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Migraine in monogenic disorders: Shedding light on new therapeutic targets

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Abstract

Background: Migraine is a common neurological disorder with a strong genetic component, yet the precise mechanisms underlying its genetic susceptibility remain largely unknown. Genome-wide association studies (GWAS) have identified multiple risk loci, but monogenic forms of migraine, particularly Familial Hemiplegic Migraine (FHM), have provided deeper insights into the pathophysiology of migraine. Studying monogenic disorders that present migraine as a symptom could help identify novel therapeutic targets by uncovering shared molecular pathways.

Methods: A narrative literature review was conducted using a stepwise approach in the PubMed database. Reviewers were divided into three groups, each focusing on different aspects of migraine genetics. The first group analyzed monogenic migraine syndromes, including FHM and related ion-channelopathies. The second group examined clinical manifestations and phenotypic spectrum of FHM-related genes. The third group expanded the search to other monogenic disorders associated with migraine, such as Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS), and Familial Advanced Sleep Phase Syndrome (FASPS). Additional searches were conducted using the Compendium of Causative Genes for Monogenic Disorders.

Results: The review identified multiple monogenic disorders associated with migraine, revealing distinct but interconnected mechanisms. Ion-channel dysfunction (*CACNA1A*, *SCN1A*, *ATP1A2*), vascular impairment (*NOTCH3*, *TREX1*), mitochondrial dysfunction (*MT-TL1*), and circadian dysregulation (*CSNK1D*) emerged as critical contributors to migraine pathophysiology. These findings highlight the roles of neuronal excitability, cortical spreading depression, trigeminal sensitization, and neurovascular dysfunction in migraine.

Conclusions: Monogenic migraine disorders offer valuable insights into migraine pathogenesis, emphasizing the importance of ion homeostasis, vascular function, and circadian regulation. Although genetic studies have not yet directly translated into new therapeutic targets, the study and knowledge of these rare conditions is pivotal for neurologists and

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migraine specialists, as it might improve diagnosis and care, and provide new insights into migraine pathophysiology that may ultimately inform future treatments.

Keywords
migraine, monogenic disorders, familial hemiplegic migraine, genetic migraine, CACNA1A, ATP1A2

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Introduction

Genetic diseases encompass a group of pathologies that arise due to alterations in the genetic material. Monogenic diseases result from mutations in a single gene, whereas polygenic or complex diseases develop due to the interaction between various genetic variants and environmental factors.

A complex interplay between genetic and environment shapes the clinical phenotype of migraine, a disabling and multifaceted neurological disorder (1,2) affecting almost 15% of the population worldwide (3) and with an estimated heritability of 37–54% (4). A growing body of evidence has identified multiple genetic variants associated with migraine (1,5–8). Populational genomics, specifically, genome-wide association studies, have identified more than 100 susceptibility loci (5,9), affecting genes involved in neuronal excitability, neurotransmission, the vascular system and genes related to migraine-specific drug targets (Calcitonin-Related Polypeptide Alpha (CALCA) / Calcitonin-Related Polypeptide Beta (CALCB), Serotonin Receptor 1 (HTR1F)). Recent advances in polygenic risk scores (PRS) have provided a means to quantify an individual's genetic predisposition to migraine by aggregating the effects of these susceptibility loci. PRS models have shown promise in identifying high-risk individuals and may aid in patient stratification for targeted preventive treatments. However, their clinical utility remains an area of ongoing research, particularly in integrating PRS with environmental and lifestyle factors for a more comprehensive risk assessment (10,11). However, the study of monogenic migraine forms, such as Familial Hemiplegic Migraine (FHM) (5,6), has also proven useful in understanding aspects of migraine pathophysiology, including in developing animal models of migraine. In line with this, the study of other monogenic disorders reporting migraine as a common condition can unravel potential shared pathophysiological mechanisms.

The aim of this review is to describe monogenic disorders that involve migraine as one of their symptoms to provide an important source of knowledge for the understanding of migraine pathophysiology, and to uncover novel potential targets for migraine therapeutics. It must be recognized that, despite more than three decades of genetic research, no therapeutic targets have yet been directly identified through genetics alone. Nevertheless, monogenic conditions are important for clinicians to know about, not only to improve diagnosis and management of affected patients, but also to enhance understanding of migraine mechanisms.

Search strategy and selection criteria

This is a narrative literature review. The reviewers were divided into three groups and worked independently, conducting an extensive literature search in the PubMed database. A stepwise approach was applied to ensure a comprehensive selection of relevant studies. The first group focused on identifying genetic disorders associated with migraine, particularly Familial Hemiplegic Migraine (FHM), by searching for terms related to monogenic conditions, chromosomal aberrations, and genetic mechanisms in migraine. Additionally, specific queries were designed to explore the role of *CACNA1A*, *ATP1A2*, *SCN1A*, and *PRRT2* in migraine pathophysiology. The second group examined the clinical spectrum of FHM-related genes, using search terms that combined genetic variants with key phenotypic descriptors such as clinical presentation and disease spectrum. This allowed for the identification of studies detailing the neurological and systemic manifestations associated with mutations in these genes. The third group expanded the search to include other monogenic disorders linked to migraine, using a combination of genetic and clinical search terms. Additionally, this group utilized the Compendium of Causative Genes for Common Monogenic Disorders (12) to systematically explore genes associated with migraine-related conditions. No publication date restrictions were applied, but preference was given to original research articles published in the last ten years, the final search was conducted between November 2024 and February 2025. Reviews were considered when a broader discussion was necessary. Letters to editors, and articles in languages other than English were excluded. As this is a narrative review based primarily on PubMed, we acknowledge the potential for selection bias; however, given PubMed's coverage of neurology/genetics and our citation-tracking steps, we believe the likelihood of missing pivotal studies is low. Each group independently screened relevant articles, resolving conflicts through

consensus, and two senior reviewers (E.C., P.P.-R.) supervised the selection process. After an initial screening, all researchers reviewed the full texts of the selected studies, refining the reference list based on research quality and relevance. The final reference selection was approved by the senior reviewers after resolving any remaining conflicts.

Familial hemiplegic migraine (FHM) and other monogenic disorders with mutations in the FHM-associated genes

FHM is a monogenic, autosomal dominant subtype of migraine with aura, clinically characterized by hemiparesis or hemiplegia during the aura phase, often accompanied by visual, sensory, speech, or language disturbances (7,13). Affected individuals frequently have a first-degree or second-degree relative with hemiplegic migraine. Genetically, FHM is caused by single-gene mutations in *CACNA1A*, *ATP1A2*, *SCN1A*, and *PRRT2* (6–8). The functional consequences of these mutations typically differ by gene: gain-of-function mutations are most often observed in *CACNA1A* and *SCN1A*, whereas *ATP1A2* mutations generally lead to loss-of-function (6–8). Beyond migraine, mutations in these genes are implicated in other neurological disorders, highlighting their broader significance in neuronal excitability and synaptic function (Table 1).

CACNA1A

The *CACNA1*A gene is located at 19p13 and encodes the alpha 1A subunit of P/Q-type calcium channels (CaV2.1) found on presynaptic neurons in the brain and cerebellum (Online Mendelian Inheritance in Man, OMIM: 601011) (5,7,8,14). Mutations in the *CACNA1A* gene can either result in a gain or a loss of function. With gain-of-function mutations, there is prolonged opening of the affected calcium channels with an increased influx of calcium ions and neuronal excitability (15). Conversely, with loss of function, there is impaired or improper opening of the calcium channels, leading to less influx of calcium ions and decreased neuronal excitability. Several mutations in the *CACNA1A* gene with variable phenotypic expressions have been identified (15). Of the more than 25 different *CACNA1A* mutations associated with FHM1, T666 M and S218L are the most common (6). Clinically, patients with T666 M and S218L mutations typically present with severe hemiplegic migraine attacks, accompanied by coma and fever. Cerebellar degeneration has also been reported in FHM1 (16). Mutations of the *CACNA1A* gene have been identified in other monogenic disorders, including episodic ataxia type 2 (EA2), developmental and epileptic encephalopathy 42 (DEE42), and spinocerebellar ataxia type 6 (SCA6) (15,17). EA2 is a monogenic disorder with an autosomal dominant pattern of inheritance. Patients with EA2 present clinically with recurrent episodes of imbalanced vertigo and ataxia. Attacks or episodes are usually precipitated by physical or emotional stress (18). Most cases of *CACNA1A* mutations associated with EA2 are loss-of-function point mutations, which result in decreased neuronal excitability and progressive loss of Purkinje cells in the cerebellum (18). Spinocerebellar ataxia type 6 is a subtype of spinocerebellar ataxia (autosomal dominantly inherited progressive neurodegeneration of the cerebellum) and is characterized by adult-onset, progressive cerebellar-type ataxia, dysarthria, and nystagmus (19,20). DEE42 is characterized by neonatal-onset refractory seizures of various types, which typically begin in the first hours or days of life and are associated with significant developmental delay and intellectual impairment (21). Affected infants may also present hypotonia, tremor, ataxia, and abnormal eye movements. Most patients with DEE42 have heterozygous mutations in the *CACNA1A* gene (21).

ATP1A2

ATP1A2, located on chromosome 1q23.2 (OMIM 182340), encodes the catalytic α2-subunit of the Na+/K + -ATPase (14,22). The α2-subunit is abundantly expressed in muscle tissue (skeletal, cardiac and vascular smooth muscle) and in the brain, where it is primarily found in cortical astrocytes, though neuronal expression has been described during developmental periods (23). The Na+/K + -ATPase regulates electrochemical Na + and K + gradients across the plasma membrane, which are essential for cellular resting potential and excitability, and activity of secondary active transporters (23). Dysfunction of neuronal and astrocytic Na+/K + -ATPases results in hyperexcitability due to extracellular K + and intracellular Ca2 + accumulation, and failure to clear neurotransmitters such as glutamate from the synaptic cleft, which increases susceptibility to CSD(23).

ATP1A2 mutations in FHM2 typically cause partial or complete loss of function. However, certain variants that subtly affect the voltage dependence of the pump may exhibit voltage-dependent functional effects, resulting in loss of function at some membrane potentials and gain of function at others (23). *ATP1A2* mutations have also been implicated in sporadic hemiplegic migraine (SHM2) and common forms of migraine (i.e., migraine with and without aura); familial migraine with brainstem aura (24); FARIMPD, an autosomal recessive syndrome with fetal akinesia, respiratory insufficiency, microcephaly, polymicrogyria, and dysmorphic facies, typically resulting in death in infancy (25); developmental and epileptic encephalopathy-98 (26); and alternating hemiplegia of childhood 1 (27). Recently, an association between a novel heterozygous missense mutation in *ATP1A2*, resulting in a depolarizing inward leak current in skeletal muscle under hypokalaemic conditions, and hypokalemic

Table 1. Other monogenic disorders involving mutations in FHM-associated genes

Gene (cytogenic location)*and associated disorder	Nature of mutation in FHM	Protein encoded and role	Other clinical presentation	Co-occurrence with FHM	Studies included	Limitations
CACNA1A(19p13) mutations are associated with Familial Hemiplegic Migraine type 1 (FHM1) (1)	Primarily missense mutations (Gain of function) (2,3)	**a**1A-subunit of P/Q-type calcium channels (CaV2.1) found on presynaptic neurons in the brain and cerebellum ➔ The **a**1A-subunit P/Q-type calcium channels form pores on the presynaptic membranes through which calcium ions flow during neurotransmission. They also control the release of neurotransmitters (3).	**Episodic ataxia type 2, EA2 (AD):** typically loss-of-function point mutations, which result in decreased neuronal excitability and progressive loss of Purkinje cells in the cerebellum. Characterized by recurrent episodes of imbalanced vertigo and ataxia. Attacks or episodes are usually precipitated by physical or emotional stress (4).	Yes	Narrative and systematic reviews Case reports Case series	Most studies were case reports, this limits the generalizability of the results.
			Developmental and epileptic encephalopathy 42, DEE42: characterized by neonatal-onset refractory seizures of various types, which typically begin in the first hours or days of life and are associated with significant developmental delay and intellectual impairment (5). Affected infants may also present hypotonia, tremor, ataxia, and abnormal eye movements. Most patients are heterozygous mutations in the CACNA1A gene (5).	Yes	Narrative and systematic reviews Case reports	Most studies were case reports with limited generalizability of evidence, evidence from case reports are usually not strong enough to establish cause-effect relationship
			Spinocerebellar ataxia type 6, SCA6 (AD): subtype of spinocerebellar ataxia with progressive neurodegeneration of the	Yes	Case reports Case series	Limited generalizability, weak evidence to establish cause-and-effect relationships, risk

Table 1. (continued)

Gene (cytogenic location)*and associated disorder	Nature of mutation in FHM	Protein encoded and role	Other clinical presentation	Co-occurrence with FHM	Studies included	Limitations
			cerebellum characterized by adult-onset, progressive cerebellar-type ataxia, dysarthria, and nystagmus (6,7)			of overinterpretation based on a single case
ATP1A2 (1q23.2) mutations are associated with Familial Hemiplegic Migraine type 2 (FHM2) (1)	Primarily missense mutations resulting in partial-to-complete loss of function. Rare deletions ± insertions, polymorphisms, Nonsense mutations, frameshift mutations with premature stops, read-through mutations etc. (8)	Catalytic α2-subunit of the Na^+/K^+-ATPase ➔ regulation of physiological Na^+ and K^+ gradients across cell-membranes by translocating $3Na^+$ ions out and $2K^+$ ions in via hydrolysis of 1 ATP molecule as the driving force, thereby maintaining cellular resting potential and excitability, and facilitating the activity of secondary active transporters (9).	**Familial basilar migraine (AD)**: basilar migraine (BM, currently classified as migraine with Brainstem Aura) is a subtype of migraine with aura, with symptoms that clearly originate from the brainstem, but no motor symptoms (1). A heterozygous mutation in the ATP1A2 gene was identified in members of a family with basilar migraine.	Phenotypically similar entities. Possibly allelic disorders. Hemiplegic migraine did not co-occur within the same family in the case study (8)	Case study of one Italian family.	Risk of chance association, though causality seems likely due to phenotypic similarities and because the mutation is in a highly conserved residue and segregated in three patients (first-degree relatives) with similar aura phenotypes but absent in a large subset of control chromosomes
			Common types of migraine (migraine with and without aura) (1,10,11)	Yes	Case studies.	Risk of chance association. However, several factors indicate that variants in ATP1A2 could increase susceptibility to migraine with and without aura (absence of ATP1A2 alterations in controls, pattern of segregation + clustering within FHM families, high conservation of residues in ATP1A2, involvement of ATP1A2 mutations in monogenic migraine).

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Gene (cytogenic location)*and associated disorder	Nature of mutation in FHM	Protein encoded and role	Other clinical presentation	Co-occurrence with FHM	Studies included	Limitations
			Fetal Akinesia, Respiratory Insufficiency, Microcephaly, Polymicrogyria, and Dysmorphic facies, FARIMPD (AR): syndrome caused by biallelic or homozygous loss-of-function mutation of the ATP1A2 gene characterized by hypotonia in utero with resultant fetal akinesia, generalized joint contractures and arthrogryposis at birth, severe respiratory insufficiency, dysmorphic facial features, microcephaly and significant malformations of cortical development (lissencephaly,/pachygyria/ polymicrogyria). Prenatal/ neonatal seizures can occur. Usually not compatible with life (12–16). Heterozygous variants may play a role in non-specific intellectual deficiency, and cases of compound heterozygosity have been reported in patients with hemiplegic	No (usually lethal)	Case reports.	Variable phenotypes, some lethal and others compatible with longer survival, likely reflecting differential genetic variants (13,15,17,18)

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Gene (cytogenic location)*and associated disorder	Nature of mutation in FHM	Protein encoded and role	Other clinical presentation	Co-occurrence with FHM	Studies included	Limitations
			migraine with longer survival (17,18).			
			Developmental and epileptic encephalopathy 98, DEE98 (AD): characterized by early-onset, often severe epileptic seizures and EEG abnormalities associated with developmental impairment that tends to worsen as a consequence of the epilepsy. May also include features of hypotonia, spasticity, quadriparesis and non-specific and variable abnormalities of the brain, including polymicrogyria. It is estimated that ~5% of ATP1A2 mu (18,19).	Yes	Case reports, WES (whole exome sequencing) analysis, targeted resequencing analysis, reviews	Few cases described in the literature with variable phenotypes, i.e., small samples, and overlap with other disorders. Some methodological limitations, e.g., use of designs/chart views, risk of confounding variables, and observer's bias
			Alternating hemiplegia of childhood 1, AHC1 (AD): rare syndrome caused by heterozygous mutation in the ATP1A2 gene with resultant hemi- or quadriplegia lasting minutes to days, often with tonic or dystonic attacks, choreoathetoid movements, nystagmus or strabismus and other ocular motor abnormalities, autonomic disturbances, and	**Yes**	Case reports, case reviews, database search (omim.org)	Few cases described in the literature with variable phenotypes and overlap with other disorders. Risk of chance association. Methodological limitations, e.g., use of retrospective chart views, risk of confounding variables, and observer's bias (22).

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Gene (cytogenic location)*and associated disorder	Nature of mutation in FHM	Protein encoded and role	Other clinical presentation	Co-occurrence with FHM	Studies included	Limitations
			progressive cognitive decline. Seizures and seizure-like episodes may occur (18,20,21).			
			Hypokalaemic periodic paralysis, HypoPP (AD): a rare neuromuscular disease characterized by paralytic episodes with concomitant hypokalemia (serum-K + < 3.5 mmol/L). Usually debuts in early teens and is caused by sustained depolarization of the skeletal muscle cell membrane. About 70–90% of HypoPP cases are due to pathogenic CACNA1S (α subunit of voltage-gated calcium (Cav1.1) channels) and SCN4A (α subunit of sodium (Nav1.4) channels) gene variants that are essential for excitation-contraction coupling and sarcolemmal excitability in muscle. Mutations cause a net inward leak current that depolarizes the muscle, particularly in hypokalemic conditions. The recently reported heterozygous ATP1A2 missense mutation gene product was associated	No	Single case report	Risk of chance association. Methodological limitations associated with electrophysiological measurements (heterologous expression system, i.e., simplified, without additional regulatory subunits usually expressed in skeletal smooth muscle, lower extracellular Na^+ concentrations compared with physiological conditions, room temperature etc.).

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Gene (cytogenic location)*and associated disorder	Nature of mutation in FHM	Protein encoded and role	Other clinical presentation	Co-occurrence with FHM	Studies included	Limitations
			with lower turnover rates in physiological extracellular K^+ and an anomalous inward leak current in hypokalemic conditions, which was predicted to lead to muscle depolarization (23).			
			Sensorineural hearing loss (24,25)	Sensorineural hearing loss did not co-occur with FHM, but did co-occur (co-segregate) with migraine without aura in a Korean family.	Case reports.	Small sample size – chance association? Occurrence in relation to other ATP1A2 related disorders (here migraine without aura and alternating hemiplegia of childhood) - part of the ATP1A2 phenotype spectrum?
			Epilepsy, seizures and convulsions: epilepsy in general has been described in association with ATP1A2 mutations, often concomitant with other ATP1A2 related disorders, e.g., hemiplegic migraine. ~10–30% of individuals with FHM and ATP1A2 mutations had co-occurrence of epilepsy, however, penetrance is variable and can range up to 30–60% in minor subsets of FHM2 families. Cases of benign familial	Yes	Case reports, comparative studies, reviews, systematic reviews.	Well-described. Association between ATP1A2 and epilepsy described in several instances.

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Gene (cytogenic location)*and associated disorder	Nature of mutation in FHM	Protein encoded and role	Other clinical presentation	Co-occurrence with FHM	Studies included	Limitations
			infantile convulsions (BFIC), febrile seizures and genetic/generalized epilepsy with febrile seizures plus (GEFS+), absence epilepsy and generalized tonic-clonic seizures (GTCS), benign myoclonic and benign Rolandic epilepsy etc. have been described (26–37).			
			Pulmonary arterial hypertension (PAH) (38)	Yes, the reported proband had co-occurrence of FHM and PAH and several family members had FHM.	One case report (38)	The phenotype of FHM segregated with the ATP1A2 mutation, but only the proband had concomitant PAH at age 24–25 – Possible chance association.
			Reversible cerebral vasoconstriction (39)	Yes, reversible cerebral vasoconstriction occurred in relation to hemiplegic migraine attack.	Case study.	Occurrence in association with hemiplegic migraine– symptom/consequence or independent entity/ risk from FHM?
			Psychosis and transient neuropsychological deficits (40,41)	Yes	Case reports	Occurrence in association with hemiplegic migraine– symptom/consequence or independent entity/ risk from FHM)? Environmental factors may also modulate the presence, occurrence and interpretation of these psychotic symptoms.

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Gene (cytogenic location)*and associated disorder	Nature of mutation in FHM	Protein encoded and role	Other clinical presentation	Co-occurrence with FHM	Studies included	Limitations
			Bipolar disorder and other mood disorders (10,42–44)	Yes, though it is unclear whether the mood disorders occur due to the FHM2 mutation (segregation does not provide convincing evidence in one study due to size of families) or due to other etiological factors that increases susceptibility to FHM and psychiatric disorders separately (45)	Case reports, Association study, postmortem case-control investigation of brain tissue from individuals with bipolar disorder	Chance association between ATP1A2 mutation and bipolar disorder (case-control investigation of postmortem brain tissue and association study on relation between SNPs and affected individuals – requires futures studies on actual protein expression, sequencing, and measurements of mutant activity to further understand the possible role of ATP1A2 mutations in bipolar disorder).
			Myocardial dysfunction (46,47)	No	Association study of Na^+/K^+-ATPase expression levels in human heart necropsies or biopsies and myocardial dysfunction using 3H-ouabain binding, animal study (mice) linking ATP1A2 mutations to cardiac dysfunction.	Chance finding–cause or consequence of myocardial dysfunction, genetics (mutation) or epigenetic changes? Animal study linked ATP1A2 mutation to cardiac dysfunction, however, species differences in expression patterns cause translational problems (48)
			Benign paroxysmal torticollis of infancy (49)	Yes, the variant of unclear significance found in the study by Danielsson et al.	Case series with long term follow-up.	Small sample size. Only one participant had a variant of unclear significance in ATP1A2,

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Table 1. (continued)

Gene (cytogenic location)*and associated disorder	Nature of mutation in FHM	Protein encoded and role	Other clinical presentation	Co-occurrence with FHM	Studies included	Limitations
				(49) was considered pathogenic due to it having been described earlier in hemiplegic migraine.		though the authors considered it pathogenic due to it having been described earlier in hemiplegic migraine. However, family members of the child declined genetic testing, i.e., the sequence variant of ATP1A2 could not be assessed in the family–chance association?
SCN1A (2q24.3) mutations are associated with Familial Hemiplegic Migraine type 3 (FHM3) (1)	Missense mutations (gain of function) (50)	Sodium voltage-gated channel α subunit 1 ➔ Propagation of action potentials of cortical neurons, especially in GABAergic inhibitory interneurons (51).	**Dravet syndrome (DS)**: DEE characterized by early-onset, treatment-resistant seizures, accompanied by cognitive, motor and developmental impairments. A mutation in SCN1A is found in more than 80% of patients with DS, usually de novo: about 50% of patients have truncation variants and about 50% have missense variants, determining a loss-of-function effect (52).	Yes	Case study, review	None
			Epilepsy with myoclonic atonic seizures/ Doose syndrome (EMAtS): syndrome characterized by abrupt onset of multiple generalized seizure types, including myoclonic-atonic seizures, in early	No	Few cases described in literature, reviews	Small sample size.

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Table 1. (continued)

Gene (cytogenic location)*and associated disorder	Nature of mutation in FHM	Protein encoded and role	Other clinical presentation	Co-occurrence with FHM	Studies included	Limitations
			childhood, and developmental stagnation or regression during the phase of active seizures. Epilepsy remission is achieved in about two thirds of cases, despite initial drug-resistant seizures. Only a small percentage of cases have a mutation in SCN1A, most of them are missense mutations (52,53).			
			Epilepsy of infancy with migrating focal seizures (EIMFS): rare DEE, characterized by high frequency, intractable multifocal migrating seizures with developmental regression in the first year of life. SCN1A is currently considered the third most mutated gene in EIMFS after KCNT1 and SCN2A (54).	No	Genotype-phenotype correlation study of large EIMFS cohort via an international collaborative study	Correlation study.
			Early onset SCN1A DEE: characterized by early infantile seizure onset, profound intellectual disability, and a severe hyperkinetic movement disorder, caused in most patients by a de novo missense mutation Thyr226Met,	No	Review	None

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Table 1. (continued)

Gene (cytogenic location)*and associated disorder	Nature of mutation in FHM	Protein encoded and role	Other clinical presentation	Co-occurrence with FHM	Studies included	Limitations
			having a gain-of-function effect on the channel but paradoxically determining rapid development of depolarization block (52).			
			Nonsyndromic epileptic encephalopathy (NEE): clinically diagnosed EE without the inclusion of a specific syndrome or epileptic disorder. SCN1A mutations are rarely found in NEE (55–57).	No	Few cases described in literature.	Risk of chance association.
			Genetic epilepsy with febrile seizures plus (GEFS+): characterized by febrile seizures in an individual with a family history of seizures/ epilepsy.SCN1A was first discovered in GEFS + families. About 20% of reported families have pathogenic variants in SCN1A (52).	No?	Review	None
			Autism spectrum disorder (ASD): characterized by defective communication and social skills, as well as restricted and repetitive behaviors. Pathogenic variants in SCN1A (usually determining a loss-of-function) have been associated with ASD, both associated with epilepsy	No	Few cases described in literature.	Pathogenic mechanism unclear and possibly different in cases associated with epilepsy and not.

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Table 1. (continued)

Gene (cytogenic location)*and associated disorder	Nature of mutation in FHM	Protein encoded and role	Other clinical presentation	Co-occurrence with FHM	Studies included	Limitations
			(especially DS) and by itself (53).			
			Sudden unexpected death in epilepsy (SUDEP): sudden, accidental death of a person with epilepsy, not from trauma, drowning, epilepsy status, structural or toxic cause. SUDEP occurs at a higher rate in DS than in other childhood epilepsies, accounting for up to about 50–60% of mortality. Also two cases of SUDEP in a family with GEFS + SCN1A mutated have been reported. Animal models and human studies point towards a neurocardiac or solely cardiac pathogenic mechanism (58,59).	No	Review, case study	Pathogenic mechanism unclear.
			Nonepileptic SCN1A-related sudden death: Sudden death at a young age (SIDS, sudden infant death syndrome, and SUDC, sudden unexplained death in childhood) has also been reported in nonepileptic patients with missense mutations in SCN1A (60,61).	No	Few cases described in literature.	Pathogenic mechanism unclear.
			West syndrome: DEE	No		Unclear association with

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Table 1. (continued)

Gene (cytogenic location)*and associated disorder	Nature of mutation in FHM	Protein encoded and role	Other clinical presentation	Co-occurrence with FHM	Studies included	Limitations
			characterized by the triad of epileptic spasms with onset in the infant, hypsarrhythmia on EEG and developmental plateauing or regression. Missense mutations and deletion of SCN1A have been reported, although rarely (53).		Few cases described in literature.	deletion of SCN1A (concomitant deletion of 2q31.3 region) (62).
			Lennox- Gastaut Syndrome (LGS): DEE characterized by multiple types of drug-resistant seizures, among which tonic seizures, cognitive and often behavioral impairments, and diffuse slow spike-and wave and generalized paroxysmal fast activity on EEG. A missense mutation and a splice site mutation in SCN1A have been reported, although rarely responsible for LGS (63).	No	Few cases described in literature.	Risk of chance association. Overlapping features with DS.
			Rett syndrome (RTT): rare disorder affecting primarily females, characterized by normal early development followed by a period of regression, associated with intractable epileptic seizures. Two patients who met the classic diagnostic criteria for RTT	No	Two cases described in literature.	Risk of chance association; unclear pathogenic mechanism.

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Table 1. (continued)

Gene (cytogenic location)*and associated disorder	Nature of mutation in FHM	Protein encoded and role	Other clinical presentation	Co-occurrence with FHM	Studies included	Limitations
			had a negative genetic testing for MECP2, CDKL5, and FOXG1 genes, but had mutations in SCN1A (64).			
			Arthrogryposis multiplex congenital (AMC): congenital condition characterized by multiple joint contractures, deriving from reduced fetal movements Only two reports documented association with missense mutations in SCN1A (53,65,66).	No	Few cases described in literature.	Risk of chance association; possible role of other genetic/ environmental factors
			Melkersson-Rosenthal syndrome (MRS): characterized by tongue cheilitis, recurrent episodes of orofacial swelling and palsy. A missense mutation in SCN1A has been found in one patient (67).	No	Single case report.	Risk of chance association
PRRT2 (16p11.2) Mutations in which have recently been associated with hemiplegic migraine, and due to its prevalence suggested as the fourth hemiplegic migraine gene (FHM4) (68).	Loss-of-function mutations causing haploinsufficiency (nonsense, missense, deletions, duplications, frameshift mutations leading to premature stop codonsor read-through resulting in	Proline Rich Transmembrane Protein 2 ➔ protein localized at pre-synaptic terminals at glutamatergic synapses where it interacts with and modulates ion channels and proteins involved in synaptic transmission, e.g., the	**Episodic/Paroxysmal kinesigenic dyskinesia 1, EKD1/PKD (AD)**: paroxysmal movement disorder caused by heterozygous mutation in the PRRT2 gene and affecting ~1:150 000 in the general population. It is estimated that ~38.7% of PRRT2-associated diseases	Yes	Reviews, Cohort-study, Online Mendelian Inheritance in Man–compendium on human genes and genetic phenotypes (omim.org)	Methodological limitations with the cohort study (missing data, time-related biases as study was conducted across > 20 years, reporting bias), not fully delineated spectrum of PRRT2-associated diseases, need for extensive genetic,

(continued)

Table 1. (continued)

Gene (cytogenic location)*and associated disorder	Nature of mutation in FHM	Protein encoded and role	Other clinical presentation	Co-occurrence with FHM	Studies included	Limitations
	longer transcripts). Dominant-negative effects have also been suggested (68–70).	synaptosomal-associated protein 25 (SNAP25), implicating PRRT2 functioning in synaptic endocytosis, vesicle docking and Ca^{2+} -mediated neurotransmitter release	present with EKD1. EKD1 is the most common paroxysmal dyskinesia, usually debuts at 10.3 ± 4.9 years of age (range 1–42 years) and symptoms usually respond favorably to anticonvulsant medication and become less severe with age. EKD1 is characterized by frequent but usually brief attacks (< 1 min) of involuntary hyperkinetic movements precipitated by sudden voluntary movements (kinesigenic triggers), though additional non-kinesigenic triggers have been reported in ~40% of cases, e.g., intention of movement alone, stress, sleep deprivation, startle and anxiety etc. Attacks do not involve loss of consciousness, pain or weakness, and do not occur during sleep. Attacks can involve bilateral (~3.5 times more common) or unilateral attacks of dystonic postures, chorea, athetosis, and less often ballism and hemiballism, tongue movements,			functional, and phenotypic characterization.

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Table 1. (continued)

Gene (cytogenic location)*and associated disorder	Nature of mutation in FHM	Protein encoded and role	Other clinical presentation	Co-occurrence with FHM	Studies included	Limitations
			perioral dyskinesias, clawing of the hands, frozen gaze, etc. About 10% of affected individuals have aura symptoms, e.g., crawling sensation, paresthesias, or non-specific epigastric discomfort, can occur prior to the attack. Attacks involving the face and neck region, though rare, can cause dysarthria/anarthria (68–71).			
			Benign familial infantile seizures/convulsions, (BFIS2/BFIC2), Self-limited (familial) infantile epilepsy (SeLIE) (AD): caused by heterozygous mutation in the PRRT2 gene and characterized by non-febrile seizures, partial complex or generalized tonic-clonic, usually debuting between 3 and 12 months of age and remitted by 18 months, with a good response to medication and no neurologic sequelae. Seizures often consist of motor arrest, deviation of gaze and/or head, hypertonia, limb jerks and cyanosis. It is estimated	Yes	Reviews, Cohort-study, Online Mendelian Inheritance in Man–compendium on human genes and genetic phenotypes (omim.org)	Methodological limitations with the cohort study (missing data, time-related biases as study was conducted across > 20 years, reporting bias), not fully delineated spectrum of PRRT2-associated diseases, need for extensive genetic, functional, and phenotypic characterization.

(continued)

Table 1. (continued)

Gene (cytogenic location)*and associated disorder	Nature of mutation in FHM	Protein encoded and role	Other clinical presentation	Co-occurrence with FHM	Studies included	Limitations
			that ~41.7% of PRRT2-associated diseases present with BFIS2 (68–72).			
			Familial Infantile Convulsions with Paroxysmal Choreoathetosis, ICCA/Paroxysmal kinesigenic dyskinesia with infantile convulsions, PKD-IC (AD): heterozygous mutation in the PRRT2 gene resulting in syndrome with overlapping features from BFIS2/BFIC2 and EKD1/PKD, i.e., these presentations occur in the same patient. It is estimated that ~14.3% or cases with PRRT2-mutations present as ICCA (68–70,72).	Yes	Reviews, Online Mendelian Inheritance in Man–compendium on human genes and genetic phenotypes (omim.org)	Not fully delineated spectrum of PRRT2-associated diseases, need for extensive genetic, functional, and phenotypic characterization
			Paroxysmal movement disorder: PRRT2 mutations have also been associated with other paroxysmal movement disorder, including: paroxysmal torticollis of infancy, intermittent non-epileptic head drops, "galloping tongue" syndrome, paroxysmal non-kinesigenic dyskinesia (PNKD) or PNKD-like	Yes	Reviews, cohort-study.	Not fully delineated spectrum of PRRT2-associated diseases, need for extensive genetic, functional, and phenotypic characterization. Genotype- phenotype correlations in humans are not strict – the same mutation can give different phenotypes – possible role of

(continued)

Table 1. (continued)

Gene (cytogenic location)*and associated disorder	Nature of mutation in FHM	Protein encoded and role	Other clinical presentation	Co-occurrence with FHM	Studies included	Limitations
			disorders, Paroxysmal exercise-induced dystonia (PED), writer's cramp, episodic ataxia (EA) (68–70).			environmental or genetic modifiers. Chance association? It was estimated that only ~5.3% of PRRT2 mutation cases had a primary diagnosis other than EKD1/PKD, BFIS2/BFIC2 and ICCA/PKD-IC. Methodological limitations with the cohort study (missing data, time-related biases as study was conducted across > 20 years, reporting bias)
			Seizure disorders: PRRT2 mutations have also been mentioned in relation to other seizure disorders, including: febrile seizures (FS) and febrile seizures plus (FS+), generalized epilepsy with febrile seizures plus (GFES+), epilepsy (complex partial, generalized tonic-clonic, absence, and non-convulsive), severe myoclonic epilepsy of infancy, Dravet syndrome, West syndrome, Rolandic epilepsy, etc. (68–70).	Yes	Reviews, cohort-study.	Not fully delineated spectrum of PRRT2-associated diseases, need for extensive genetic, functional, and phenotypic characterization. Genotype- phenotype correlations in humans are not strict – the same mutation can give different phenotypes – possible role of environmental or genetic modifiers. Chance association. Occurrence of FS, FS + and GFES + was estimated at 3.5%, which is comparable with the reported

(continued)

Table 1. (continued)

Gene (cytogenic location)*and associated disorder	Nature of mutation in FHM	Protein encoded and role	Other clinical presentation	Co-occurrence with FHM	Studies included	Limitations
						general prevalence of febrile seizures in children of 6 months to 5 years of age (2-5%), indicating that the association of PRRT2 and febrile seizures is coincidental and not causal. Studies screening for PRRT2 mutations in benign familial and sporadic infantile epilepsies indicate that PRRT2 mutations are unlikely to cause other epilepsy phenotypes other than BFIS2/BFIC2). Methodological limitations with the cohort study (missing data, time-related biases as study was conducted across > 20 years, reporting bias)
			Intellectual disability and/or developmental delay: biallelic mutations (homozygous or compound heterozygous) observer in < 1% of individuals with PRRT2 variants or microdeletions of PRRT2 often result in more severe phenotypes with additional cognitive and neurodevelopmental	Yes	Reviews, Cohort study	Methodological limitations with the cohort study (missing data, time-related biases as study was conducted across > 20 years, reporting bias), not fully delineated spectrum of PRRT2-associated diseases, need for extensive genetic, functional, and

(continued)

Table 1. (continued)

Gene (cytogenic location)*and associated disorder	Nature of mutation in FHM	Protein encoded and role	Other clinical presentation	Co-occurrence with FHM	Studies included	Limitations
			deficits (spanning normal development to intellectual disability, learning disabilities, autism spectrum disorder, attention-deficit disorder, and seizures), besides paroxysmal movement disorders and seizures. Around 52.4% of cases present with intellectual disability and 14.3% with learning difficulties compared with 0.6% and 0.8%, respectively, in heterozygous carriers (68–70).			phenotypic characterization (72).
PNKD (2q35)	Deletion (few cases described) causing truncation of protein – loss of function (73,74)	PNKD protein ➔ interacts with the synaptic active zone proteins RAB-interacting molecule (RIM)1 and RIM2, and modulates release of neurotransmitters	**Paroxysmal nonkinesigenic dyskinesia 1 (PNKD1)**: characterized by unilateral or bilateral dystonic posturing with choreic and ballistic movements. Attacks are usually triggered by coffee, tea, or alcohol, excitement, stress, or fatigue, but can also be spontaneous. Attacks can be accompanied by a preceding aura (73,75).	Unknown/No report of co-occurrence within family/ patient	Reviews	None
SLC4A4 (4q13.3)	Missense and frameshift mutations (homozygous),– loss of function (76)	NBCe1 Na+/HCO_3^- cotransporter (2 N-terminally spliced variants, NBCe1A and NBCe1B, and 1	**Proximal renal tubular acidosis-ocular anomaly syndrome (pRTAO):** ocular anomalies are most often	Yes	Most studies are case reports or case series.	Small sample

(continued)

Table 1. (continued)

Gene (cytogenic location)*and associated disorder	Nature of mutation in FHM	Protein encoded and role	Other clinical presentation	Co-occurrence with FHM	Studies included	Limitations
		C-terminally spliced variant, NBCe1C) – NBCe1C expression is primarily limited to the brain, NBCe1B can be found in the brain among other tissues, NBCe1A is primarily found in the kidneys ➔ in the brain found in astrocytes and believed to regulate neuronal excitability by modulating synaptic pH.	glaucoma, band keratopathy and cataracts. Affected individuals might also have impaired intellectual development, short stature and dental defects (76–78).			
ATP1A3 (19q13.2)	In general, mutations in the ATP1A3 gene are missense, splice, or in-frame codon insertion/deletions causing loss-of-function by haploinsufficiency or dominant negative effects. Few cases of missense mutation described in relation to FHM (74,79,80).	Catalytic α3-subunit of the Na^+/K^+ -ATPase ➔ regulation of physiological Na^+ and K^+ gradients across cell-membranes by translocating $3Na^+$ ions out and $2K^+$ ions in via hydrolysis of 1 ATP molecule as the driving force, thereby maintaining neuronal resting potential and regulating excitability, likely at inhibitory synapses.	**Rapid-onset dystonia parkinsonism, RDP/ Dystonia-12, DYT12 (AD)**: characterized by sudden onset (days to weeks) of asymmetric dystonia and parkinsonism (bradykinesia and postural instability), typically in young adulthood (range: 4–55 years, though childhood variation with onset between 9–14 months has been reported), and often with slowly progressive neurologic deterioration with bulbar involvement (e.g., dysarthria, dysphagia, drooling etc.). In up to 75%, a stress-related trigger (psychological/	Unknown/No However, headache has been reported in 68% of individuals with RDP compared with 40% in familial controls (79,82,83).	Reviews, Cohort-study, Online Mendelian Inheritance in Man–compendium on human genes and genetic phenotypes (omim)	None. Documentation of the disease course is incomplete.

(continued)

Table 1. (continued)

Gene (cytogenic location)*and associated disorder	Nature of mutation in FHM	Protein encoded and role	Other clinical presentation	Co-occurrence with FHM	Studies included	Limitations
			physical) can be identified. Dystonia rarely improves significantly after onset, though some individuals report mild improvement over time. Symptoms often stabilize after their initial appearance, however, second episodes with abrupt worsening of symptoms do occur. Headaches, migraine, seizures, psychosis, and cognitive impairment etc. Have also been described in association with DYT12 (71,79,81,82).			
			Alternating hemiplegia of childhood 2, AHC2 (AD): rare syndrome caused by heterozygous mutation in the ATP1A3 gene with resultant infantile onset (< 18 months) of episodic hemi- or quadriplegia lasting minutes to days, often with tonic or dystonic attacks, choreoathetoid movements, nystagmus or strabismus and other ocular motor abnormalities, autonomic disturbances, and progressive cognitive decline and developmental delay. Motor symptoms	Unknown/No	Case reports, Reviews, Whole-exome sequencing gene-identification study, Online Mendelian Inheritance in Man–compendium on human genes and genetic phenotypes (omim.org)	Few cases described in the literature with variable phenotypes and overlap with other disorders. Risk of chance association. Methodological limitations, e.g., use of retrospective chart views, risk of confounding variables, and observer's bias

(continued)

Table 1. (continued)

Gene (cytogenic location)*and associated disorder	Nature of mutation in FHM	Protein encoded and role	Other clinical presentation	Co-occurrence with FHM	Studies included	Limitations
			remit during sleep, only to return after awakening. Seizures and seizure-like episodes may occur. Cardiovascular (cardiac conduction abnormalities) and gastrointestinal manifestations also occur (79,81,84–87).			
			Cerebellar Ataxia, Areflexia, Pes Cavus, Optic Atrophy, and Sensorineural Hearing Loss (CAPOS) (AD): syndrome characterized by early-childhood onset, often between 6 months to 5 years of age, of recurrent episodes of acute ataxic encephalopathy in relation to fever. Other symptoms include hypotonia, flaccidity, nystagmus, strabismus, dysarthria/ anarthria, lethargy, loss of consciousness/coma. Acute episodes often decrease with time, though neurologic complications are permanent and progressive, resulting in cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss (71,79–81,87,88).	Yes	Review, Case study (+ letter), Retrospective study	Small sample. Onset and progression of optic atrophy and sensorineural hearing loss is not well delineated.

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Table 1. (continued)

Gene (cytogenic location)*and associated disorder	Nature of mutation in FHM	Protein encoded and role	Other clinical presentation	Co-occurrence with FHM	Studies included	Limitations
			Developmental and Epileptic Encephalopathy 99, DEE99 (AD): loss-of-function mutations in the ATP1A3 gene resulting in early-onset, often severe epileptic seizures and EEG abnormalities associated with global developmental and severe intellectual impairment that tends to worsen as a consequence of the epilepsy. May also include features of hypotonia, quadriparesis, nystagmus, apnea, and non-specific and variable abnormalities of the brain, including cerebral atrophy and polymicrogyria. It is estimated that ~12% of ATP1A3 mutations are associated with DEE and ~5.5% of patients with ATP1A3 mutations may have polymicrogyria (71,89–91).	No	Case reports, Reviews, Cohort study (clinical, neuroimaging and neuropathological investigations, in silico and in vitro assays of the mutations' effects on function, genotype-phenotype correlations), Online Mendelian Inheritance in Man–compendium on human genes and genetic phenotypes (omim.org)	Few cases described in the literature–small sample–with variable phenotypes and overlap with other disorders. Some methodological limitations, e.g., use of retrospective designs/ chart views, risk of confounding variables, and observer's bias.
			Relapsing encephalopathy with cerebellar ataxia, RECA / Fever-induced paroxysmal weakness and encephalopathy, FIPWE (AD): primarily presents with recurrent fever-induced episodes of	Not reported/No	Review	Not yet fully characterized entity

(continued)

Table 1. (continued)

Gene (cytogenic location)*and associated disorder	Nature of mutation in FHM	Protein encoded and role	Other clinical presentation	Co-occurrence with FHM	Studies included	Limitations
			motor-manifestations (ataxia, weakness) or non-motor manifestations (encephalopathy) in childhood. May rarely occur in young adults during illnesses such as mononucleosis. Episodes can vary among affected individuals and can co-occur in the same individual in different episodes. The RECA/FIPWE phenotype has not been fully characterized, i.e., long-term disease course is unknown with reports of individuals experiencing betterment and decrease in frequency and severity vs. individuals experiencing worsening of manifestations. Most acute manifestations resolve gradually after fever resolves, however areflexia, apraxia and ataxia can persist. Cognitive challenges and neurobehavioral/psychiatric manifestations have been reported (79,81,87).			
SLC2A1 (1p34.2)	Missense mutations, loss of function (50,74).	Glucose transporter GLUT1 (or EAAT2) ➔ Facilitates uptake of glucose into the brain	**Glucose Transporter Type 1 Deficiency Syndrome (GLUT1 DS):** continuum that	Yes	Case reports, Reviews, Online Mendelian Inheritance in Man–	None. Rare disorder with wide phenotypic

(continued)

Table 1. (continued)

Gene (cytogenic location)*and associated disorder	Nature of mutation in FHM	Protein encoded and role	Other clinical presentation	Co-occurrence with FHM	Studies included	Limitations
		across the blood-brain barrier	includes the classic phenotype (GLUT1 DS1, **AD/AR**), dystonia 18 (also known as DYT18, paroxysmal exercise-induced dyskinesia and epilepsy, and GLUT1 DS2, **AD**), dystonia 9 (DYT9, paroxysmal choreoathetosis with spasticity, **AD**). atypical childhood absence epilepsy, myoclonic astatic epilepsy, and paroxysmal non-epileptic findings such as intermittent ataxia, choreoathetosis, dystonia, and alternating hemiplegia. Classic GLUT1 DS is characterized by infantile-onset (usually within the first 4 months of life) epileptic encephalopathy associated with delayed development (cognitive impairment ranging from learning disabilities to mental retardation), acquired microcephaly, motor incoordination, and spasticity. Intermittent ataxia, confusion, lethargy, sleep disturbance, and headache also occur. Diagnostic findings for the disorder include: hypoglycorrhachia (<		compendium on human genes and genetic phenotypes (omim.org)	heterogeneity, full still delineation lacking.

(continued)

Table 1. (continued)

Gene (cytogenic location)*and associated disorder	Nature of mutation in FHM	Protein encoded and role	Other clinical presentation	Co-occurrence with FHM	Studies included	Limitations
			60 mg/dl) and low CSF lactate, heterozygous or biallelic pathogenic variants in SLC2A1 on molecular testing. Reports of cases without seizures, with dystonia and choreoathetosis, and rare individuals with absence seizures and no movement disorder have also been made. In paroxysmal exercise-induced dyskinesia and epilepsy, affected individuals seem to have later onset of seizures (childhood onset) and paroxysmal exercise-induced dyskinesia, involving transient abnormal involuntary movements, e.g., dystonia and choreoathetosis, induced by exercise/ exertion, and affecting the exercised limbs. Reports of epilepsy, typically childhood absence epilepsy, and mild mental retardation have also been made. Paroxysmal choreoathetosis with spasticity is characterized by childhood onset of paroxysmal choreoathetosis and			

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Table 1. (continued)

Gene (cytogenic location)*and associated disorder	Nature of mutation in FHM	Protein encoded and role	Other clinical presentation	Co-occurrence with FHM	Studies included	Limitations
			progressive spastic paraplegia, often in relation with cognitive deficits. Dyskinesias are mainly exercise-induced but also include triggers such as anxiety and emotional stress. Reports of seizures and ataxia have also been made (71,92–96).			
			Stomatin-deficient cryohydrocytosis with neurologic defects, SDCHCN (AD): disorder characterized by delayed psychomotor development, seizures, cataracts, and pseudohyperkalemia due to erythrocyte membrane defects (71,97–99).	No	Case reports, DNA sequencing analysis and protein analysis	Small sample size, association by chance, part of the GLUT1 deficiency syndrome.
			Susceptibility to Idiopathic Generalized Epilepsy 12, EIG12 (AD): Conferred by heterozygous mutation in the SLC2A1 gene. Idiopathic generalized epilepsies are characterized by generalized seizure types and generalized spike waves on electroencephalogram (EEG) in patients without structural lesions. SLC2A1	Unknown	Case study, comparative study, population-study, sequencing analyses/ mutational studies of larger cohorts of patients from e.g., epilepsy genetics databases with well documented idiopathic generalized epilepsies	None

(continued)

Table 1. (continued)

Gene (cytogenic location)*and associated disorder	Nature of mutation in FHM	Protein encoded and role	Other clinical presentation	Co-occurrence with FHM	Studies included	Limitations
			mutations contribute to approximately 1% of Idiopathic generalized epilepsies (100–104)			
SLC1A3 (5p13.2)	Missense mutations, truncations–loss of function mutations Gain-of-function SLC1A3 c.657G > C (p.Glu219Asp) mutation has been described – unlikely to be solely causal due to being a common variant (74,105,106)	Encodes glial glutamate transporter EAAT1 transporter → Na^+/K^+-dependent glutamate transporter that recaptures glutamate from the synaptic cleft into glial cells such as astrocytes to stop glutamate's postsynaptic action.	**Episodic ataxia, type 6 (EA6)**: characterized by severe episodic and progressive ataxia, seizures, alternating hemiplegia, and migraine headache, is determined by missense mutations in SCL1A3 that result in a partial-to-complete loss of function of glutamate uptake (genotype-phenotype correlation present) (107).	No, only associated with sporadic hemiplegic migraine	Case reports	Few cases described in the literature; possible role of other genetic/ environmental factors; functional studies conducted on in-vitro-models (108).

(continued)

Table 1. (continued)

Gene (cytogenic location)*and associated disorder	Nature of mutation in FHM	Protein encoded and role	Other clinical presentation	Co-occurrence with FHM	Studies included	Limitations
ATP1A4 **(**1q23.2**)**	Missense mutations. identified in a cohort undergoing targeted analyses of WES related to FHM (74).	α4 subunit of the Na^+/K^+-ATPase → regulation of physiological Na^+ and K^+ gradients across cell-membranes by translocating $3Na^+$ ions out and $2K^+$ ions in via hydrolysis of 1 ATP molecule as the driving force, thereby generating an electrochemical gradient that is essential for maintaining membrane potentials and for Na^+-coupled cotransport of various molecules.	**Early-onset idiopathic tachyarrhythmia:** some members of the identified FHM family had ventricular and supraventricular ectopic beats (109).	Yes	Single case report	Chance association, though ATP1A4 is expressed in testes, spermatozoa, kidney, and muscles (including myocardium and the cardiovascular system), and to a lesser extent in the brain.

All references for studies in this table are listed in the online supplementary references.
*Cytogenetic location refers to the chromosomal band where the gene is mapped, based on OMIM/HGNC nomenclature.

periodic paralysis (HypoPP) with CNS involvement was suggested. HypoPP is a rare neuromuscular disease, usually caused by an aberrant depolarizing leak current through mutant sarcolemmal voltage-gated calcium or sodium channels. Mutations in *ATP1A2* have not previously been linked to muscle dysfunction (28). Other pathologies have also been reported, often in relation to the above-mentioned disorders (see Table 1). Phenotypic overlap can present a diagnostic challenge.

SCN1A

SCN1A, located on chromosome 2 (OMIM 182389) (14), encodes the alpha subunit of the sodium voltage-gated channel Nav1.1. This channel plays a critical role in generating and propagating action potentials in cortical neurons, especially in GABAergic inhibitory interneurons (29).

Mutations in *SCN1A* are implicated in numerous monogenic disorders besides FHM3: in particular, *SCN1A* is one of the most important epilepsy genes, resulting in a wide phenotypic and prognostic spectrum ranging from self-limited and pharmacoresponsive epilepsies to developmental and epileptic encephalopathies (DEEs).

SCN1A is most notably associated with Dravet syndrome (DS), a refractory DDE in which about 80% of cases are attributed to more than 1800 pathogenic variants (30). Additionally, about 20% of families with Genetic Epilepsy with Febrile Seizures Plus (GEFS+) harbor mutations in this gene (30).

Other epileptic encephalopathies linked to *SCN1A* include Epilepsy with Myoclonic Atonic Seizures (EMAtS), Epilepsy of Infancy with Migrating Focal Seizures (EIMFS), West syndrome, Lennox-Gastaut syndrome, Rett syndrome and Nonsyndromic Epileptic Encephalopathies (NEE) (31).

Beyond epileptic disorders, *SCN1A* mutations are also associated with non-epileptic conditions, such as autism spectrum disorder (ASD), Sudden Unexpected Death in Epilepsy (SUDEP) and non-epileptic sudden deaths (31); rarely, they have been linked to Arthrogryposis Multiplex Congenital (AMC) and Melkersson-Rosenthal syndrome (MRS) (32).

The diversity in phenotypes is partly explained by the functional effects of *SCN1A* mutations. The mutational spectrum of FHM3 is limited to missense mutations, typically resulting in a gain of function and enhancing NaV1.1 activity and triggering cortical spreading depression (CSD) (33). In contrast, epileptic phenotypes often arise from missense or truncating mutations that cause loss-of-function, consistent with haploinsufficiency, leading to reduced GABAergic interneuron inhibition, network hyperexcitability, and thus seizures.

PRRT2

PRRT2, located on chromosome 16p11.2 (OMIM 614386), encodes the Proline Rich Transmembrane Protein 2 and is highly expressed in the human brain, particularly in the cerebral cortex, basal ganglia and cerebellum (34,35). *PRRT2* localizes to presynaptic terminals, especially at glutamatergic synapses, where it interacts with and modulates different ion channels, e.g., GRIN1A, a glutamate receptor and member of the AMPA receptor family, and voltage-gated Nav1.2 and Nav1.6 channels (34,35). Additionally, *PRRT2* interacts with proteins of the exocytosis complex, e.g., the synaptic t-SNARE protein Synaptosomal-Associated Protein 25 (SNAP25), indicating that *PRRT2* has a possible role in synaptic endocytosis, vesicle docking, and Ca2+-mediated neurotransmitter release (34,35). *PRRT2* also plays an important role in brain development and synaptogenesis (34,35). Mutations in *PRRT2* have recently been associated with hemiplegic migraine, and due to its prevalence, it has been suggested as the fourth HM gene (FHM4) (36). FHM4 associated mutations typically involve loss-of-function caused by nonsense/missense mutations, deletions, duplications, frameshift mutations leading to premature stop codons or read-through mutations resulting in longer transcripts, which result in synaptic dysfunction and increased excitability of neural networks (34–36). Mutations in the gene have also been implicated in benign familial infantile seizures (BFIS2) (14,34,35); Episodic kinesigenic dyskinesia 1 (EKD1) and Familial Infantile Convulsions with Paroxysmal Choreoathetosis (ICCA), a syndrome with overlapping features from BFIS2 and EKD1 (14,34,35). Other pathologies relating to paroxysmal movement disorders, seizures, and intellectual disability and/or developmental delay have also been reported (see Table 1). Different phenotypic presentations can occur from the same mutations in *PRRT2*, and overlap can happen (14,34–36).

Potential genes involved in FHM and associated disorders. While *CACNA1A*, *ATP1A2*, *SCN1A*, and *PRRT2* are the primary genes implicated in FHM, their mutations do not fully explain the full spectrum observed in clinical practice, suggesting additional genetic contributors (37). Several other genes, including *PNKD*, *SLC4A4*, *SLC1A3*, *SLC2A1*, *ATP1A3*, and *ATP1A4*, have been linked to FHM and related neurological disorders, influencing synaptic function, ion transport, and neurotransmitter regulation (14,38–40). A detailed overview of these genes, their functions, and associated phenotypes is provided in Table 1.

Monogenic disorders reporting association with migraine

The literature review showed different monogenic disorders reporting significant association with migraine (see Table 2).

Table 2. Monogenic disorders associated with increased migraine prevalence

Disorder	Gene involved	Mechanism	Migraine subtype	Migraine prevalence reported	Studies available	limitations
CADASIL	*NOTCH-3*	Toxic gain of function mutation of NOTCH-3 gene mediated by cysteine changes in EGF-like repeats led to aggregation of the protein (GOM) in brain small cerebral arteries.	Migraine with aura is the most prevalent subtype	Higher prevalence of migraine with aura (up to 45%)	16 studies (retrospective studies and case series) (1–16)	Retrospective studies, case series, heterogeneity of genetic testing and clinical variability (17)
RVCL-S	*TREX1*	Endothelial damage and chronic inflammation leading to lower migraine threshold	Migraine with aura	33–59%	One retrospective cohort (78 patients) one small prospective study (18 patients) (18,19)	Small sample size; lack of longitudinal studies.
KCNK18 related disorders	*KCKN18*	Dysfunction of the TRESK potassium channel leading to increased neuronal excitability and trigeminal sensitization	Migraine with aura	High prevalence in affected families and individuals	Case reports of single individuals or families; animal models (20–22)	Small sample sizes; lack of large-scale genetic studies; unclear genotype-phenotype correlation
FASPS	*CKIδ*	Mutation in casein kinase Iδ (CKIδ) disrupts circadian rhythms, affecting sleep-wake cycles and increasing cortical excitability	Migraine with aura	High prevalence in affected families	Case reports and family studies; experimental models in mice and Drosophila (23,24)	Small sample sizes; limited generalizability; clarification needed on causal relationship
MELAS	*MT-TL1*	Mutation in MT-L1 gene causes defective mitochondrial translation and protein synthesis resulting in energy production deficiency. Although the exact mechanism of MELAS and migraine is not known, neuronal hyperexcitability and trigeminovascular activation have been suggested.	Migraine without aura, probable migraine without aura	Migraine prevalence in MELAS syndrome ranges from 35.5% to 55%, 67% and 70% depending on the population.	Case report, case series, cohort studies, clinical trial, case control studies (25–29)	Varying prevalence when compared with hospital and population studies.
Catecholaminergic polymorphic ventricular tachycardia (CPVT)	*RYR2*	Point mutation in RYR2 gene causes defective calcium channel activities	Migraine without aura	Migraine may feature as symptoms in a carrier of RYR2 mutation (30)	GWAS studies	Limited evidence directly linking RYR2 mutations to migraine
Congenital bilateral absence of vas deferens/ Cystic Fibrosis	*STX1A*	Syntaxin-1A dysfunction affects synaptic vesicle release, potentially altering neurotransmitter regulation (e.g., serotonin, glutamate) and migraine susceptibility)	Migraine with aura	Meta-analysis showed significant association between STX1A polymorphism with migraine	Case reports, meta-analysis (31,32)	Limited functional studies on STX1A variants; unclear causal relationship

(continued)

Table 2. (continued)

Disorder	Gene involved	Mechanism	Migraine subtype	Migraine prevalence reported	Studies available	limitations
Sturge-Weber Syndrome	*GNAQ*	Leptomeningeal angiomas lead to venous congestion and neuronal hyperexcitability, contributing to migraine-like headaches	Migraine-like headaches, often prolonged or with motor aura	37–71% in different studies; migraine-like headaches in up to 52%	Systematic reviews, case series, and observational studies (33,34)	Heterogeneous headache presentations; uncertain classification as primary or secondary headache
COL4A1 related disorder	*COL4A1*	Vascular fragility and cerebral microangiopathy	Migraine with aura	Not quantified in the available data	Case Report (35)	Small sample sizes, non-standard methodologies, comorbidities confounding contribution analysis
Marfan Syndrome	*FBN1*	Connective tissue dysfunction due to fibrillin-1 mutations may contribute to endothelial dysfunction and vascular instability, increasing migraine susceptibility. Aortic root pathology has been linked to a higher prevalence of migraine with aura	Migraine with aura (most frequent), migraine without aura	40% overall migraine prevalence; 22–30% for migraine with aura	Large cohort studies, questionnaire-based epidemiological research (36–38)	Possible selection and recall bias; limited mechanistic studies; unclear direct causality between connective tissue defects and migraine
Sickle Cell Disease (SCD)	*HBB*	Chronic anemia and altered cerebral blood flow contribute to cerebral hyperperfusion and vascular instability, increasing migraine susceptibility	Migraine-like headaches, often severe and frequent; migraine without aura is most common	15.1% for migraine; 36.4% for recurrent headaches (39,40)	Large cohort studies, cross-sectional study, transcranial Doppler study	Heterogeneous headache presentations; unclear distinction between primary migraine and SCD-related secondary headaches
Hereditary Hemorrhagic Telangiectasia (HHT)	*ENG, ACVRL1, SMAD4*	Arteriovenous malformations (AVMs) cause right-to-left shunting, leading to paradoxical embolism and increased cortical excitability, contributing to migraine, particularly with aura	Migraine with aura (most common), migraine without aura	39.6% overall; 38.5% in HHT patients with pulmonary AVMs, 17% for migraine with aura	Population-based studies, case-control studies, case reports (41–44)	Possible selection bias in studies; confounding by coexisting vascular pathology; unclear causality between AVMs and migraine

All references for studies in this table are listed in the online supplementary references.

Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)

CADASIL is one of the most common causes of inherited monogenic cerebral small-vessel disease characterized by severe leukoencephalopathy and high risk of recurrent ischemic events and vascular dementia in adults. The prevalence of CADASIL is estimated to be 2–5 cases per 100,000 individuals (41). It is caused by mutations in the *NOTCH3* gene (>95% of cases) (42), which encodes a transmembrane receptor primarily expressed in vascular smooth muscle cells. More than one hundred mutations are reported, all occurring in exons 2–24, with strong clustering in exons 3 and 4 which encode several EGF-like extracellular domains. The majority are missense mutations involving a cysteine residue, others are small-in frame deletions or splice-site mutations. The histopathological hallmark is the degeneration of vascular smooth muscle cells, characterized by local accumulation of the Notch3extracellular domain, aggregation, and impaired endocytosis. This prevents protein ubiquitination and degradation and leads to the formation of extracellular deposits of granular osmiophilic material and fibrous thickening of the arterial walls (43,44). Immunofluorescence techniques reveal the accumulation of *NOTCH3* protein in the vessel walls (42). Although these histopathological findings are systemic (45), in the cerebral vessels they can lead to cerebral dysfunction.

The main clinical features include migraine with aura, recurrent subcortical/lacunar ischemic events, mood disturbances, apathy, cognitive impairment, and seizures (46–49). Brain MRI shows classical white matter hyperintensities in typical sites: anterior temporal pole lobe, periventricular white matter, internal and external capsule, pons, multiple lacunar infarcts and microbleeds. Also, lacunar infarcts are frequent, with association with cognitive dysfunction.

Migraine prevalence in CADASIL patients ranges from 14 to 72% (50) with variability in different geographic areas (higher in occidental countries compared to Asian countries) and a pooled prevalence of 38% (95% CI of 33–42%). The prevalence of migraine with aura is higher in CADASIL patients (51), compared to the general population, and is more frequent in females who presented the first attacks at younger age than men.

Migraine with aura is the most frequent and with an earlier clinical presentation occurring in the second-third decade of life, also migraine without aura and tension type headache are reported. The aura is typical visual or sensory aura in almost half of the cases (52), while the other half could present with atypical features: aura without headache, hemiplegic auras, brainstem aura, prolonged aura, and acute onset aura. Rarely patient with CADASIL may present with acute status migrainosus with persistent aura or with prolonged and persisting headache, acute altered mental status (visual hallucinations, behavioral disturbances), speech difficulties and memory deficits that could also evolve to coma (53–56).

The exact mechanism linking CADASIL to migraine manifestation is not fully understood. However, it is hypothesized that the vascular abnormalities caused by *NOTCH3* mutations may lead to chronic subcortical ischemia, which can trigger cortical spreading depression, a phenomenon associated with migraine aura. No association between onset and severity of migraine presentation and the MRI signs of microvascular damage in both white matter and basal ganglia (52) was found nor association with CGRP levels (57).

Another known associated factor that could modulate migraine susceptibility is the hyperhomocysteinemia that could lead to a younger age of onset (58). Different *NOTCH3* gene variants may influence the presentation and severity of migraine attacks in CADASIL patients. Some variants have been linked to variable headache courses, as shown in a recent study identifying specific pathogenic mutations (e.g., p.Tyr189Cys, p.Arg153Cys, p.Cys144Arg). Additionally, certain benign mutations are associated with specific migraine phenotypes, such as aura type (59). However, these findings are limited by small sample sizes and geographically restricted cohorts. There is no specific targeted treatment for CADASIL, nor for migraine associated with CADASIL, clinicians should also consider other comorbidities and eventual symptom worsening (e.g., neuropsychiatric manifestations). No clinical trials are available for this rare condition, but according to an individual case level meta-analysis beta-blockers and simple analgesics are the most commonly prescribed drugs (60).

However, the authors stated that beta-blockers should be avoided in CADASIL patients due to the potential for adverse events, possibly related to impaired cerebral vasoreactivity and reduced perfusion reserve (61–63). In contrast, acetazolamide and valproate showed neutral results compared to other preventive treatments and did not exhibit adverse effects. However, they warrant further investigation, as their potential efficacy is supported by specific mechanisms of action on smooth muscle vessels and anecdotal evidence from small cohorts and case series (61,62,64,65).

Retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations (RVCL-S)

RVCL-S is an autosomal dominant systemic small-vessel disease, caused by mutations in the *TREX1* gene (66). Clinically, RVCL-S is characterized by progressive white matter lesions, focal neurological deficits, migraine,

cognitive decline, psychiatric disturbances, and seizures. Systemic features include vascular retinopathy, liver dysfunction, nephropathy, hypertension, anemia, Raynaud's phenomenon, and gastrointestinal bleeding. The disorder typically manifests around the age of 40, with a median survival age of 53 years (67,68).

TREX1 encodes a 3′-5′ DNA exonuclease that plays a crucial role in clearing cytosolic DNA and preventing activation of the innate immune response (67). Mutations in *TREX1* result in the accumulation of cytosolic DNA, triggering chronic inflammation via the STING pathway, which underpins the systemic vasculopathy observed in RVCL-S (1,68). Migraine is a common feature in *TREX1*-associated disorders, affecting 42–59% of individuals with mutations (67,68). Migraine attacks often present with aura and may precede other systemic or neurological symptoms, complicating early diagnosis (1). The pathophysiology linking *TREX1* mutations to migraine is not fully understood, but vascular dysregulation and chronic inflammation likely lower the threshold for migraine initiation. The overlap between migraine aura phenomena and other neurological symptoms of RVCL-S, such as visual disturbances and cognitive changes, further highlights the complexity of this relationship.

Current research on *TREX1*-related disorders faces several limitations. Most studies involve small sample sizes or retrospective data collection. Furthermore, migraine progression in relation to other RVCL-S symptoms is poorly documented due to a lack of longitudinal studies (1,67,68).

KCNK18 related disorders

Mutations in the *KCNK18* gene, encoding the TWIK-related spinal cord potassium channel (TRESK), are associated with familial migraine with aura. *KCNK18* mutations were first linked to migraine through the identification of a frameshift mutation (F139WfsX24) in a multigenerational family, where it segregated with typical migraine with aura in an autosomal dominant pattern (69–71). TRESK is a two-pore domain potassium channel highly expressed in trigeminal and dorsal root ganglion neurons. It regulates resting membrane potential and reduces neuronal excitability, thus acting as a brake on nociceptive signaling. Loss-of-function mutations in TRESK increase the excitability of trigeminal nociceptors, enhancing susceptibility to migraine attacks. In experimental models, TRESK-deficient neurons exhibit increased calcitonin gene-related peptide (CGRP) release, which contributes to central and peripheral sensitization observed in migraine (69–71).

Beyond migraine, *KCNK18* mutations have also been implicated in intellectual disability and neurodevelopmental disorders. Biallelic variants affecting TRESK function have been reported in individuals with global developmental delay, cognitive impairment, and seizures, suggesting a broader role of *KCNK18* in neuronal homeostasis and brain function (72).

Individuals carrying the F139WfsX24 mutation typically report severe migraine, accompanied by visual aura, photophobia, and nausea, often beginning in adolescence. However, inconsistent findings regarding the pathogenicity of some *KCNK18* variants in sporadic migraine suggest that additional genetic or environmental factors modulate this relationship (73,74).

Current research on *KCNK18* and its role in migraine faces notable limitations. While the F139WfsX24 mutation is well-characterized, other missense variants demonstrate variable effects on channel function, complicating genotype-phenotype correlations. Studies often involve small cohorts, with limited representation of diverse populations, reducing the generalizability of findings. Hence, despite evidence linking TRESK dysfunction to trigeminal hyperexcitability, the precise molecular pathways connecting *KCNK18* mutations to migraine remain inadequately understood (69,75).

Familial advanced sleep phase syndrome (FASPS)

FASPS is a rare, autosomal-dominant circadian rhythm disorder characterized by early sleep onset and early morning awakening, often beginning in childhood or adolescence. This condition is associated with mutations in the *CSNK1D* gene, encoding casein kinase Iδ (CKIδ), a critical regulator of circadian rhythms through phosphorylation of core clock proteins such as PER2 (76,77). The CKIδ-T44A mutation results in reduced kinase activity, which shortens the circadian period in humans and animal models, leading to the FASPS phenotype (76). Headaches, including migraine with aura, are frequently observed in FASPS-affected individuals. In one study, all CKIδ-T44A mutation carriers experienced migraine, predominantly with aura, characterized by visual disturbances and heightened sensitivity to light and sound (77). Experimental models have shown that CKIδ mutations increase cortical spreading depression susceptibility (78), a key mechanism underlying migraine aura, and enhance nitroglycerin-induced hyperalgesia, further supporting a mechanistic link between circadian dysregulation and migraine pathophysiology. Moreover, some studies described the role of CK1δ in regulating astrocytic connexin-43 (Cx43) forming gap junctions between astrocytes (79). Mice lacking Cx43 in astrocytes showed an increased velocity of hippocampal spreading depolarization waves (79). Although evidence remains limited to single reports and pre-clinical studies, the FASPS model offers valuable insights into how circadian rhythms interact with migraine (80).

Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS)

MELAS is a mitochondrial disorder that manifests with migraine or migraine-like features (81,82). The prevalence of MELAS based on specific mutation is estimated to be 236 per 100,000 (0.24%;95% CI 0.10–0.49%) in Caucasian populations (83). This syndrome is typically maternally inherited and occurs in children and young adults (84,85), although adult-onset (86,87) cases have been reported.

MT-TL1 is the implicated gene in MELAS syndrome (84). This gene, located at position 12 on the short arm of the mitochondrial DNA, facilitates the transfer of the amino acid leucine to the polypeptide chain during translation. The most common variant accounting for approximately 80% of cases is the A3243G mutation which involves substitution of Adenine(A) to Guanine(G) in the nucleotide of the transfer RNA (tRNA) (81,87). Other mutations include m.3271T > C, m.3252 A > G (88). This point mutation causes defective mitochondrial translation and protein synthesis resulting in energy production deficiency. This energy deficiency leads to abnormal proliferation of mitochondria, which manifests in different organ-systems like myopathy, cardiomyopathy, and angiopathy and impairs blood perfusion to major organs. Clinical features of MELAS include stroke-like episodes, ataxia, intellectual disability, hearing loss, seizures, cortical blindness, hypertrophic cardiomyopathy, renal failure, diabetes mellitus, hypothyroidism or hyperthyroidism and psychiatric disorders (82,84,89). Headache prevalence ranges from 35.5% to 70% depending on the population (82,87,90). Headaches may present as recurrent migraine attacks, migraine-like headaches that resemble migraine in their clinical features – such as unilateral throbbing pain with photophobia – but do not meet the full diagnostic criteria. These migraine-like episodes may also overlap with or be precipitated by stroke-like events (82,85,86). The frequency and duration of headaches are variable, with no reported racial predilection. Although the exact mechanism of MELAS and migraine is not known, neuronal hyperexcitability and trigeminovascular activation have been suggested (91). The severity of migraine headaches may be associated with defects in the respiratory chain (82).

Treatment is primarily symptomatic and multidisciplinary, depending on the affected organs or systems. An open-label clinical trial reported that taurine combined with L-arginine reduced the frequency of stroke-like episodes (92). L-arginine is effective for acute episodes, and oral supplementation reduces stroke-like episodes (93). Additionally, erenumab at a dose of 70 mg was reported to be effective and well tolerated in a patient with MELAS with chronic treatment-refractory migraine (94). Although clinical trials are available, there is a lack of consensus on medications to treat MELAS Syndrome.

COL4A1 related disorder

Mutations in the *COL4A1* gene, responsible for type IV collagen synthesis, are associated with a variety of clinical phenotypes, including juvenile stroke, leukoencephalopathy and ocular abnormalities (95). These mutations can cause vascular fragility and cerebral microangiopathy. A history of migraine has been reported in several studies, often involving familial cases with documented genetic mutations (96,97). Available evidence is limited by small sample sizes and non-standardized methodologies.

Therapeutic considerations in FHM and other monogenic causes of migraine

Since controlled trials are not available, current evidence is based on single reports and case series. An 11-case study involving four FHM patients and seven Sporadic Hemiplegic Migraine patients demonstrated that onabotulinumtoxinA treatment reduced both headache intensity and aura severity and frequency in most participants. The majority of patients received a 150-U modified PREEMPT protocol under the 12-week cycle which resulted in a typical "wear-off" period between weeks 9 and 10 (98). The anti-CGRP monoclonal antibodies have demonstrated therapeutic effects across different genetic backgrounds; galcanezumab reduced headache days and acute medication use and MIDAS scores and attack severity in *PRRT2*-associated FHM patients in a small family study (99) and a sporadic HM patient with *SCN1A* variant mutation showed positive response to an anti-CGRP mAb after standard preventive treatments failed (100). Observational studies of FHM1 patients with *CACNA1A* T666 M mutation show that calcium antagonist medications like verapamil and flunarizine provide long-term benefits, while studies suggest acetazolamide and lamotrigine could work for specific patient phenotypes (101).

Two patients with chronic migraine in CADASIL showed enduring benefits from erenumab treatment without any adverse effects according to research (102). However, caution has been raised regarding the use of CGRP blockade in small-vessel disease, as CGRP might exert vasoprotective functions during ischemia, and its inhibition might theoretically worsen cerebrovascular outcomes (103). No published evidence is currently available on the use of gepants in FHM or CADASIL. Overall, the reported benefits of onabotulinumtoxinA and peripherally acting CGRP-targeted therapies suggest that such approaches may have a role in managing disorders characterized by Central Nervous System dysfunction, although further research is warranted to clarify safety and efficacy across genetic subtypes.

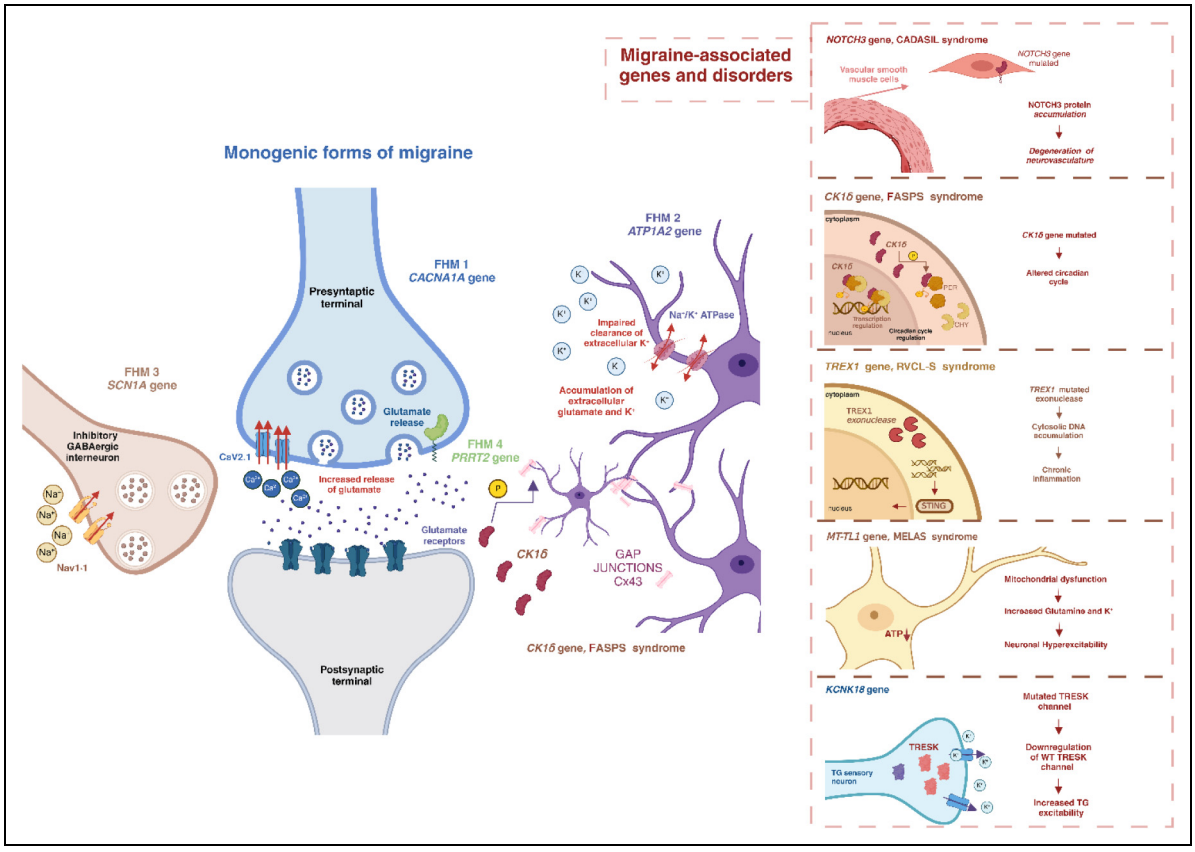

Figure 1. Genes involved in monogenic forms of migraine and migraine-associated disorders. Representation of the function and localization of genes involved in FHM in an excitatory presynaptic and postsynaptic terminal, an inhibitory GABAergic interneuron and astrocytes. *CACN1A* gene encoding for the voltage-gated calcium channel CaV2.1, and responsible for FHM1, regulates the calcium influx and the release of glutamate in the synaptic cleft. ATP1A product is localized in astrocytes and is involved in the clearance of extracellular K^+ and glutamate. Located in a GABAergic interneuron can be found represented the gene responsible for FHM3, *SCN1A*, which encodes a Na^+ channel and regulates the ion influx. FHM4 involves the *PRRT2* gene, which has been associated with the regulation and fusion of synapse vesicles to the plasma membrane. All the genes implicated in FHM contribute to an increase in extracellular K^+ and glutamate, which results in increased hyperexcitability and susceptibility to CSD. *NOTCH3*, *CK1δ*, *KCNK18*, *TREX1* and *MT-TL1* are some of the genes that have been associated with migraine and are responsible for other monogenic disorders. *NOTCH3* is a gene expressed in vascular smooth muscle cells and accumulates in the cerebral vasculature causing neurovascular degeneration. *CK1δ* gene encodes a kinase which plays a key role in regulating the circadian cycle by interacting with core clock proteins PER and CRY. In addition, *CK1δ* interacts with astrocytic Connexin-43. *KCNK18* gene encodes for a two-pore domain potassium channel named TRESK, whose mutated form interacts with the wild-type protein and causes its downregulation resulting in an increased excitability. TREX1 mutated exonuclease, related to RVCL-S syndrome, leads to an accumulation of cytosolic DNA which results in chronic inflammation through STING pathway. *MT-TL1* mutated gene, which is responsible for MELAS syndrome, results in increased neuronal hyperexcitability due to mitochondrial dysfunction. ATP1A = ATPase Na^+/K^+ transporting subunit alpha 1. CACN1A = calcium voltage-gated channel subunit alpha1. Cav2·1 = calcium voltage-gated channel subunit α1 A. CRY = cryptochrome proteins. CK1δ = casein kinase 1 isoform delta. Cx43= Connexin 43 protein. FHM = familial hemiplegic migraine. KCNK18 = potassium two pore domain channel subfamily K member 18. Nav1·1 = sodium voltage-gated channel α subunit 1. MELAS = maternally inherited mitochondrial disorder. MT-TL1 = mitochondrially encoded tRNA-Leu (UUA/G) 1. NOTCH3 = notch receptor 3. PER = period circadian protein homolog 1. PRRT2 = proline rich transmembrane protein 2. SCN1A = sodium voltage-gated channel alpha subunit 1. STING = cGAMP–stimulator of interferon genes pathway. TREX1 = three prime repair exonuclease 1. RVCL-S = Retinal Vasculopathy with Cerebral Leukoencephalopathy and Systemic Manifestations. Figure created with BioRender.com

Insights

Monogenic diseases provide crucial insights into migraine pathophysiology and may help identify new therapeutic targets. Investigating these genetic conditions enhances our understanding of both migraine aura and headache mechanisms, paving the way for innovative treatment strategies. The genetic landscape of monogenic migraine disorders mirrors the complexity observed in GWAS studies, where multiple genes with diverse functions—vascular

regulation, inflammation, and neuronal excitability—contribute to disease susceptibility. This supports the notion that migraine is a multifactorial disorder influenced by various genetic pathways. (Figure 1) A key feature of monogenic migraine disorders is the disruption of ion homeostasis in both neuronal and glial cells. In FHM type 1 and 3, gain-of-function mutations in ion channels lead to excessive glutamatergic transmission and an increased susceptibility to cortical spreading depression (CSD), a critical event in migraine aura. Meanwhile, FHM type 2, associated with *ATP1A2* mutations, highlights the role of glial cells in synaptic ionic balance, where loss-of-function mutations result in neuronal hyperexcitability and heightened susceptibility to CSD (22,104). These findings align with GWAS research identifying migraine risk loci within glutamate receptor genes, reinforcing the central role of synaptic excitability in migraine pathogenesis (9). Beyond ion homeostasis, monogenic disorders such as *KCNK18*-related disorders may be linked to increased excitability of trigeminal neurons, which could trigger migraine attacks. CADASIL exemplifies how vascular dysfunction can predispose individuals to migraine. The vascular abnormalities in CADASIL likely trigger ischemic events and facilitate CSD, reinforcing the vascular component in migraine pathophysiology (46). On the other hand, FASPS highlights the potential role of circadian biology and hypothalamic function in migraine. The mutation alters the regulation of core clock proteins, which not only affects sleep-wake cycles but also increases susceptibility to CSD in preclinical models (77). These findings suggest that circadian misalignment and hypothalamic dysregulation may act as migraine triggers, offering potential pathways for interventions targeting circadian biology and hypothalamic pathways. Among the different migraine phenotypes, migraine with aura appears to have a stronger genetic basis than migraine without aura. This is supported by its predominant presence in monogenic disorders, likely due to the direct impact of genetic mutations on neuronal excitability and CSD. The link between aura and these mutations provides a crucial perspective on the underlying biological processes that distinguish migraine subtypes. Further reinforcing the genetic connection, the genes implicated in FHM are often associated with other episodic neurological disorders, such as epilepsy and ataxias. While some of these conditions are neurodegenerative, most involve transient dysfunction rather than progressive deterioration, suggesting shared genetic pathways between migraine and other paroxysmal disorders. A particularly illustrative case is MELAS, where mitochondrial dysfunction, particularly affecting the respiratory chain and energy metabolism, plays a central role (84). This highlights the importance of cellular energy homeostasis in migraine pathogenesis and suggests potential therapeutic avenues aimed at improving mitochondrial function. In parallel, therapeutic observations from case reports highlight that peripherally acting treatments such as onabotulinumtoxinA and anti-CGRP monoclonal antibodies can reduce attack frequency and severity in FHM, while preliminary data in CADASIL suggest possible benefits but also raise safety considerations due to the vasoprotective role of CGRP. Although anecdotal, these findings provide practical insights for clinicians managing patients with genetic migraine syndromes and underscore the need for systematic studies. By understanding these genetic pathways, we could not only enhance migraine treatment but also improve care for a range of related neurological and systemic disorders providing broad therapeutic benefits across neurological and systemic disorders.

Conclusions

Migraine is a complex genetic disorder that involves various biological pathways. The study of monogenic forms of migraine and of monogenic disorders reporting strong association with migraine can help in the identification of pathophysiological mechanisms of migraine, including ion homeostasis, vascular function, and circadian regulation. Future studies will be essential to better characterize these pathways. Even if direct genetic-to-therapy translation has not yet occurred, knowledge of monogenic conditions remains vital for accurate diagnosis, optimized patient care, and deeper pathophysiological understanding that could eventually guide therapeutic innovation.

Key findings

- Monogenic disorders offer a natural model to dissect migraine pathophysiology, particularly in relation to Migraine with Aura
- Genes such as *CACNA1A*, *ATP1A2*, and *SCN1A* are central to our understanding of familial hemiplegic migraine and highlight the role of ion channel dysfunction.
- Overlap with other rare genetic syndromes (e.g., *PRRT2*-related paroxysmal disorders, mitochondrial and vascular diseases) suggests shared complex and multifaced neuronal mechanisms.
- Insights from these disorders may guide precision medicine, identifying potential targets for future disease-modifying therapies.
- This review offers a comprehensive, updated synthesis of migraine-related monogenic conditions.

Author contributions

D.M.: literature research and data curation, writing original draft, editing and reviewing manuscript, project supervision. Z.A.Z.: Literature research and data curation, writing original draft, subgroup supervision. O.G.: literature research and data curation, writing original draft, subgroup supervision, visualization. F.D.S., C.R., A.D., M.N.N., E.M., F.E.A.: literature research and data curation, writing original draft. E.C., P.P.-R.: conceptualization and methodology, editing and reviewing manuscript. project supervision.

Data availability statement

Complete search methods and articles found and selected are available upon request.

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