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Familial Hemiplegic Migraine

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Summary

Clinical characteristics

Familial hemiplegic migraine (FHM) falls within the category of migraine with aura. In migraine with aura (including FHM) the neurologic symptoms of aura are unequivocally localizable to the cerebral cortex or brain stem and include **visual disturbance** (most common), **sensory loss** (e.g., numbness or paresthesias of the face or an extremity), and **dysphasia** (difficulty with speech). FHM must include **motor involvement**, such as hemiparesis (weakness of an extremity). Hemiparesis occurs with at least one other symptom during FHM aura. Neurologic deficits with FHM attacks can be prolonged for hours to days and may outlast the associated migrainous headache. FHM is often earlier in onset than typical migraine, frequently beginning in the first or second decade; the frequency of attacks tends to decrease with age. Approximately 40%-50% of families with *CACNA1A*-FHM have cerebellar signs ranging from nystagmus to progressive, usually late-onset mild ataxia.

Diagnosis/testing

The clinical diagnosis of FHM can be established in a proband: (1) who fulfills criteria for migraine with aura; (2) in whom the aura includes fully reversible motor weakness and visual, sensory, or language symptoms; and (3) who has at least one first- or second-degree relative with similar attacks that fulfill the diagnostic criteria for hemiplegic migraine. The molecular diagnosis can be established in a proband by identification of a heterozygous pathogenic variant in *ATP1A2*, *CACNA1A*, or *SCN1A*.

Management

Treatment of manifestations: A trial of acetazolamide for individuals with *CACNA1A*-FHM or a trial of prophylactic migraine medications (e.g., tricyclic antidepressants, beta blockers, calcium channel blockers, antiepileptic medications) for all FHM types may be warranted for frequent attacks. Antiepileptic treatment may be necessary for seizures, which are prevalent in *ATP1A2*-FHM.

Surveillance: Neurologic evaluation to assess change in attack frequency and/or seizures, annually or more frequently for worsening symptoms.

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Agents/circumstances to avoid: Vasoconstricting agents because of the risk of stroke; cerebral angiography as it may precipitate a severe attack.

Genetic counseling

FHM and simplex hemiplegic migraine caused by a heterozygous *ATP1A2*, *CACNA1A*, or *SCN1A* pathogenic variant are inherited in an autosomal dominant manner. Because the diagnosis of FHM requires at least one affected first-degree relative, most individuals diagnosed with FHM have an affected parent. Individuals with simplex hemiplegic migraine (i.e., individuals with an FHM-causing pathogenic variant and an apparently negative family history) may have a *de novo* pathogenic variant or a pathogenic variant inherited from an asymptomatic parent. Each child of an individual with FHM has a 50% chance of inheriting the pathogenic variant. Once an FHM-causing pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Diagnosis

Consensus clinical diagnostic criteria for familial hemiplegic migraine (FHM) have been published by the Headache Classification Committee of the International Headache Society [2018] (full text).

Suggestive Findings

FHM is a category of migraine with aura.

Note: Migraine with aura is a recurring disorder of neurologic symptoms unequivocally localizable to the cerebral cortex or brain stem. The aura usually develops over a period of five to 20 minutes and lasts less than 60 minutes. Headache, nausea, and/or photophobia usually follow neurologic aura symptoms, either immediately or after a symptom-free interval of less than an hour. The headache usually lasts four to 72 hours but may be completely absent (acephalagia).

Diagnostic criteria for HM

- Headaches that fulfill criteria for migraine with aura
- Aura consisting of **both** of the following:
  - Transient (generally >72 hours but may be prolonged) but fully reversible motor weakness
  - Fully reversible visual, sensory, and/or speech/language symptoms

HM is categorized as **familial** if at least one first-degree relative (i.e., parent, sib, and/or offspring) or second-degree relative has similar attacks that fulfill the diagnostic criteria for HM.

Note: HM is sporadic if no first- or second-degree relative meets criteria for HM.

Diagnostic criteria for migraine with aura

- At least two episodes fulfilling criteria for migraine
- Migraine with at least one of the following fully reversible aura symptoms:
  - Visual
  - Sensory
  - Speech and/or language
  - Motor
  - Brain stem
  - Retinal
- At least three of the following characteristics:
  - At least one aura symptom spreads gradually over five minutes.

- Two or more aura symptoms occur in succession.
- Each individual aura symptom lasts five to 60 minutes.
- At least one aura symptom is unilateral.
- At least one aura symptom is positive.
- The aura is accompanied – or followed within 60 minutes – by headache.

- Absence of other causes of headache (e.g., head trauma, vascular disorders, nonvascular intracranial disorders, substance use or their withdrawal, non-cephalic infection, metabolic disorder, pain associated with other facial or cranial disorders)

Establishing the Diagnosis

The clinical diagnosis of FHM can be **established** in a proband based on clinical diagnostic criteria described in Suggestive Findings, or the molecular diagnosis can be established in a proband by identification of a heterozygous pathogenic variant by molecular genetic testing in one of the genes listed in Table 1.

Molecular genetic testing approaches can include **serial single-gene testing**, a **multigene panel**, or **exome sequencing**.

Note: (1) In the majority of persons with adult-onset hemiplegic migraine without nystagmus, seizures, or other unusual associated neurologic features, the yield for genetic testing is low. (2) Multiple studies have shown that pathogenic variants in the genes listed in Table 1 are not a major cause of simplex hemiplegic migraine (i.e., hemiplegic migraine in a single person in a family).

Serial single-gene testing

- In individuals with **nystagmus**, **ataxia**, **paroxysmal tonic upgaze**, **or developmental delay**, sequence analysis of ***CACNA1A*** can be performed first. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications [Ophoff et al 1996].
- In individuals with **epilepsy**, sequence analysis of ***ATP1A2*** can be performed first [De Fusco et al 2003].

A multigene panel that includes some or all of the genes listed in Table 1 and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used. For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Familial Hemiplegic Migraine

Gene [1, 2]	Proportion of FHM Attributed to Pathogenic Variants in Gene	Proportion of Probands with a Pathogenic Variant [3] Detectable by Method	
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
ATP1A2	~10%	~99% [6]	1 person [7]
CACNA1A	10%-15%	~95% [6]	Multiple families [8]
SCN1A	<1%	100% [6]	None reported
Unknown [9]	66%-80%	NA	

1. Genes are listed in alphabetic order.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. See Molecular Genetics for information on variants detected in these genes.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2017]
7. An intragenic duplication involving exon 21 was reported in one individual with hemiplegic migraine [Gagliardi et al 2017].
8. A 39.5-kb *CACNA1A* deletion of the last 16 coding exons was reported in three affected members of one family with episodic ataxia [Riant et al 2008]. *CACNA1A* rearrangements have also been reported in families with hemiplegic migraine [Labrum et al 2009].
9. A heterozygous *ATP1A4* pathogenic variant was reported in one family; to date, the report has not been confirmed.

Clinical Characteristics

Clinical Description

In migraine with aura, including familial hemiplegic migraine (FHM), the neurologic symptoms of aura are unequivocally localizable to the cerebral cortex or brain stem and include fully reversible **visual disturbance** (most common), **sensory loss** (e.g., numbness or paresthesias of the face or an extremity), and **dysphasia** (difficulty with speech), and for FHM must include **motor involvement** (e.g., hemiparesis [weakness of an extremity]):

- Visual disturbances can include scotoma (blind spots), photopsia (flashing lights), fortification spectra (zigzag pattern), and diplopia (double vision).
- Dysphasia usually occurs when hemiplegia is right-sided.
- Hemiparesis (unilateral weakness), not necessarily hemiplegia (unilateral paralysis), occurs with at least one other symptom during FHM aura.

Some confusion and/or drowsiness may be present even without dysphasia. Impaired consciousness ranging from drowsiness to coma is well described in FHM [Terwindt et al 1998, Chabriat et al 2000, Vahedi et al 2000]. Intermittent confusion and psychosis have been reported [Feely et al 1982], including one probable family with *CACNA1A*-FHM and ataxia [Spranger et al 1999].

Neurologic deficits with hemiplegic migraine attacks can be prolonged for hours to days and may outlast the associated migrainous headache. Persistent attention and memory loss can last weeks to months [Kors et al 2003]. Permanent motor, sensory, language, or visual symptoms are extremely rare [Ducros et al 2001].

FHM is a rare and extreme phenotype of migraine with aura. The frequency of attacks ranges from one per day to fewer than five in a lifetime (mean: 2-3/year). Long attack-free intervals are often reported (range: 2-37 years).

The frequency of FHM attacks tends to decrease with age. FHM attacks may be provoked by typical migraine triggers (e.g., foods, odors, exertion, stress), minor head trauma, cerebral angiography, and minor head trauma.

The eventual neurologic outcome is often benign in the pure FHM group without interictal deficits (e.g., seizures/epilepsy, ataxia, nystagmus, cognitive impairment / learning disability).

Note: Cerebral infarction and death have rarely been associated with hemiplegic migraine and should instead raise the possibility of other disorders associated with migraine and stroke (see Differential Diagnosis).

Seizures are a recognized feature in those with FHM-related pathogenic variants, which reflects much clinical and mechanistic overlap between epilepsy and migraine. Seizures during severe attacks have been reported in some families with *ATP1A2*-FHM along with coma and encephalopathy [Echenne et al 1999, Deprez et al 2008]. Focal seizures during severe attacks have been described in two individuals with simplex *CACNA1A*-FHM [Chabriat et al 2000], including one with severe intellectual disability, congenital ataxia, and early cerebellar atrophy [Vahedi et al 2000]. *De novo CACNA1A* pathogenic variants are a common cause of epileptic encephalopathy [Allen et al 2016], and epileptic encephalopathy may be the presenting phenotype in an individual who develops *CACNA1A*-FHM.

Imaging studies. There are no pathognomonic neuroradiographic findings for FHM. The only abnormalities observed on traditional imaging studies are vermian cerebellar atrophy in some families with *CACNA1A*-FHM [Battistini et al 1999]. Rare ictal studies demonstrated transient diffusion-weighted signal changes on brain MRI, suggesting cytotoxic edema during severe prolonged attacks in individuals with *CACNA1A*-FHM [Chabriat et al 2000, Vahedi et al 2000], with hemispheric cerebral atrophy usually contralateral to the hemiparesis [Hayashi et al 1998, Chabriat et al 2000, Vahedi et al 2000].

Abnormalities in the cerebellum on magnetic resonance spectroscopy have been reported [Dichgans et al 2005].

Phenotype Correlations by Gene

CACNA1A. Compared to families without an identified FHM-related pathogenic variant, families with *CACNA1A*-FHM have a higher incidence of cerebellar signs ranging from nystagmus to progressive ataxia, which occurs in up to 40%-50% of families with *CACNA1A*-FHM [Ducros et al 2000]; within such families, up to 60% of affected individuals have permanent cerebellar signs [Ducros et al 2001].

Those with identified FHM-related pathogenic variants tend to present with earlier age of onset, more severe symptoms, and associated interictal symptoms and signs (nystagmus, episodic or progressive ataxia, learning disability, epilepsy). In the report of Ducros et al [2001], the attacks started at a young age in the majority of individuals with *CACNA1A*-FHM (mean: 11.7±8 years; range: 1-51 years). Findings from subsequent series confirmed the observation of early age of onset and more severe attacks in those with FHM-related pathogenic variants compared to those with FHM and no pathogenic variant identified [Hiekkala et al 2018, Pelzer et al 2018].

Genotype-Phenotype Correlations

ATP1A2

- A severe phenotype with seizures, coma, and elevated temperature has been reported with the p.Gly301Arg pathogenic variant in *ATP1A2* [Spadaro et al 2004, Santoro et al 2011].
- A severe phenotype with seizures and intellectual disability has been reported with the pathogenic variants p.Asp718Asn and p.Pro979Leu [Jurkat-Rott et al 2004].

CACNA1A. Although further correlation is needed, some suggestive genotype-phenotype correlations exist based on limited data regarding *CACNA1A* pathogenic variants commonly presenting with nystagmus and other cerebellar signs [Ophoff et al 1996, Ducros et al 2001].

- p.Arg192Gln and p.Val1456Leu [Carrera et al 1999] are associated with hemiplegic attacks only, whereas unconsciousness occurs commonly during attacks with the p.Val714Ala pathogenic variant [Terwindt et al 1998].
- p.Thr666Met, p.Ile1810Leu, p.Arg583Gln [Alonso et al 2003], and p.Asp715Glu [Ducros et al 1999] have been associated with hemiplegic attacks plus ataxia. According to Ducros et al [2001], p.Thr666Met was associated with the highest frequency of hemiplegic migraine, severe attacks of coma, and nystagmus. During attacks, unconsciousness sometimes occurs in individuals with the p.Thr666Met or p.Ile1810Leu pathogenic variant [Terwindt et al 1998].
- p.Arg583Gln can be associated with stupor, fever, and progressive ataxia [Battistini et al 1999, Ducros et al 2001]. Affected individuals were thought to have fewer attacks after treatment with acetazolamide.
- p.Asp715Glu has the lowest frequency (64%) of attacks of hemiplegic migraine [Ducros et al 2001].
- p.Ser218Leu has been associated with delayed cerebral edema and fatal coma after minor head trauma [Kors et al 2001, Stam et al 2009].

Penetrance

Penetrance appears to be high and is estimated at 80% [Jurkat-Rott et al 2004, Riant et al 2005].

Nomenclature

Although families with FHM in which attacks are strikingly identical do exist, the term FHM is often used inconsistently to describe families in which different forms of migraine occur, as most individuals with hemiplegic attacks have these attacks intermingled with more frequent attacks of migraine without hemiparesis.

Prevalence

In Denmark, Thomsen et al [2002] found the prevalence of hemiplegic migraine to be 0.01% with a M:F sex ratio of 1:3 and equal prevalence of familial and simplex cases.

Genetically Related (Allelic) Disorders

Other phenotypes associated with germline pathogenic variants in *ATP1A2, CACNA1A*, and *SCN1A* are summarized in Table 2.

Table 2. Allelic Disorders

Gene	Clinical Characteristics
ATP1A2	Alternating hemiplegia of childhood (OMIM 104290), characterized by intermittent recurrent prolonged hemiplegic episodes that mimic hemiplegic migraine
	Polymicrogyric syndrome [1]

Table 2. continued from previous page.

Gene	Clinical Characteristics
CACNA1A	Episodic ataxia type 2 (OMIM 108500). Episodes of ataxia & sometimes migrainous headache w/interictal nystagmus. In 1 family, affected members experienced hemiplegia; 1 family member had migraine during episodes of ataxia. [2] Assoc pathogenic variants: nonsense, frameshift, & splice site variants & multiexon deletions that disrupt the open reading frame
	Progressive cerebellar ataxia. Severe progressive ataxia & cerebellar atrophy. Assoc pathogenic variants: missense variants incl p.Gly293Arg in P loop of 1st domain; p.Ala454Thr in I-II loop; p.Arg1664Gln
	Spinocerebellar ataxia type 6 (SCA6). Adult-onset, slowly progressive cerebellar ataxia, dysarthria, & nystagmus. Assoc w/a CAG repeat expansion; this expansion has not been observed in families w/FHM [3] but some persons w/SCA6 may have migraine.
	Developmental & epileptic encephalopathy 42 (OMIM 617106). *De novo* pathogenic variants in *CACNA1A* are recognized to be an important cause of epileptic encephalopathy. [4]
SCN1A	The vast majority of pathogenic variants in *SCN1A* cause epilepsy. *SCN1A* seizure disorders encompass a spectrum from simple febrile seizures & generalized epilepsy w/febrile seizures plus to Dravet syndrome & intractable childhood epilepsy w/generalized tonic-clonic seizures. Phenotypes w/intractable seizures incl Dravet syndrome are usually assoc w/progressive cognitive & motor decline.
	Interstitial deletions of 2q24-q3 (incl a cluster of voltage-gated sodium channel genes: *SCN1A*, *SCN2A*, *SCN3A*, *SCN7A*, *SCN9A*) are assoc w/tonic focal & myoclonic jerks that tend to appear in infancy & are later followed by mixed-type seizures, which persist to late childhood & are drug resistant. [5]
	Larger deletions of 2q24.3 are assoc w/dysmorphic features (e.g., microcephaly, ptosis, downslanting palpebral fissures, long eyelashes, micrognathia), [6] & digit anomalies in persons w/2q24-q31 deletions. [7]
	Reported duplications of 2q24.2-q3 involving the cluster of voltage-gated sodium channel genes *SCN1A*, *SCN2A*, *SCN3A*, *SCN7A*, & *SCN9A* vary in size. Reported persons presented w/focal seizures & epileptic spasms w/neonatal onset (as early as 3rd day of life). [8]
	Familial autism [9]
	Rasmussen encephalitis assoc w/pathogenic variant p.Arg1575Cys [10]

1. Chatron et al [2019]
2. Jen [1999]
3. Carrera et al [1999], Ducros et al [1999]
4. Allen et al [2016]
5. Grosso et al [2007]
6. Pescucci et al [2007]
7. Boles et al [1995]
8. Goeggel Simonetti et al [2012]
9. Weiss et al [2003]
10. Ohmori et al [2008]

Note: In one large family with pathogenic variants in *CACNA1A*, some individuals had only hemiplegic migraine, some had only ataxia, and some had both [Alonso et al 2003].

Differential Diagnosis

Migraine without aura (OMIM 157300) (common migraine) is an idiopathic, recurring headache disorder manifesting in attacks lasting four to 72 hours. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity, and association with nausea, photophobia, and phonophobia. This headache occurs without neurologic aura symptoms and specifically without hemiparesis.

Hemiplegia. The differential diagnosis of hemiplegia includes post-ictal weakness following seizure, transient ischemic attack, stroke, and other non-genetic causes of transient hemiparesis.

Stroke. When family history is positive for hemiparetic attacks with migraine, the presence of infarct on imaging studies raises the possibility of inherited disorders such as MELAS, CADASIL, or thrombophilia (e.g., factor V Leiden). Additional stroke risk factors may also be present.

Caution: Even with normal imaging studies and description of spreading aura, an age-appropriate stroke evaluation should be considered at presentation. Overlap in clinical features, inaccuracies of historical family information, rarity of FHM, and the seriousness of stroke-related disorders warrant this cautious approach. Stroke or other CNS-related disorders should be strongly considered if family history is negative for hemiplegic migraine.

Migrainous headache that may include hemiplegic aura. Other hereditary disorders associated with migrainous headache that may include hemiplegic aura are summarized in Table 3.

Table 3. Hereditary Disorders with Migrainous Headache That May Include Hemiplegic Aura in the Differential Diagnosis of Familial Hemiplegic Migraine

Gene(s)	Disorder	MOI	Headache Phenotype	Other Clinical Characteristics
ACVRL1 *ENG* *GDF2* *SMAD4*	Hereditary hemorrhagic telangiectasia	AD	Migraine w/aura reported in 50% of affected persons (Migraine headache may be a complication of pulmonary AVMs.)	Multiple AVMs that lack intervening capillaries & → direct connections between arteries & veins. Small AVMs (telangiectases) close to skin surface or mucous membranes that often rupture & bleed after slight trauma. Most common clinical sign: spontaneous & recurrent nosebleeds from age ~12 yrs.
APP	Dutch form of hereditary cerebral amyloid angiopathy (OMIM 605714)	AD	Migraines often precede onset of cerebral & cerebellar hemorrhage in 4th or 5th decade.	Senile plaques & vascular wall amyloid found in the brain in assoc w/amino acid changes in APP beta-amyloid precursor protein, a protease inhibitor
ATP1A2 *ATP1A3*	Alternating hemiplegia of childhood (OMIM PS104290)	AD	Early onset of recurrent transient hemiplegia	Recurrent hemiplegia w/onset age <18 mos, variable other transient neurologic findings, & progressive cognitive decline
CCM2 *KRIT1* *PDCD10*	Familial cerebral cavernous malformations	AD	Nonspecific headaches	Vascular malformations in brain & spinal cord consisting of closely clustered enlarged capillary channels (caverns) w/a single layer of endothelium w/o normal intervening brain parenchyma or mature vessel wall elements. Typically presents in 2nd-5th decade. ~50%-75% of persons w/CCM have symptoms incl seizures, focal neurologic deficits, & cerebral hemorrhage.
mtDNA	MERRF [2]	Mat	Migraine headaches reported in 5%-14.9% of those w/m.8344A>G in *MT-TK*	Multisystem disorder characterized by myoclonus followed by generalized epilepsy, ataxia, weakness, & dementia; onset usually in childhood after normal early development
mtDNA [1]	MELAS [2]	Mat	Migrainous headaches (recurrent attacks of severe pulsatile headache w/frequent vomiting) are typical & can precipitate stroke-like episodes. Headache episodes are often more severe during stroke-like episodes.	Multisystem disorder w/onset at age ~2-40 yrs. Common clinical manifestations: stroke-like episodes, encephalopathy w/seizures &/or dementia, muscle weakness & exercise intolerance, normal early psychomotor development, recurrent vomiting, hearing impairment, peripheral neuropathy, learning disability, & short stature

Table 3. continued from previous page.

Gene(s)	Disorder	MOI	Headache Phenotype	Other Clinical Characteristics
NOTCH3	CADASIL	AD	Migraine may be 1st symptom; occurs in 30%-75% of persons, w/1st attack at a mean age of 26-29 yrs. 80%-90% of those w/ migraine have migraine w/aura. Migraine auras are sometimes confused w/transient ischemic symptoms, as aura may incl focal neurologic deficits. 60% of those w/migraine w/aura have experienced an atypical migraine attack: prolonged, basilar or hemiplegic aura, confusion, fever, or coma.	Mid-adult onset of recurrent ischemic stroke, cognitive decline progressing to dementia, mood disturbance, apathy, & diffuse white matter lesions & subcortical infarcts on neuroimaging
TREX1	Retinal vasculopathy w/cerebral leukoencephalopathy & systemic manifestations	AD	Migraine ± aura	Small-vessel disease that affects highly vascularized tissues incl retina, brain, liver, & kidneys. Onset age: ~35-50 yrs. Most common presenting finding: ↓ visual acuity &/or visual field defects. Neurologic manifestations may incl hemiparesis, facial weakness, aphasia, & hemianopsia.

AD = autosomal dominant; AVM = arteriovenous malformation; CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CCM = cerebral cavernous malformation; Mat = maternal; MOI = mode of inheritance; mtDNA = mitochondrial DNA

1. The most common mtDNA pathogenic variant, present in more than 80% of individuals with typical clinical findings of MELAS, is an A-to-G transition at nucleotide 3243 in the tRNALeu(UUR) of mtDNA.

2. Other mitochondrial disorders can also be considered. Common central nervous system findings in mitochondrial disorders are fluctuating encephalopathy, seizures, dementia, migraine, stroke-like episodes, ataxia, and spasticity. A high incidence of mid- and late pregnancy loss is a common occurrence that often goes unrecognized.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with familial hemiplegic migraine (FHM) or simplex hemiplegic migraine (i.e., individuals with an FHM-causing pathogenic variant and an apparently negative family history), the evaluations summarized in this Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Familial Hemiplegic Migraine

System/Concern	Evaluation
Neurologic	• Quantitative eye movement exam in persons w/nystagmus or complaints of incoordination or imbalance to look for additional clues of cerebellar involvement • EEG & neuroimaging studies if seizures are present in order to further characterize seizure disorder
Genetic counseling	By genetics professionals [1] to inform affected persons & their families re nature, MOI, & implications of FHM in order to facilitate medical & personal decision making

Table 4. continued from previous page.

System/Concern	Evaluation
Family support/ resources	Assess: • Use of community or online resources such as Parent to Parent; • Need for social work involvement for parental support; • Need for home nursing referral.

FHM = familial hemiplegic migraine; MOI = mode of inheritance
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Symptomatic support during an episode of hemiplegic migraine is the only therapy available.

Table 5. Treatment of Manifestations in Individuals with Familial Hemiplegic Migraine

Manifestation/Concern	Treatment	Considerations/Other
Frequent attacks	• Trial of acetazolamide for persons w/*CACNA1A*-FHM • Trial of standard migraine prophylactic drugs (e.g., tricyclic antidepressants, beta blockers, calcium channel blockers, AEDs)	Limited correlation exists between drug response & hemiplegic migraine type.
	Consider AEDs incl topiramate, lacosamide, levetiracetam, & valproate, along w/other medications commonly used for migraine prophylaxis.	There are anecdotal reports of therapeutic response.
Seizures	Antiepileptic treatment	

AED = antiepileptic drug

Surveillance

Table 6. Recommended Surveillance for Individuals with Familial Hemiplegic Migraine

System/Concern	Evaluation	Frequency
Neurologic	Eval by neurologist to assess change in attack frequency &/or seizures	Annually or more frequently for worsening symptoms

Agents/Circumstances to Avoid

In general, vasoconstricting agents should be avoided because of the risk of stroke.

Cerebral angiography is hazardous as it may precipitate a severe attack [Chabriat et al 2000].

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Familial hemiplegic migraine (FHM) and simplex hemiplegic migraine caused by a heterozygous *ATP1A2*, *CACNA1A*, or *SCN1A* pathogenic variant are inherited in an autosomal dominant manner.

Note: The term "simplex hemiplegic migraine" is used in this section to refer to individuals with hemiplegic migraine and a heterozygous pathogenic variant in *CACNA1A*, *ATP1A2*, or *SCN1A* who do not have a first- or second-degree relative who meets criteria for hemiplegic migraine.

Risk to Family Members

Parents of a proband

- Because the diagnosis of FHM requires at least one affected first-degree relative, most individuals diagnosed with FHM have an affected parent.
- Individuals with simplex hemiplegic migraine (i.e., individuals with an FHM-causing pathogenic variant and an apparently negative family history) may have a *de novo* pathogenic variant [Terwindt et al 2002, de Vries et al 2007, Thomsen et al 2008, Riant et al 2010] or a pathogenic variant inherited from an asymptomatic parent.
- Recommendations for the evaluation of the parents of an individual who appears to be the only affected family member include clinical interview, neurologic examination, and molecular genetic testing if a molecular diagnosis has been established in the proband.
- If a pathogenic variant identified in the proband is not identified in either parent, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant. Note: A pathogenic variant is reported as "*de novo*" if: (1) the pathogenic variant found in the proband is not detected in parental DNA; and (2) parental identity testing has confirmed biological maternity and paternity. If parental identity testing is not performed, the variant is reported as "assumed *de novo*" [Richards et al 2015].
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.
- The family history of some individuals diagnosed with *CACNA1A*, *ATP1A2*, or *SCN1A*-related hemiplegic migraine may appear to be negative because of failure to recognize the disorder in affected family members or reduced penetrance. Therefore, an apparently negative family history cannot be confirmed without appropriate clinical evaluation of the parents and/or molecular genetic testing (to establish that neither parent is heterozygous for a causative pathogenic variant identified in the proband).

Sibs of a proband. The risk to the sibs of a proband depends on the clinical/genetic status of the parents:

- If a parent of the proband is affected and/or is known to have an FHM-causing pathogenic variant, the risk to the sibs of inheriting the pathogenic variant is 50%. There is a high likelihood that a sib who inherits an FHM-causing pathogenic variant will have clinical manifestations of the disorder. Intrafamilial

clinical variability has been observed in age at onset and severity of manifestations, including attack frequency, severity, and associated symptoms.
- If the proband has a known *CACNA1A*, *ATP1A2*, or *SCN1A* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the proband does not have a known FHM-related pathogenic variant and both of the proband's parents are clinically unaffected, the risk to the sibs of a proband appears to be low.

Offspring of a proband. Each child of an individual with familial hemiplegic migraine has a 50% chance of inheriting the pathogenic variant.

Other family members. The risk to other family members depends on the genetic status of the proband's parents. If a parent is affected, his or her family members are at risk.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk of being affected.

DNA banking. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative genetic alteration/s are unknown).

Prenatal Testing and Preimplantation Genetic Testing

Once an FHM-causing pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **CACNA1A Foundation**
  Email: info@cacna1a.org
  www.cacna1a.org
- **Medline Plus**
  Familial hemiplegic migraine
- **National Headache Foundation**
  Phone: 888-NHF-5552; 888-643-5552
  Email: info@headaches.org
  www.headaches.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Familial Hemiplegic Migraine: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ATP1A2	1q23.2	Sodium/potassium-transporting ATPase subunit alpha-2	ATPase, Na+/K+ transporting, alpha 2 (+) polypeptide (ATP1A2) @ LOVD Familial Hemiplegic Migraine (FHM) Variation Database (ATP1A2)	ATP1A2	ATP1A2
CACNA1A	19p13.13	Voltage-dependent P/Q-type calcium channel subunit alpha-1A	Calcium channel, voltage-dependent, P/Q type, alpha 1A subunit (CACNA1A) @ LOVD	CACNA1A	CACNA1A
SCN1A	2q24.3	Sodium channel protein type 1 subunit alpha	SCN1A gene database	SCN1A	SCN1A

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Familial Hemiplegic Migraine (View All in OMIM)

141500	MIGRAINE, FAMILIAL HEMIPLEGIC, 1; FHM1
182340	ATPase, Na+/K+ TRANSPORTING, ALPHA-2 POLYPEPTIDE; ATP1A2
182389	SODIUM VOLTAGE-GATED CHANNEL, ALPHA SUBUNIT 1; SCN1A
601011	CALCIUM CHANNEL, VOLTAGE-DEPENDENT, P/Q TYPE, ALPHA-1A SUBUNIT; CACNA1A
602481	MIGRAINE, FAMILIAL HEMIPLEGIC, 2; FHM2
609634	MIGRAINE, FAMILIAL HEMIPLEGIC, 3; FHM3

Molecular Pathogenesis

The three FHM-related genes identified to date encode ion channels and transporters important in regulating neuronal excitability and cortical synaptic transmission. The observation of seizures and epilepsy in individuals with FHM-causing variants further emphasizes the mechanistic overlap between migraine and epilepsy from dysregulation of cortical excitation/inhibition balance.

Accumulating evidence supports the hypothesis that the electrophysiologic correlate underlying migraine aura is cortical spreading depolarization (CSD) of Leão, which is characterized by a slowly propagating wave 2-6 mm/min of hyperexcitation followed by sustained depression. Mouse models generated from *ATP1A2*-FHM variants p.Trp887Arg or p.Gly301Arg [Leo et al 2011, Kros et al 2018] and *CACNA1A* variants p.Arg192Gln and p.Ser218Leu [van den Maagdenberg et al 2004, van den Maagdenberg et al 2010] all demonstrated increased susceptibility to induced CSD from decreased glutamate clearance or increased glutamate release, respectively. A newly generated mouse model with the *SCN1A*-FHM variant p.Leu263Val demonstrated spontaneous CSD attributed to overall gain of sodium channel function leading to hyperexcitation of GABAergic inhibitory interneurons [Jansen et al 2020].

Mechanism of disease causation

- ***ATP1A2.*** The two pathogenic variants found by De Fusco et al [2003], p.Leu764Pro and p.Trp887Arg, cause loss of function of the α2-subunit leading to haploinsufficiency, which appears to be the general rule

for *ATP1A2*-FHM variants. Loss of transporter function would lead to impaired glutamate clearance from the synaptic cleft.

- ***CACNA1A.*** There is much clinical overlap between FHM and allelic disorders such as episodic ataxia type 2 (EA2) and spinocerebellar ataxia type 6 (SCA6). In general, FHM-causing variants lead to gain of channel function, while EA-causing variants lead to loss of function. Gain of channel function is thought to lead to increased glutamate release from cortical synapses.
- ***SCN1A.*** FHM-causing variants generally lead to gain of channel function, which contrasts with loss-of-function variants that account for the vast majority of *SCN1A* variants causing various epilepsy syndromes including Dravet syndrome.

Table 7. Familial Hemiplegic Migraine: Gene-Specific Laboratory Considerations

Gene	Special Consideration
CACNA1A	*CACNA1A* is alternatively spliced, notably w/an alternative exon 37 (NM_001127221.1 RefSeq transcript variant 3) & an alternative splice site for exon 47 which contains polymorphic CAG repeats, w/the longer transcript rendering the CAG repeats in frame for polyglutamine. Pathogenic variants have been identified in exon 37a & exon 37b. Furthermore, CAG repeat expansions w/>21 repeats cause SCA6 w/incomplete penetrance.

Table 8. Familial Hemiplegic Migraine: Notable Pathogenic Variants by Gene

Gene [1]	Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
ATP1A2	NM_000702.4 NP_000693.1	c.901G>A	p.Gly301Arg	Severe phenotype reported [Spadaro et al 2004, Santoro et al 2011]
		c.2152G>A	p.Asp718Asn	Severe phenotype reported [Jurkat-Rott et al 2004]
		c.2936C>T	p.Pro979Leu	
		c.2291T>C	p.Leu764Pro	De Fusco et al [2003]
		c.2659T>C	p.Trp887Arg	
CACNA1A	NM_001127221.2 NP_001120693.1 X99897 [2]	c.575G>A	p.Arg192Gln	Hemiplegic attacks [Carrera et al 1999]
		c.653C>T	p.Ser218Leu	Kors et al [2001], Stam et al [2009]
		c.1748G>A	p.Arg583Gln	Battistini et al [1999], Ducros et al [2001]
		c.1997C>T	p.Thr666Met	Most common pathogenic variant w/no evidence for founder effect [Ducros et al 1999]
		c.2141T>C	p.Val714Ala	Hemiplegic attacks & unconsciousness [Terwindt et al 1998]
		c.2145C>G	p.Asp715Glu	Lowest frequency (64%) of attacks of hemiplegic migraine [Ducros et al 2001]
		c.4366G>T (c.4369G>T) [2]	p.Val1456Leu (p.Val1457Leu) [2]	Hemiplegic attacks [Carrera et al 1999]
		c.5428A>C (c.5431A>C) [2]	p.Ile1810Leu (p.Ile1811Leu) [2]	Hemiplegic attacks + ataxia [Ducros et al 1999]

Table 8. continued from previous page.

Gene [1]	Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
SCN1A	NM_001165963.4 NP_001159435.1	c.787C>G	p.Leu263Val	Jansen et al [2020]

Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Genes from Table 1 in alphabetic order
2. Variant designations are given for an alternate reference sequence. X99897 is an alternate cDNA commonly used in the literature. Compared to NM_001127221.2, it has an extra three nucleotides (AAG) at nucleotide 3623_3625, resulting in an additional Glu residue.

Chapter Notes

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