deletion variants that impair glucose transport[27]
SLC4A4	SLC4A4 or NBCe1	Sodium bicarbonate cotransporter involved in regulation of bicarbonate secretion and absorption and regulation of intracellular pH and homoeostasis; high expression in the kidney, retina, pancreas, and brain, where it is important for astrocytic functions	Hemiplegic migraine, autosomal recessive	RTA (604278), autosomal recessive	RTA and hemiplegic migraine are caused by missense, nonsense, or frameshift variants that reduce transport activity of NBCe1;[34] hemiplegic migraine variants often result in truncated proteins that have trafficking defects;[34] dysregulation of synaptic pH resulting from loss of astrocytic NBCe1 activity might be involved in causing migraine
Genes that have been implicated in Mendelian migraine with aura					
KCNK18	KCNK18 or TRESK	Produces rapidly activating outward rectifier K^+ currents; might function as background potassium channel that sets resting membrane potential	Migraine with aura (613656), autosomal dominant	..	Frameshift TRESK variant (Phe139TrpfsX24) identified in one family;[35] appears to have a dominant negative effect as it results in alternative translation of a short TRESK fragment that co-assembles with, and inhibits, the KCNK2 and KCNK10 potassium channels;[36] inhibition of TREK1 and TREK2 could lead to increased trigeminal neuron excitability and trigger migraine[12,37]
CSNK1D	CK1δ	Serine kinase that phosphorylates several target proteins, including the mammalian clock PER proteins controlling their nuclear transport and degradation to regulate circadian period length; reported role in regulating glutamate-induced neuronal excitation	Migraine with aura, autosomal dominant	Familial advanced sleep phase syndrome 2 (615224), autosomal dominant	Familial advanced sleep phase syndrome 2 and migraine with aura missense variants Thr44Ala or His46Arg in catalytic domain reduce CK1δ enzyme activity and affect the sleep–wake cycle;[38] suggests possible involvement of hypothalamic functions in migraine; mice with the CKIδ–Thr44Ala variant show increased sensitivity to pain and a reduced threshold for cortical spreading depression due to a stimulus-dependent presynaptic gain of function at glutamatergic synapses[12,14,38,39]

(Table 1 continues on next page)

	Encoded protein	Function	Migraine-related disorder in which gene is implicated (OMIM number), inheritance mode	Other disorders in which gene is implicated (OMIM number), inheritance mode	Pathogenic variant effects
(Continued from previous page)					
Genes that can lead to monogenic cerebral vascular disorders that can feature migraine					
NOTCH3	NOTCH3	Receptor for jagged 1, jagged 2, and δ 1 that establish intercellular signalling pathways involved in cell fate; key role in neural development	Migraine with or without aura	Cerebral small vessel disease and CADASIL (125310), autosomal dominant; lateral meningocele syndrome (130720), autosomal dominant	CADASIL variants mostly involve cysteine residues and result in an odd number of EGF repeats in the extracellular domain of NOTCH3, which causes toxic NOTCH3 accumulation and progressive degeneration of cerebral vasculature;[12,40] variants early in EGF repeats 1–6 usually have a more severe phenotype than those further on in the protein; lateral meningocele syndrome variants occur late in the protein sequence and result in premature termination and a truncated protein, postulated to have a dominant gain-of-function effect
COL4A1 and *COL4A2*	COL4A1 and COL4A2	Structural components of basement membranes; each polypeptide forms a triple helix structure with two other chains to generate type-IV collagen network, which also interacts with other extracellular matrix components	Migraine with or without aura	Cerebral small vessel disease; stroke and small vessel disease (eg, porencephaly or leukodystrophy); eye problems (eg, retinal arterial tortuosity, Axenfeld-Rieger syndrome, or cataract); systemic effects (eg, kidney, muscle cramps, Raynaud syndrome, cardiac arrhythmia, and haemolytic anaemia)	COL4A1 and COL4A2 variants are usually missense, effecting highly conserved glycine residues in the Gly-X-Y repeat of the collagen triple-helical domain, which impairs collagen-IV heterotrimer assembly and can lead to intracellular accumulation of mutant collagen in vascular endothelial cells and pericytes;[40] some nonsense, splice site, and frameshift truncating pathogenic variants result in haploinsufficiency
TREX1	TREX1	3′-to-5′ DNA exonuclease that digests single-stranded and double-stranded DNA and mismatched 3′ termini; prevents cell-intrinsic initiation of autoimmunity	Mostly migraine without aura	Cerebral small vessel disease and RVCL (192315), autosomal dominant; Aicardi-Goutieres syndrome 1 (225750), autosomal dominant or autosomal recessive	In RVCL, C-terminal frameshift variants produce truncated TREX1 that retains exonuclease activity but loses normal perinuclear localisation; mislocalised TREX1 results in damage to the lining of blood vessels;[40] Aicardi-Goutieres syndrome 1 variants are missense, nonsense, and truncating and result in impaired nuclease activity
GLA	Galactosidase α (α-galactosidase A)	Lysosomal enzyme that hydrolyses glycosphingolipids to enable their degradation	Migraine	Fabry disease (301500), X-linked	Fabry disease pathogenic variants are heterogeneous, include missense, nonsense, and splice site and short indels and large rearrangements, which result in loss of function of enzymatic activity; progressive accumulation of glycosphingolipids damages cells, including lining of blood vessels[40]
CTSA	Cathepsin A	Associates with and exerts a protective function essential for the stability and activity of both β-galactosidase and neuraminidase in the lysosome; regulates metabolism and functions of bioactive peptides, including endothelin-I and substance P	Headache, mostly migraine	CARASAL, autosomal dominant; galactosialidosis (256540), autosomal recessive	CARASAL variants are missense; pathogenic Arg325Cys variant has been identified in multiple families;[40] galactosialidosis variants are missense, affect splicing, or frameshift loss of function; they impair interaction with lysosomal enzymes, reducing their activity

Information compiled from PubMed, OMIM, and GeneCards. ATP1A2=ATPase Na^+–K^+-transporting subunit α2. ATP1A3=ATPase Na^+–K^+ transporting subunit α3. CADASIL=cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy. CAPOS=cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss. CARASAL=cathepsin A-related arteriopathy-strokes-leukoencephalopathy. Cav2·1=calcium voltage-gated channel subunit α1 A. CK1δ=casein kinase 1δ. COL4A1=collagen type IV α 1 chain. COL4A2=collagen type IV α 2 chain. EAAT1=excitatory amino acid transporter 1. EGF=epidermal growth factor. FARIMPD=fetal akinesia, respiratory insufficiency, microcephaly, polymicrogyria, and dysmorphic facies. GEFSP2=generalised epilepsy with febrile seizures plus, type 2. GLUT1=glucose transporter type 1. KCNK18=potassium two-pore domain channel subfamily K member 18. Nav1.1=sodium voltage-gated channel α subunit 1. Nav1·2=sodium voltage-gated channel α subunit 2. Nav1·6=sodium voltage-gated channel α subunit 6. NBCe1=sodium bicarbonate cotransporter 1. NOTCH3=notch receptor 3. OMIM=Online Mendelian Inheritance in Man. PRRT2=proline rich transmembrane protein 2. RTA=renal tubular acidosis, proximal, with ocular atypicalities. RVCL=retinal vasculopathy with cerebral leukodystophy. SLC1A3=solute carrier family 1 member 3. SLC2A1=solute carrier family 2 member 1. SLC4A4=solute carrier family 4 member 4. TRESK=TWIK-related spinal cord K^+ channel. TREX1=three prime repair exonuclease 1.

Table 1: **Genes implicated in monogenic disorders that feature migraine**

functions around the synapse. Testing for mutations in these genes, as well as *PRRT2* and *PKND*, can increase diagnostic rates for hemiplegic migraine; nevertheless, most people with suspected hemiplegic migraine remain without a molecular diagnosis.[26,47] Other types of pathogenic variant, or other genes, might be involved in the remaining patients. These variants could include structural variations, such as copy-number variants (CNVs), or large insertions or deletions not easily detected by short-read sequencing methods. As well as *PRRT2* deletions,[26] examples of intragenic deletions of C-terminal exons of *CACNA1A* and exonic duplications

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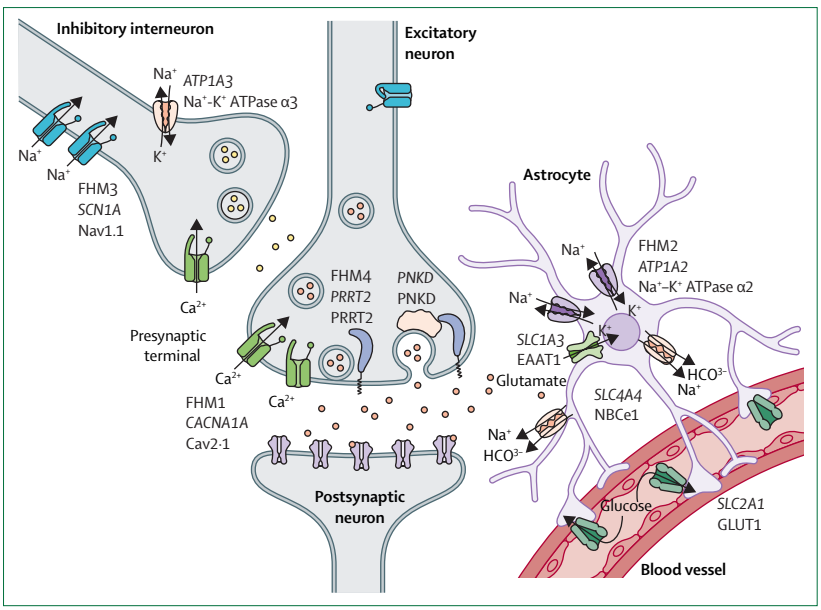

Figure 2: **Functions of proteins encoded by hemiplegic-migraine genes in the CNS**
Localisation of proteins encoded by hemiplegic-migraine genes at a tripartite synapse composed of a presynaptic excitatory neuron, its postsynaptic terminal, and an associated astrocyte connected to a blood vessel. An inhibitory GABAergic interneuron that also regulates firing of target neurons is also shown. The FHM1 gene *CACNA1A* encodes the Cav2·1 voltage-gated calcium channel, which allows influx of Ca^{2+} and triggers glutamate release into the synaptic cleft in response to an action potential. The FHM2 gene *ATP1A2* encodes a glial Na^+–K^+-ATPase α2 that removes K^+ from the synaptic cleft to limit neuronal excitability and maintain a Na^+ gradient across the cell membrane. Na^+–K^+-ATPase α2 also interacts with the glutamate transporters EAAT1 and EAAT2, and its loss in FHM2 results in reduced density of these glutamate transporters at astrocytic processes. The FHM3 gene *SCNA1A* encodes Nav1·1 channels that mediate voltage-dependent Na^+ entry and regulate excitability of GABAergic neurons. PRRT2 (implicated in FHM4) and PNKD proteins localise to glutamatergic synapses where they interact with SNAREs and synaptic proteins to mediate and regulate neurotransmitter release. PRRT2 also regulates the density of P-type and Q-type channels, including Cav2·1 (*CACNA1A*), at the active zone of synapses. Furthermore, it negatively modulates membrane expression of the sodium channels Nav1·2 (encoded by *SCN2A*) and Nav1·6 (encoded by *SCN8A*). Other channel or transport proteins might be associated with hemiplegic migraine: the *ATP1A3*-encoded Na^+–K^+-ATPase α3 pump, which regulates membrane excitability and at inhibitory synapses; *SLC1A3* encoding the Na^+-K^+-dependent glutamate transporter EAAT1, which recaptures glutamate from the synaptic cleft into glia, including astrocytes, to restrict neurotransmitter levels within the synapses and prevent spillover; the *SLC4A4*-encoded electrogenic Na^+–HCO_3^- cotransporter NBCe1, which regulates synaptic pH; and the *SLC2A1*-encoded GLUT1 glucose transporter present at the blood–brain barrier, which facilitates glucose transport into the brain. Figure created with BioRender.com. Cav2·1=calcium voltage-gated channel subunit α1 A. EAAT1=excitatory amino acid transporter 1. EAAT2=excitatory amino acid transporter 2. FHM=familial hemiplegic migraine. GLUT1=glucose transporter type 1. Nav1·1=sodium voltage-gated channel α subunit 1. Nav1·6=sodium voltage-gated channel α subunit 6. NBCe1=sodium bicarbonate cotransporter 1. PNKD=paroxysmal non-kinesiogenic dyskinesia. PRRT2=proline rich transmembrane protein 2.

in *ATP1A2* have been reported in some people with sporadic hemiplegic migraine.[48–50]

Additional hemiplegic migraine genes are likely to be discovered as patient genomic-sequencing data accumulates. For example, an increased burden of rare missense variants in various voltage-gated calcium channel genes related to *CACNA1A,* in particular *CACNA1I* and *CACNA1H*, were identified in a cohort of probands with hemiplegic migraine.[51] Encoding T-type channels calcium voltage-gated channel subunit α1 I (Cav3.3) and calcium voltage-gated channel subunit α1 H (Cav3.2), these calcium channels have important roles in neuronal excitability and the thalamocortical circuitry.[52] Electrophysiological testing of selected *CACNA1I* variants found in patients with hemiplegic migraine showed effects on properties of the Cav3.3 channel, such as current density, activation kinetics, and pH sensitivity.[53] Another protein family of interest is the transient receptor potential (TRP) ion channels, which have been implicated in pain and migraine pathways.[54] TRP melastatin 7 (*TRPM7*) gene variants (predicted loss of function) have been identified both in people with vestibular migraine and in people with hemiplegic migraine accompanied by hypomagnesemia.[55,56] *TRPM7* is permeable to a range of cations and has an essential role in maintenance of cellular magnesium homoeostasis, suggesting that along with calcium, dysregulation of magnesium ion balance could play a role in migraine. Validation of these candidate genes in more patients, and functional studies, are required to understand the mechanisms that might lead to migraine.

Some of these putative migraine genes might also involve more complex modes of inheritance in which rare, high-impact variants interact with other modifying gene-susceptibility variants.[53] Patients with FHM without classic FHM gene mutations have a higher genetic load of rare frameshift indels in genes associated with synaptic signalling in the CNS compared with patients with more common non-Mendelian forms of migraine.[57] Furthermore, a higher burden of common migraine susceptibility variants (measured as a polygenic risk score, which sums risk alleles weighted by their effect sizes) is found in familial migraine compared with individuals in the general population.[58] These data, along with the fact that identifying additional specific hemiplegic-migraine genes has been challenging,[43] further support the idea that hemiplegic migraine is not necessarily a single-gene disorder, but might result from accumulation of common risk variants[58] in addition to rare, highly penetrant variants (figure 1).

Familial non-hemiplegic migraine

Migraine in most people is assumed to be polygenic. However, some families show Mendelian-like segregation, suggesting the presence of large-effect, highly penetrant gene variants. Potassium two pore domain channel subfamily K member 18 (*KCNK18*), encoding a brain-expressed potassium channel also known as TWIK-related spinal cord K^+ channel (TRESK; table 1), was the first proposed monogenic cause of migraine with aura.[35] Segregating with migraine with aura in a single large pedigree, a frameshift mutation in *KCNK18* (Phe139Trpfs*24) results in loss of TRESK at the cell membrane and corresponds with a significant increase in neuronal excitability in patient-derived nociceptor neurons.[36] However, an unusual mechanism might underlie the migraine phenotype: the frameshift results in production of an alternatively translated protein fragment that can co-assemble with and inhibit two other potassium channels, KCNK2 and KCNK10, leading to trigeminal hyperexcitability.[37] Phe139Trpfs*24

is present in the UKBiobank in similar frequencies in both people inferred to have migraine (from their prescribed medicines) and people who do not, suggesting it might not be solely causal.[59]

Pedigree analysis also identified *CSNK1D* as a monogenic migraine gene (table 1).[38] *CSNK1D* encodes casein kinase 1δ (CKIδ), a central component of the mammalian circadian clock, regulating the rhythmicity of cellular PER2 protein levels and the circadian cycle. In two large, independent pedigrees, mutations in *CSNK1D* (ie, Thr44Ala and His46Arg) were found to cause familial advanced sleep phase syndrome, in which affected individuals have significantly altered sleep–wake patterns.[38] This phenotype also co-segregated with migraine with aura in these pedigrees. These variants are rare, with each only present in a few individuals in the Genome Aggregation Database, in which migraine status in not reported. The role of circadian factors, sleep, and neurotransmitters involved in sleep is of great interest in migraine, and the co-occurrence of sleep disorders with migraine might partly have a genetic basis.[60–62] Genetic studies could provide an insight into this connection, and whether other mutations in circadian or sleep-related genes are implicated in migraine will be an interesting topic for investigation. However, the migraine-related phenotype of the CKIδ–Thr44Ala mutation might not particularly relate to its circadian effects. A 2023 study of synaptic functions in CKIδ–Thr44Ala knock-in mice showed that their neurons were more excitable upon repetitive stimulation compared with those of wild-type mice, owing to a calcium-dependent enhancement of the size of the readily releasable pool of synaptic vesicles, which increases glutamate release.[39] Reduction in presynaptic adaptation was observed at excitatory but not inhibitory synapses, and the enhanced cortical excitation contributes to susceptibility to spreading depression, as occurs with some FHM-type mutations.

Large pedigrees are not always available, and whole-exome or whole-genome sequencing of multiple smaller families with migraine can also reveal large effect gene variants. By integrating gene networks co-expressed in migraine-related brain and vascular tissues with whole-genome sequencing of 117 families with Mendelian-like segregation of migraine, Rasmussen and colleagues[63] found a significant burden of rare variants in one module, with *CACNA1B*, *ATXN1*, and *FAM153B* being the most commonly mutated genes (ie, in >15 families each). Mutations in *CACNA1B*, encoding a calcium channel related to *CACNA1A*, have been found in patients with a progressive epilepsy-dyskinesia syndrome[64] and *ATXN1* mutations can cause spinocerebellar ataxia 1.[65] Although a functional role of these genes in migraine is still to be shown, a relationship of migraine with epilepsy and ataxia and overlap of genes[66–68] that have been implicated in both migraine and epilepsy has been shown before.

Cerebrovascular disorders that feature migraine

Several monogenic cerebrovascular disorders commonly feature migraine (table 1).[40] Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leuko-encephalopathy (CADASIL) is the most common inherited cause of stroke and vascular dementia. Migraine is often present, sometimes occurring many years before other typical symptoms. CADASIL is caused by particular cysteine-affecting, toxic gain-of-function mutations in *NOTCH3*. Notch receptor 3 (NOTCH3) is a receptor expressed in vascular smooth muscle cells and pericytes, with important effects on vascular maintenance and integrity. Variants in other genes with vascular involvement, including *COL4A1*, *COL4A2*, *TREX1*, *GLA*, and *CTSA*, can cause a range of rare cerebrovascular disorders, which often feature overlapping symptoms including migraine (table 1). Although the mechanisms of migraine generation through these pathways is not well understood, these disorders highlight the fact that vascular aspects of migraine could be underpinned by genetic factors, which has been further substantiated for more common migraine subtypes via GWAS.[69–71]

For the **Genome Aggregation Database** see https://gnomad.broadinstitute.org/

Common polygenic forms of migraine

GWAS and loci that influence migraine risk

Although Mendelian migraine disorders have been instrumental in understanding some molecular aspects of migraine pathophysiology, they are relatively rare. Common non-Mendelian migraine is generally considered to have a polygenic architecture with variations across many genes contributing to susceptibility. GWAS use an agnostic approach, scanning common SNPs across the genome for association with the trait of interest. A large GWAS of 102 084 people with migraine and 771 257 control individuals by Hautakangas and colleagues[71] found 123 loci to be significantly associated with migraine. They built on previous studies, confirming loci reported by Gormley and colleagues[69] and many of the 79 loci reported in a large, multiethnic meta-analysis by Choquet and colleagues.[70] Many GWAS loci are in intergenic regions, and which gene or genes are relevant can be ambiguous (panel 1). Nevertheless, many potential genes that influence migraine susceptibility have been identified and support a neurovascular cause of common migraine; risk loci are enriched with genes expressed in both CNS and vascular cell types, with roles in neuronal excitability, synaptic plasticity, neuronal development and patterning, and vascular development and function (figure 3).[69–71]

A GWAS meta-analysis published in 2023 by Bjornsdottir and colleagues,[74] using whole-genome sequencing data combined with SNP arrays to enable more, and rarer, variants to be called (down to 0·001% minor allele frequency), and which included individuals with proxy (or self-reported) migraine and migraine with aura symptoms (eg, bad and recurrent headaches or visual disturbances preceding headache), found many

Panel 1: **Linking single-nucleotide polymorphisms identified in migraine genome-wide association studies with involved genes, and their role in pathogenesis**

Of the lead single nucleotide polymorphisms (SNPs) for the 123 risk loci reported by Hautakangas and colleagues,[71] five were missense variants and 40 were in close proximity with a missense variant; these missense SNPs might have functional effects on the protein product of the gene they are in, and therefore identify the probable causal or contributing gene and variant. Three other risk SNPs were predicted to either affect splicing of their gene transcript or result in a prematurely truncated protein. The remaining lead SNPs are outside protein-coding sequences. Many polymorphisms identified via genome-wide association studies (GWAS) localise to intronic or intergenic gene regions and are likely to influence susceptibility via affecting expression of a neighbouring gene or genes. They might occur in regulatory elements, such as promoters, enhancers, and silencers, and could affect gene-transcript levels, or expression in a particular cell type or of a particular isoform. Some loci might not act on the closest gene and can exert influence from a long distance. Numerous candidates in the surrounding area can complicate establishing which gene is affected. Probable causal SNPs can be fine-mapped and relevant susceptibility genes identified via various statistical, functional, and population-based approaches.[72] For example, transcription factor binding information and epigenetic data, such as histone modifications, chromatin accessibility, and 3D chromatin interactions (eg, Hi-C) from relevant cell types, might suggest which regulatory elements are in active chromatin or in contact with the particular SNPs; another approach is expression quantitative trait locus association, using a gene-expression database (eg, Genotype-Tissue Expression). Functional experiments, such as testing alleles with reporter constructs, investigating phenotypic consequences of overexpression, knockout of suspected genes, and genome editing of specific variants, would be required to validate the effects of specific susceptibility genes and alleles, but are time and labour intensive and therefore take longer than genomic analyses. For example, the pleiotropic phosphatase and actin regulator 1 gene (*PHACTR1*) GWAS locus (ie, the specific region in the gene associated with the disorder) has been associated with migraine and multiple vascular disorders, and was first reported in 2009.[73] Investigations have led to identification of a co-localised, vascular-specific, non-coding regulatory element thought to affect expression of the endothelin-1 (*EDN1*) gene 600 kb away. *EDN1* knockout and transgenic mice display vascular phenotypes, whereas three separate mouse lines with *PHACTR1* knocked out in different cell types did not, suggesting that *EDN1* is probably the main gene relevant to the various disorders. Nevertheless, *PHACTR1*, or other genes, might also have an effect.[73]

For the **Genotype-Tissue Expression portal** see https://www.gtexportal.org/home

overlapping, but also some new, loci.[74] These variants included both non-coding and protein-altering variants.[74] For example, the frameshift *PRRT2* variants (previously implicated in movement disorders and hemiplegic migraine; table 1) are also associated with migraine with aura and show a strong founder effect in Iceland; both common missense and rare loss-of-function variants in *SCN11A* (encoding a voltage-gated sodium channel involved in pain perception) effect migraine risk; and a cis-regulatory variant for the potassium channel gene *KCNK5* confers a large protective effect against migraine. Notably, the rare risk variants detected have clearly larger effect sizes than the common variants.[74]

Merging of genes involved in monogenic and polygenic migraine subtypes

GWAS findings have now shown there is some direct overlap between genes involved in monogenic and polygenic migraine. An intronic SNP in the FHM1 gene *CACNA1A* (rs10405121) and the *PRRT2* frameshift (rs587778771-GCC; Arg217ProfsTer8) are associated with common migraine, specifically migraine with aura.[71,74] Migraine-susceptibility SNPs were also localised near other genes involved in monogenic migraine-related disorders. rs4278223 on chromosome 9 is upstream of *CACNA1B*[71] and is frequently mutated in familial migraine families.[63] Furthermore, risk SNPs were located near *JAG1* encoding the NOTCH ligand Jagged 1 (chromosome 20: rs111404218), *COL4A1* (chromosome 13: rs2000660), *TREX1* (chromosome 3: rs7618883), and *HTRA1* (chromosome 10: rs2672592),[71] which are all causal genes for monogenic cerebrovascular or stroke disorders and often feature migraine as a symptom (table 1).[75] Further studies might reveal more reciprocity between monogenic and complex migraine forms.

Effects of genes on migraine subtype and sex differences

Some migraine susceptibility loci might be subtype specific. *CACNA1A*, heme oxygenase 2 (*HMOX2*), and *MPPED2* (a brain expressed metallophosphoesterase) were particularly found to be associated with migraine with aura.[71] Although *CACNA1A* variants have been shown to facilitate CSD initiation and aura,[13] the relationship between the *HMOX2* and *MPPED2* loci and migraine with aura is unclear. Additional variants in the *PRRT2*, *PALMD*, *ABO*, and *LRRK2* loci that primarily associated with migraine with aura symptoms were identified in the GWAS by Bjornsdottir and colleagues.[74] Previous GWAS had suggested some loci associated with migraine without aura.[69] Hautakangas and colleagues[71] found two lead variants (near *SPINK2* and near *FECH*) with a more than 95% probability of being specific for migraine without aura, and Bjornsdottir and colleagues[74] classified 13 SNPs that conferred a higher risk for migraine without aura than for migraine with aura. Most migraine-susceptibility variants, however, appear to be common between migraine subtypes. A GWAS for broadly defined headache that used UK Biobank data identified 28 risk loci, many the same as those found for migraine, but of which 13 were distinct.[76] Similarly, the migraine-risk loci *FHL5*, *LRP1*, and *PLCE1* were also identified in GWAS for cluster headache, along with other distinct loci.[77] Thus, the genetic data suggest that common migraine subtypes are not completely different entities, sharing many genetic factors, although differences at specific genes might influence manifestation of symptoms. Furthermore, there is some overlap, but also genetic distinction, between migraine and other headache disorders.

Three times as many women are affected by migraine than men,[78] with hormonal influences mainly thought to account for the difference in prevalence. Sex-stratified GWAS analysis found some susceptibility loci specific to women (ie, *ASTN2*, *CPS1*, *PBRM1*, and

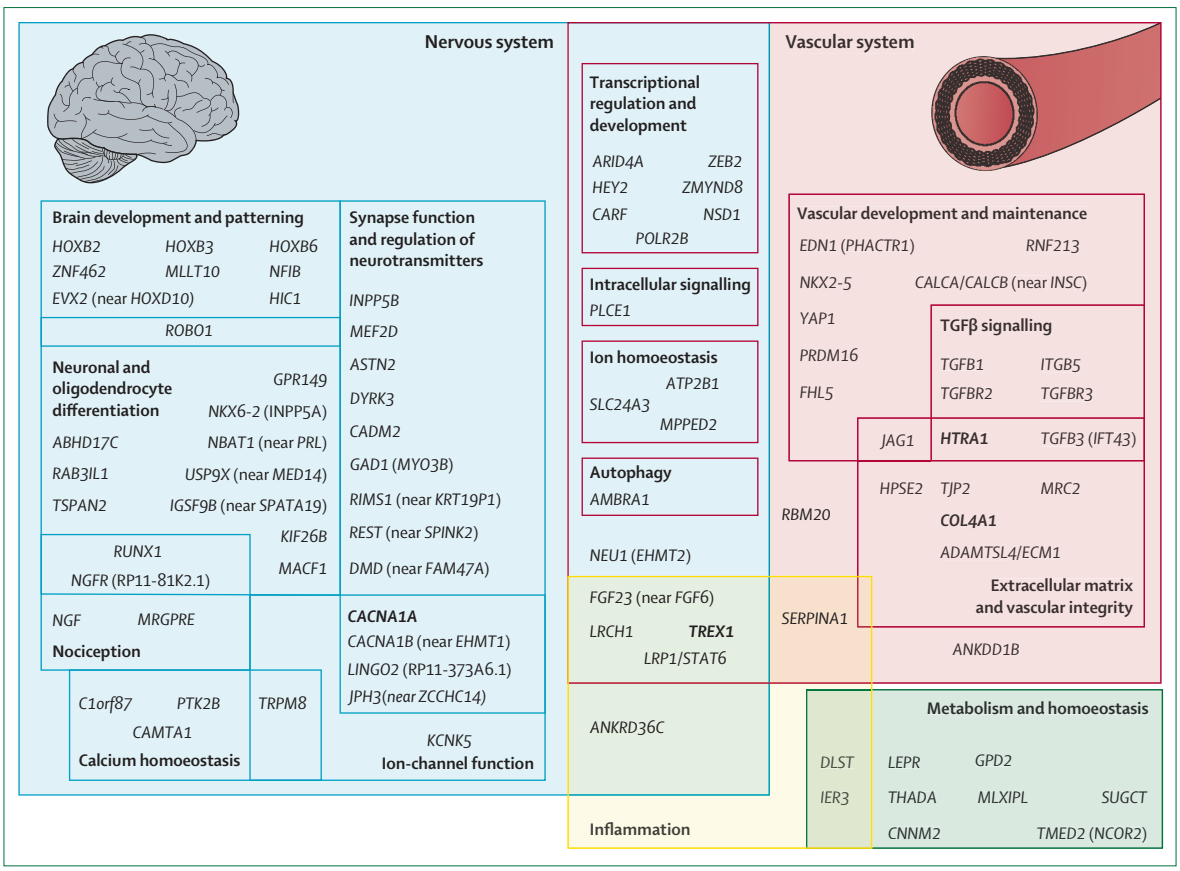

***Figure 3*: Functional themes of probable candidate genes influenced by migraine GWAS susceptibility loci**
We identified probable genes influenced by migraine GWAS susceptibility loci from fine-mapping causal gene sets and expression-association studies by Choquet and colleagues[70] and Hautakangas and colleagues,[71] and we subsequently categorised the loci into the systems and general pathways in which they have an effect that might be relevant to migraine pathogenesis. Names in brackets are names of genetic loci annotated in the study by Hautakangas and colleagues, if they differ from the candidate gene. Bold genes are causal for Mendelian migraine and related cerebrovascular disorders. GWAS=genome-wide association study.

SLC25A21).[70] Although their specific effects in migraine are largely unknown, they might interact with hormonal factors. Studies to find genetic variants for other particular subgroups or aspects of migraine such as ethnicity[70] or age of onset[79] have been done. However, these studies are often limited by the number of available samples to produce significant findings that can be replicated in other data sets.

Application of GWAS findings for prediction of migraine risk

The small effect sizes of most genetic loci that contribute to complex polygenic disorders mean that large sample sizes are required in GWAS to comprehensively identify all the genes involved in the genetic spectrum. Although migraine seems to involve fewer genes than some psychiatric disorders, Bahrami and colleagues[80] still estimate that approximately 2800 genetic variants contribute to migraine. Known susceptibility variants can be used to calculate a polygenic risk score, a weighted sum of the variants and their effect sizes (derived from GWAS), which can be used to try and predict the predisposition of an individual to a trait or disease. For migraine, such scores are not yet clinically useful; however, high risk scores were found to be correlated with typical and complex migraine symptoms according to ICHD-3 diagnostic criteria,[81] and polygenic risk scores could be useful in identifying migraine-related heritable traits or in predicting drug responses.[82] Adding more variants, both common and rare, into a polygenic risk score, and combining it with additional epigenetic information, such as DNA methylation markers that might be associated with migraine risk, is likely to improve sensitivity and specificity.

Exploring migraine-related traits and comorbidities through genetics

Genetic data in understanding relationships between traits, diseases, and external factors

Genes and SNPs identified in GWAS can aid in understanding pathways perturbed in migraine (figure 3). Furthermore, they can be used to dissect correlation and the shared genetic architecture of migraine with other traits and comorbidities (eg, neurological, psychiatric, and vascular).[83] Cross-trait analyses, with various statistical

methods, can quantify genetic correlations and polygenic overlap between traits and identify pleiotropy, either due to the effect of genetic variants on two or more traits via independent biological pathways or if the effect of the variant on one trait is causally related to variation in another trait.[80,84,85] Genetic biomarkers can also be combined with Mendelian randomisation to identify potential causal relationships.[86,87] Genetic variants that are robustly associated with a biomarker, exposure, or modifiable risk factor can be used as a proxy to genetically predict that factor and estimate its causal effects on migraine (or vice versa, by analysis in the reverse direction; panel 2). Numerous Mendelian randomisation studies have investigated relationships between migraine and a wide range of factors (table 2).[108]

Panel 2: **Use of genetic factors in Mendelian randomisation studies for making causal inferences**

Mendelian randomisation is a method of understanding causality. The use of genetics in Mendelian randomisation studies has become a powerful approach to begin disentangling cause and correlation with biomarkers (eg, morphological measures or blood metabolites), comorbidities (eg, heart disease and blood pressure), and external or modifiable factors (eg, alcohol and smoking).[86,87] Mendelian randomisation is founded on the recognition that a genetic variant or set of genetic variants associated with a biomarker of interest can be used as an instrumental variable to estimate the causal effect of the biomarker on an outcome or disease endpoint, and thus provide evidence about putative causal relations. Through measured variation in genes (usually single nucleotide polymorphism genotyping data from unrelated individuals), Mendelian randomisation is less likely to be affected by confounding or reverse causation than conventional observational studies. For example, if individuals carrying a particular risk allele tend to have a higher level of a biomarker, exposure, or modifiable risk factor than those without the risk allele, then according to Mendel's laws of segregation and independent assortment, confounding factors should evenly affect both genotype groups. Therefore, any difference in the outcome or disease between groups (or individuals) with and without the risk allele can be attributed to the causal influence of the biomarker or exposure. As well as the requirement for a robust association of the genetic variant or variants with the exposure (strength of the instrumental variable), Mendelian randomisation assumes that the genetic variant or variants are not associated with any confounding factors and do not affect the outcome apart from via the exposure (ie, are independent from pleiotropy). Violation of these assumptions could bias exposure–outcome associations. Use of Mendelian randomisation is limited by availability of suitable genetic variants to proxy for the exposure of interest. However, with increasing availability of genetic data associated with a wide range of biological phenomena (eg, anthropomorphic measures, biomarkers, clinical features, and comorbidities) and lifestyle measures, the potential causal relationships of these biomarkers and measures with migraine can now be investigated.

Relationships between brain and migraine morphology

Studies of FHM indicate differences in the excitatory–inhibitory balance in the brain in some people with migraine.[13,17] Furthermore, for common migraine subtypes, imaging studies have shown differences in brain morphology (eg, reduced intracranial volume) and volumes of particular subcortical regions, which are associated with increased migraine risk.[4,109,110] Some genetic loci that affect brain morphometry overlap with those that influence migraine susceptibility (eg, neuronal development and patterning genes, such as *HOX* genes; figure 3).[88] Mendelian randomisation studies furthermore support possible causal relationships for some of the morphological differences (eg, total brain, hippocampal, ventral diencephalon, and amygdala volumes) and migraine risk (table 2).[88,89]

Comorbidity of migraine with neurological, neuropsychiatric, and vascular disorders

Migraine can be comorbid with epilepsy and ataxias, which co-occur at a higher frequency with migraine, and vice-versa, than in the general population.[66,67] Variants in the same gene can be associated with migraine in some people and with epilepsy in others, suggesting that genetics at least partly underlies epidemiological findings.[68,74] Migraine is also often clinically comorbid with psychiatric disorders (eg, depression is approximately 2·5 times more common in people with migraine than in the general population).[111] In combined analyses of disorders with available GWAS data, migraine showed significant genetic correlations and overlap of risk variants, especially with major depressive disorder.[80,112,113] Using bivariate causal mixture model analysis, Bahrami and colleagues[80] found that most migraine-influencing variants also influenced depression and schizophrenia, suggesting the presence of many pleiotropic variants that affect susceptibility to a range of brain-related disorders. Nevertheless, differential association of migraine subtypes or severity with subtypes of major depressive disorder[114] might reflect contributions of specific gene variants to the disorders. Mendelian randomisation also supports a causal effect of major depressive disorder on migraine (table 2).[91] Although little common genetic risk is observed between neurological and psychiatric disorders in general,[113] migraine appears to be an exception, with linkage disequilibrium score regression and genetic correlation analyses showing it shares genetic architecture with schizophrenia, attention deficit hyperactivity disorder, Tourette's syndrome, and neuroticism.[80,92,113] Significant overlap of gene loci with epigenetic changes (ie, DNA methylation) associated with either post-traumatic stress disorder or migraine have also been found.[115]

	Study reference	Result or effect	Potential clinical implications
Brain structures or biomarkers			
Total brain size	Mitchell and colleagues (2022)[88]	Genetically predicted small intracranial volume was causally associated with increased migraine risk; no evidence for causality in reverse direction	..
Hippocampal volume and surface area	Mitchell and colleagues (2022)[88] and Guo and colleagues (2023)[89]	Genetically predicted small hippocampal volume and decreased surface area were causally associated with increased migraine risk; no evidence for causality in reverse direction	..
Ventral diencephalon volume	Mitchell and colleagues (2022)[88]	Genetically predicted small ventral diencephalon volume was causally associated with increased migraine risk; no evidence for causality in reverse direction	..
Amygdala volume	Mitchell and colleagues (2022)[88]	Genetically predicted small amygdala volume was causally associated with increased migraine risk; bidirectional effect with reverse analysis showed increased migraine risk causing small amygdala volume	..
Microstructural white matter	Zhao and colleagues (2023)[90]	Three white-matter imaging-derived measures showed evidence of a causal relationship with migraine; reverse analysis found an inferred causal effect of migraine on one white-matter measure (orientation dispersion index of the left superior cerebellar peduncle)	..
Neurological disorders			
Major depressive disorder	Lv and colleagues (2023)[91]	Mendelian randomisation supports a causal relationship between genetic susceptibility to major depression disorder and increased migraine risk; no evidence for causality in reverse direction	Important to monitor migraine symptoms in people with depression as depression increases migraine risk; monitoring people with depression for signs of migraine or mixed symptoms of migraine and depression might be helpful in ensuring comorbid disorders are treated
Vascular traits			
Diastolic blood pressure	Siewart and colleagues (2020)[92]	Mendelian randomisation provides evidence that genetically mediated high DBP increases susceptibility to migraine; causality in reverse direction not tested	Supports previous findings of reduced migraine attack frequency in some people taking blood-pressure-lowering medications
Diastolic blood pressure, systolic blood pressure, and pulse pressure	Guo and colleagues (2020)[93]	Mendelian randomisation suggests a potential causal role of elevated diastolic blood pressure on migraine susceptibility, whereas conditional on diastolic blood pressure, systolic blood pressure might be causally protective; increased genetically determined pulse pressure was causally associated with reduced migraine risk; in reverse direction, increased migraine liability was causally associated with decreased SBP and pulse pressure; causal analysis of genetic variation in target genes of blood-pressure-lowering medications (eg, β blocker, ACE inhibitor, and calcium-channel blocker) did not achieve significance, although the study might be underpowered	Supports possible role for anti-hypertensives in migraine prophylaxis; further studies are warranted
Cardiovascular disorders			
Coronary artery disease	Daghlas and colleagues (2020)[94]	Evidence of increased migraine liability being causally associated with decreased risk of coronary artery disease; also suggestive of migraine having a protective effect on myocardial infarction and angina; no evidence for causality of coronary artery disease on migraine	Possibility that therapeutics modifying migraine (eg, anti-CGRP monoclonal antibodies) could increase cardiovascular-disease risk; further studies are warranted
Large-artery atherosclerosis risk	Lee and colleagues (2022)[95]	No evidence of causal relationships of migraine with all stroke, ischaemic stroke, or haemorrhagic stroke; however, Mendelian randomisation supports a causal influence of migraine on decreased risk of the large-artery atherosclerosis subtype of ischaemic stroke; causality in reverse direction not tested	..
Large-artery stroke	Daghlas and colleagues (2022)[96]	Mendelian randomisation supports causal influence of migraine on decreased risk of large-artery stroke; causality in reverse direction not tested	..
Extracranial cervical-artery dissection	Daghlas and colleagues (2022)[96]	Mendelian randomisation supports causal influence of migraine on increased risk of cervical-artery dissection; causality in reverse direction not tested	..
Sleep traits			
Insomnia	Daghlas and colleagues (2020)[61] and Chu and colleagues (2021)[62]	Genetically predicted insomnia was causally associated with increased risk of migraine; no significant causal association of genetically predicted migraine on insomnia	Treating sleep disturbances or improving sleep quality might be a promising clinical intervention in reducing migraine burden; further studies are warranted
Difficulty awakening and napping frequency	Daghlas and colleagues (2020)[61]	Evidence for potential causal effects of difficulty awakening on increased risk of migraine; little evidence for an effect of migraine liability on sleep patterns, although suggestive weak causal effect of genetically determined migraine on increased napping	Treating sleep disturbances or improving sleep quality might be a promising intervention in reducing migraine incidence; further studies are warranted
Gut health			
Irritable bowel syndrome	Chen and colleagues (2021)[97]	Mendelian randomisation supports a causal association between irritable bowel syndrome and increased migraine risk; Mendelian randomisation in reverse direction not done	Migraine might occur with increased incidence in people with irritable bowel syndrome, so migraine-preventive medications should not exacerbate constipation or diarrhoea

(Table 2 continues on next page)

	Study reference	Result or effect	Potential clinical implications
(Continued from previous page)			
Gut microbiome	He and colleagues (2023)[98]	Evidence some bacterial taxa are causally related to migraine risk (either increased or decreased); no reverse causal association of migraine on gut microbiome detected	Suggests possible effects on migraine of dietary interventions, probiotics, or faecal transplants, which correct gut dysbiosis; further studies are warranted
Laboratory biomarkers			
Serum calcium	Yin and colleagues (2017)[99]	Increased serum calcium potentially causally associated with increased migraine risk; causality in reverse direction not tested	Direct targeting of calcium levels by calcium-channel blockers might have a therapeutic effect in addition to their known vasodilatory effects for migraine; for some people with migraine and hypercalcaemia, migraine could improve by managing serum calcium; further studies are warranted
Fatty acids	Tanha and colleagues (2021)[100]	Increased lysophosphatidylethanolamine(20:4) and reduced length of fatty acids causally associated with migraine; causality in reverse direction not tested	Suggests lysophosphatidylethanolamine(20:4) as a potential therapeutic target for migraine
Blood measures of haemostasis	Guo and colleagues (2021)[101]	Mendelian randomisation supports potential causality of increased coagulation factor VIII, Von Willebrand factor, phosphorylated fibrinopeptide A, and decreased fibrinogen in migraine susceptibility (especially migraine with aura); no evidence for reverse causality, although migraine with aura was not tested due to too few suitable instruments	Supports a possible role of coagulation and thrombosis in migraine susceptibility and as a potential therapeutic target
Vitamin D	Niu and colleagues (2022)[102]	Provides evidence that increased circulating vitamin D is causally associated with decreased risk of migraine; no strong evidence for causal association of migraine on vitamin D in reverse Mendelian randomisation analysis	Suggests well designed randomised clinical trials are warranted to establish the effects of vitamin-D supplementation in people with migraine, particularly if they are deficient in vitamin D
IGF-1	Abuduxukuer and colleagues (2022)[103]	Evidence that genetically determined increased circulating IGF-1 is significantly associated with decreased migraine risk; migraine was not causally associated with IGF-1 in reverse analysis	IGF-1 could be a potential therapy for migraine; however, increased circulating IGF-1 has been associated with other diseases (eg, type 2 diabetes and some cancers)
Lifestyle and behavioural factors			
Leisure-activity participation	Harrison and colleagues (2020)[104]	Genetically predicted migraine reduced the chance of having a per-week leisure or social activity, especially in men; causality in reverse direction not tested	Encouragement and support for people with migraine to participate in leisure activities could be beneficial for overall wellness
Alcohol consumption	Yuan and colleagues (2022)[105]	Genetically predicted increased alcohol consumption was causally associated with decreased migraine risk; genetic risk of migraine was associated with reduced alcohol consumption in reverse Mendelian randomisation analysis	..
Coffee consumption	Yuan and colleagues (2022)[105]	Genetically predicted increased coffee consumption was associated with decreased migraine risk; no evidence of migraine causally influencing coffee consumption in reverse direction	..
Smoking initiation (ie, ever smoked regularly)	Yuan and colleagues (2022)[105]	Genetically predicted smoking initiation was associated with increased migraine risk; no evidence of migraine causally influencing smoking initiation	Smoking cessation to reduce cardiovascular risk might also help reduce incidence of migraine
Years of schooling	Zheng and colleagues (2023)[106]	Evidence for significant causal association of increased years of schooling with reduced migraine risk of causality in reverse direction not tested	Increased years of education might mean people have an increased likelihood of accessing migraine prophylaxis and avoiding medication-overuse headaches, suggesting importance of promoting awareness of migraine in a broad population to improve access to effective treatment
Potentially modifiable factors	Zheng and colleagues (2023)[106]	Suggestive findings that light physical activity, vitamin B12 intake, and coffee intake are protective factors, whereas stress, anxiety, and increased eicosapentaenoic acid status increase migraine risk	Further studies are warranted; however, depending on the factor, relevant interventions might reduce migraine risk
Pharmacological interventions			
Lipid-modifying drugs	Bi and colleagues (2023)[107]	Mendelian randomisation provides evidence that genetic proxies for HMGCR inhibition and lipoprotein-lipase enhancement are causally associated with decreased migraine risk	HMGCR and lipoprotein lipase are of interest as targets of migraine prevention; HMGCR is a known target of statins, so this class of drugs might be a candidate for drug repurposing; further studies are warranted

Only studies with traits, comorbidities, or biomarkers that support causal relationships with migraine have been included. Further details and Mendelian randomisation studies that found no causal relationships, can be found in Grangeon and colleagues.[108] Empty cells denote no suggested specific clinical implications for findings, but do not preclude that there are or will be any or other clinical applications. Genetically predicted is defined as the presence of a trait, comorbidity, biomarker, or factor for an individual that has been predicted via their genotypes at the known genetic polymorphisms that influence those factors. ACE=angiotensin-converting enzyme. CGRP=calcitonin gene-related peptide. HMGCR=3-hydroxy-3-methylglutaryl-CoA reductase. IGF-1=insulin-like growth factor.

Table 2: **Mendelian randomisation studies that support causal relationships of migraine with specific traits, comorbidities, or biomarkers**

Genetic findings from monogenic cerebrovascular syndromes and GWAS support the influence of disrupted vascular integrity and function in migraine, which could also relate to its comorbidities. Migraine is associated with increased long-term risk of various cardiovascular and cerebrovascular outcomes, including arterial and heart disease, myocardial infarction, stroke, and cervical-artery dissection.[96,116–118] Biological mechanisms,

including cerebral hypoperfusion, systemic vasculopathy, endothelial dysfunction, and a hypercoagulable state, might be involved,[116,117] and at least partly explained by the vascular effects of particular migraine gene variants[119] and the sharing of multiple genetic risk variants between the various disorders.[83,92] Relationships between migraine and vascular comorbidities are complex, and although epidemiological studies suggest comorbidity of migraine with ischaemic stroke, Mendelian randomisation does not support a causal association (table 2).[96,120]

Genetic factors that contribute to migraine comorbidities and blood biomarkers

Multiple other conditions have been genetically correlated with migraine, including type 2 diabetes, high serum total cholesterol and triglycerides,[92] autoimmune-related traits, insomnia, and blood pressure.[108] Insomnia and high blood pressure also directly contribute to migraine risk.[61,62,92,93] Genetic factors also influence a range of blood biomarkers; correlations and some causative associations of migraine with biomarkers have been reported (eg, serum calcium;[99] blood metabolites, such as fatty acid lipids;[100] and circulating vitamin D;[102,108] table 2). The large number of correlated traits might partly be due to the pleiotropic nature of many migraine-susceptibility variants.[121,122] Nevertheless, these findings reveal important aspects of migraine biology and potential diagnostic biomarkers or therapeutic targets.

Interactions between environmental and genetic factors and epigenetics

Environmental or external factors can trigger migraine. Several lifestyle factors, such as alcohol intake, coffee consumption, and smoking, have been proposed as migraine risk factors. A bidirectional Mendelian randomisation study found genetic evidence supporting a protective role of moderate coffee consumption and a detrimental role of cigarette smoking (table 2).[105] Perhaps surprisingly, the study also suggested a causal effect of genetically predicted alcohol consumption (ie, predicted on the basis of genotypes at the known genetic variants that influence that factor) on reduced migraine risk, although this finding might be attributable to reverse causality.[105]

Environmental factors can influence epigenetic modifications that affect gene expression. Epigenetic factors could substantially contribute to phenotypic variability and penetrance of migraine in families, as well as affect therapeutic response. Furthermore, as epigenetic modifications are potentially reversible, they might offer opportunities for intervention. Studies of epigenetic factors in migraine are still rather scarce, but differences in DNA methylation have been associated with migraine in case–control studies.[123–125] In 2023, DNA-methylation changes in the histone deacetylase 4 gene (*HDAC4*) were found to be significantly associated with a mean reduction in headache days after medication-withdrawal treatment in patients with chronic migraine, and reduced baseline methylation levels in *MARK3* were associated with reduced monthly migraine days.[126] More extensive, and longitudinal, studies are expected to uncover further epigenetic changes that might occur in migraine, or in its conversion from episodic to chronic migraine, and identify potential therapeutic targets.

Genetics in the treatment of migraine

Many pharmacological treatments are available for migraine.[127,128] Patient sex, age, weight, ethnicity, or comorbidities could influence drug pharmacodynamics and pharmacokinetics and are considered when prescribing treatments and dosing.[129] Furthermore, genetic factors might also affect drug properties and interactions, and thus treatment efficacy and response. Not all patients with migraine respond adequately to acute and prophylactic therapies, so studying differential responses to medications in individuals due to genetic variation (pharmacogenomics) might help define the most appropriate treatments. This potential application of pharmacogenomics is increasingly important as failure or poor efficacy of treatment is associated with reduced compliance with preventive therapies, thereby contributing to overuse of acute medication that, in turn, is a risk factor for chronic migraine and medication-overuse headache.[1,130]

GWAS have not investigated differences in responses to therapies. Pharmacogenomic studies of migraine therapies to date have primarily focused on polymorphisms in genes encoding proteins involved in drug metabolism, such as the cytochrome P450s (eg, *CYP1A2, CYP2D6, CYP2C19,* and *CYP3A4*); phase 2 enzymes, such as uridine 5′-diphospho-glucuronosyltransferases; transporter proteins; and the monoamine oxidase A system, which is important for metabolising triptans.[131,132] Some migraine-susceptibility gene SNPs have significantly associated with migraine drug responses (eg, rs2651899 in *PRDM16* for triptans)[133] and in phospholipase-C second-messenger pathways (eg, *PLCE1* for verapamil).[134] Furthermore, loci identified in GWAS since 2021 have included target genes for some migraine therapies (ie, *CALCA* and *CALCB,* the genes that produce CGRP; and *HTR1F,* which encodes the serotonin 5-HT1F receptor targeted by ditans).[70,71] Thus, as well as contributing to migraine pathogenesis, these genes could also theoretically influence therapy success.

In clinical trials of monoclonal antibodies targeting CGRP or its receptor, aura did not predict response, although there are reported differences in vascular reactivity and other mechanisms not mediated by CGRP in people who have migraine with aura compared with those who have migraine without aura.[135,136] These findings further illustrate the heterogeneity of causes and treatment response in migraine. Only a few studies to date have investigated genetic variations that might influence response or efficacy to new anti-CGRP

therapies, onabotulinum toxin A, or acute treatments (eg, gepants and ditans).[137,138] Large studies with a broad investigation of genetic and epigenetic factors will be necessary to define the genes and pathways that substantially affect migraine treatment response more accurately, and to define more appropriate treatment doses for individuals to enable more personalised management of migraine.

Conclusions and future directions

Migraine remains a disorder currently without any clinically useful biomarkers. Therefore genetic testing, if sensitive, specific, and available, could be useful in management. Early studies successfully identified single genes involved in subtypes of migraine, but with most migraine due to polygenic factors, exploring the wide range of associated genes, and their interplay, will be of great interest. Considerable unexplained heritability remains. Even in single-gene familial disorders, the individual clinical presentations of those affected can vary substantially. Harnessing all types of genomic information—genetic variants, transcriptomics, and epigenetic factors—will further enhance understanding of genes and pathways in migraine and support identification of potential drug targets.

Variants in many genes can cause migraine or cerebrovascular disorders with overlapping symptoms, so broadening molecular genetic testing to increase molecular diagnostic rates (eg, via comprehensive next-generation sequencing panels, whole-exome sequencing, or whole-genome sequencing) will be increasingly important. Whole-genome or long-read sequencing technologies could also allow detection of causal structural variations or large effect non-coding regulatory variants. However, increasing the amount of sequencing data obtained also increases the complexity of bioinformatic analysis required to pinpoint probable pathogenic variants. Good clinical information, and extended family testing if possible, assists in prioritisation of key variants and their curation. Functional studies are important in providing evidence for newly discovered genes and their pathological mechanisms.

Growth of genomic and bioinformatic technologies and knowledge of genetic factors in disease is driving the development of diagnostics and individualised treatment strategies based on patients' genetic make-up. Validation of a genetic cause is important for some families as it can aid in ruling out some disorders and indicate potentially useful treatments. Mutation information is already used to select treatments for some monogenic migraine disorders (eg, FHM types or PRRT2) by targeting appropriate ion channels.[42] However, absence of a single gene identified in hemiplegic migraine does not preclude a trial of these therapies or their potential use in patients with as yet unidentified genetic factors. Some families might favour not having genetic causes identified if there is potential for discrimination in insurance and employment opportunities, so genetic testing should be done in the setting of clear explanations and individual counselling.

Personalised approaches for polygenic migraine, and the role of genetic factors for new therapeutic targets, are still areas of undergoing research. Robust and broad (genome-wide) pharmacogenomic studies are required, and ideally could be included as a standard part of clinical trials, with recognition of the important role of collaboration with standardised information and testing to enhance study-population size. The complexity of comorbidities, interactions, and tolerability of therapies in migraine make it an ideal target for pharmacogenomics guidance. The current trial-and-error approach to preventive and acute therapies for migraine could be improved if genetic tests and pharmacogenomic targeting of treatments could optimise early selection of the most effective and well tolerated therapies. Migraine is a common disorder with a high burden of cost to individuals and communities. Having genetic biomarkers for responders, along with studies of cost-effectiveness, could assist in optimising allocation of expensive therapies, such as monoclonal antibodies, or other future therapies.

Many pathways might lead to migraine. Genetic studies offer insights into the heterogeneity of migraine-related disorders, including distinct disease subtypes and common comorbidities. Increased use of genetics could influence approaches to the categorisation and management of migraine, and continued efforts should further delineate the key pathways that can be targeted with current and future therapeutics. As genetics becomes increasingly useful in defining subgroups of people with migraine, and in predicting outcomes, and response to therapies, the access to genetic testing will need to increase.

Search strategy and selection criteria

We searched PubMed, OMIM, and Genecards for studies published between Jan 1, 2018, and Dec 20, 2023, using the search terms "migraine genes", "migraine genetics", "migraine genome-wide association study (GWAS)", "migraine epigenetics", "familial hemiplegic migraine", "hemiplegic migraine", "familial migraine genes", "*CADASIL* genes", "cerebrovascular migraine", "migraine Mendelian randomisation", "migraine Mendelian randomization", and "migraine pharmacogenetics" with no language restrictions. Reference lists of articles retrieved from the PubMed searches were also used to find other relevant publications. For the final list of references for this Review, we prioritised articles on the basis of relevance to the topics discussed and impact (eg, research design, sample size, interpretation, importance to the field, and citations), and we included some essential key references published before 2018 that recent papers cited or that were suggested by reviewers to include as important to the field.

Contributors

This Review was conceptualised by all authors. HGS did the initial literature searches, created the tables and figures, and wrote the first draft of the manuscript. All authors contributed to writing drafts and editing the final manuscript.

Declaration of interests

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