

# Genetics of migraine: New findings

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**Keywords:** familial hemiplegic migraine, *CACNA1A*, *ATP1A2*, *SCN1A*, *TREX1*,  
channelopathy, association studies

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## **Summary**

Identification and analysis of gene mutations in familial hemiplegic migraine (FHM) remains the focus of research of migraine genetics. Several new mutations have recently been identified in FHM1, FHM2 and FHM3 genes. Functional studies further revealed a major role for disturbed ion transport in this disorder. The findings point to an important role for cortical spreading depression in migraine pathophysiology. New genetic approaches have been tested in common migraine: novel chromosomal loci, but no gene variants have been identified. The identification of *TREX1* mutations in families with retinal vasculopathy and associated diseases such as migraine may provide new insights in migraine pathophysiology.

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## **Introduction**

Migraine is a complex genetic neurovascular disorder [1]. Mutations in the three genes for familial hemiplegic migraine (FHM) - *CACNA1A*, *ATP1A2* and *SCN1A* – still form the only established molecular knowledge of migraine so far [2-4].

FHM is a rare, severe, monogenic subtype of migraine with aura (MA), characterised by at least some degree of weakness (hemiparesis) during the aura. Apart from the hemiparesis, the headache and aura features of FHM attacks are identical to those of attacks of the more common multifactorial types of migraine. The majority of FHM patients also experience attacks of "normal" MA and migraine without aura (MO). Thus, from a clinical point of view, FHM represents one side of the spectrum that at the other end is formed by the common forms of migraine. Therefore, FHM seems a valid model to study genetic factors of migraine in general.

### ***FHM1 (CACNA1A gene)***

The *CACNA1A* gene encodes the pore-forming  $\alpha_{1A}$  subunit of  $Ca_v2.1$  (P/Q-type) voltage-gated neuronal calcium channels that modulate release of neurotransmitters at peripheral and central synapses. Over fifty *CACNA1A* mutations have been associated with a wide range of clinical phenotypes including FHM - sometimes associated with ataxia or even fatal coma -, episodic ataxia type 2 (EA-2) and spinocerebellar ataxia type 6 (SCA6). The clinical spectrum also includes various types of epilepsy and mental retardation. Recently, new families with a *CACNA1A* mutation were reported (see [3] and [4] for details). A S218L mutation was found in a sporadic patient with minor head trauma induced hemiplegic migraine coma, confirming an earlier report on the role of this specific mutation in (fatal) coma after minor head trauma. A novel missense *CACNA1A* mutation (G533A) caused an EA-2-like phenotype responsive to acetazolamide but also to valproic acid. A novel *de novo* missense mutation caused non-fluctuating limb and trunk ataxia with an early age at onset. In 44 Danish FHM families that were identified through a population-based search only C1369Y is a potential novel *CACNA1A* gene mutation; as functional studies are currently lacking [5].

### ***FHM2 (ATP1A2 gene)***

The *ATP1A2* FHM2 gene encodes the  $\alpha_2$  subunit of  $\text{Na}^+, \text{K}^+$  pump ATPases. Sodium potassium pumps transport  $\text{Na}^+$  ions out of the cell while importing  $\text{K}^+$  ions.  $\text{Na}^+$  pumping provides the steep  $\text{Na}^+$  gradient essential for the transport of glutamate and  $\text{Ca}^{2+}$ . Thus ATPases modulate the re-uptake of potassium and glutamate from the synaptic cleft into glial cells. *ATP1A2* mutations have been associated with a range of clinical phenotypes of FHM with and without cerebellar ataxia, and also with basilar migraine and alternating hemiplegia of childhood. Many patients also suffer from epilepsy [6]. Recently, several novel *ATP1A2* mutations were reported (see [3] for details). Six mutations (R65W, V138A, R202Q, I286T, T415M, and R763C) were associated with pure FHM; that is without additional clinical features such as seizures or ataxia. Two additional *ATP1A2* mutations (V362E and P796S) were found in FHM families with psychiatric and mental problems. A novel FHM2 mutation R1002Q was identified in a young patient suffering from attacks of prolonged hemiplegia, mimicking a stroke. Mutation G900R was identified in a large Belgian FHM family with nine HM patients of whom four had severe atypical attacks associated with fever, meningism and coma [7]. Three of them also had epileptic seizures independent from their migraine attacks. Remarkably, two mutation carriers, including the proband, had seizures but no migraine. Co-occurring epilepsy has been reported before, particularly in FHM2 families [6]. In another FHM family, 19 out of 20 carriers of mutation D999H suffered from HM [8]. Five of the mutation carriers also had cerebellar signs (including subtle intention tremor and nystagmus). Seizures or febrile convulsions were reported in six of them; mental retardation was observed in one.

### ***FHM3 (SCNA1 gene)***

The *SCNA1* gene encodes the  $\alpha_1$  subunit of neuronal voltage-gated sodium ( $\text{Na}_v1.1$ ) channels that play an important role in the generation and propagation of action potentials. Over 100 mutations in this gene have been associated with epilepsy syndromes such as generalized epilepsy with febrile convulsions and severe myoclonus epilepsy of infancy [9]. Migraine has not been reported in these epilepsy syndromes. In 2005, a Q1489K mutation was identified in three German FHM families of common ancestry [10]. Recently, another *SCNA1* mutation (L1649Q) was found in a North-American FHM family [11] confirming the relationship between *SCNA1* and FHM3. However, mutation scanning of a large number of other FHM families suggests that the *SCNA1* gene is a rare cause of FHM [5]. Although not an FHM3 family, a novel *SCNA1* T1174S mutation was identified in small family of which the proband had myoclonus and an abnormal electroencephalogram and her mother had attacks of migraine without aura, vertigo and ataxia [12]. No functional tests were performed for this mutant.

### **Sporadic hemiplegic migraine**

In a systematic genetic analysis, all coding exons of the three FHM genes (*CACNA1A*, *ATP1A2* and *SCN1A*) were sequenced in 39 well-characterized pure SHM patients (i.e. without associated neurological features such as ataxia or epilepsy) [13]. One *CACNA1A* mutation (R583Q) and five novel *ATP1A2* mutations (E120A, E492K, P786L, R834X, and R908Q) were identified. From this study it is apparent that approximately 15% of SHM patients (i.e. six of 39) have a functional mutation in an FHM gene. Diagnostic testing of the *ATP1A2* gene offers the highest likelihood of success in sporadic HM patients. Because FHM gene mutations were also found in family members with non-hemiplegic typical migraine with and without aura, these findings reinforce the idea that FHM, SHM and “normal” migraine, at least in part, belong to a disease spectrum with shared pathogenetic mechanisms.

### **Candidate gene association studies in migraine**

A large number of candidate gene association studies in migraine were performed but many have significant limitations (i.e. small sample size and consequent low power to detect association, no correction for multiple testing, and/or no clear description of migraine subtypes). Because of this, most of the studies are of limited value [14]. Many recent studies aimed to replicate earlier association findings in for instance the dopamine and serotonin pathways, but with limited success. One study particularly worth mentioning is the first meta-analysis of genetic association studies of migraine and the C677T polymorphism in the 5,10-methylenetetrahydrofolate reductase (*MTHFR*) gene [15]. The *MTHFR* enzyme plays a role in maintaining homocysteine levels. By combining the data of *three* positive studies and *five* negative studies (in total 2170 MA patients), a significant association was still present for the C677T polymorphism. MA patients carrying the TT genotype showed a modest increased disease risk compared with CC genotype carriers. No association was observed for migraine in general (n=2951).

### **Genetic comorbidity of migraine**

Studying the genetics of diseases that are comorbid with migraine may provide valuable insights in molecular mechanisms involved in migraine. In the case of migraine and epilepsy, a genetically determined dysfunction of ion transporters seems to point at common underlying mechanisms for both paroxysmal disorders [6]. A genetic link between migraine and epilepsy was illustrated by a family with a phenotype of occipitotemporal lobe epilepsy and migraine with aura that was linked to a locus on chromosome 9q21-q22 [16].

### ***TREX1: A new migraine-associated gene***

Recently, the causal gene for autosomal dominant Retinal Vasculopathy with Cerebral Leukodystrophy (RVCL) was identified [17]. Mutations in *TREX1*, encoding the major mammalian

3'-5' DNA exonuclease, were found in nine RVCL families. RVCL is a neurovascular disorder characterised primarily by a progressive loss of vision secondary to retinal vasculopathy. In addition, a wide range of cerebral and systemic conditions, including cerebral infarcts and white matter lesions, vascular dementia, liver and kidney dysfunction can be noticed. Especially in a large Dutch RVCL family, migraine and Raynaud phenomenon – an abnormal vasomotor reaction in response to cold exposure - are prominent in the phenotype [18]. In a genetic, family-based, association study it was demonstrated that the RVCL locus confers an increased susceptibility for both Raynaud phenomenon and migraine [19]. Consequently, *TREX1* may be considered a susceptibility gene for migraine. There is prospect that by unravelling how *TREX1* mutations cause disease one can obtain insights in the pathophysiology of migraine as well. The exact functional consequences of *TREX1* mutations still need to be established. Evidence is rapidly accumulating that *TREX1* plays a major role in a wide spectrum of diseases; from neurovascular to autoimmune-related disorders. Two distinctive syndromes with partly overlapping clinical features are caused by mutations that disrupt the enzymatic exonuclease function of Trex1: Aicardi-Goutières Syndrome (AGS), an encephalopathy characterised by elevated interferon- $\alpha$  levels in cerebrospinal fluid mimicking congenital viral infection and Familial Chilblain Lupus (FCL) manifesting in early childhood with ulcerating acral skin lesions. In addition, heterozygous *TREX1* mutations were recently reported in a small proportion of patients with Systemic Lupus Erythematosus and Sjögren's syndrome; two autoimmune diseases that are characterised by the presence of *antinuclear* antibodies and the activation of interferon- $\alpha$ . It is tempting to speculate that Trex1 plays a role in innate immune response and the defence to for instance infections. For several complex neurological disorders (for instance AGS), viral infections that occur early in life are thought to play some kind of a role in the pathophysiology of disease. Also for migraine, systemic mechanisms (including a role for oxidative stress) have been suggested. Whether this is true and relevant to migraine pathophysiology needs to be addressed in the future.

## **Conclusion**

Investigation of FHM and migraine-associated syndromes remain important in migraine research. Many novel FHM2 mutations were identified in familial and sporadic HM patients. Confirmation was obtained that the *SCN1A* gene is the FHM3 gene. The discovery of genes in clinical phenotypes in which migraine is prominent (for instance CADASIL, or more recently RVCL) seems promising to unravel migraine-relevant molecular pathways. The *direct approach* to identify genetic risk factors in patients with the common forms of migraine, for instance by association studies, seems hampered by the complex nature of the disease.

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