Hum Genet (2009) 126:115–132
DOI 10.1007/s00439-009-0684-z

REVIEW ARTICLE

Molecular genetics of migraine

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Received: 19 March 2009 / Accepted: 7 May 2009 / Published online: 20 May 2009

Abstract Migraine is an episodic neurovascular disorder that is clinically divided into two main subtypes that are based on the absence or presence of an aura: migraine without aura (MO) and migraine with aura (MA). Current molecular genetic insight into the pathophysiology of migraine predominantly comes from studies of a rare monogenic subtype of migraine with aura called familial hemiplegic migraine (FHM). Three FHM genes have been identified, which all encode ion transporters, suggesting that disturbances in ion and neurotransmitter balances in the brain are responsible for this migraine type, and possibly the common forms of migraine. Cellular and animal models expressing FHM mutations hint toward neuronal hyperexcitability as the likely underlying disease mechanism. Additional molecular insight into the pathophysiology of migraine may come from other monogenic syndromes (for instance cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, which is caused by *NOTCH3* mutations), in which migraine is prominent. Investigating patients with common forms of migraine has had limited successes. Except for 5′,10′-methylenetetrahydrolate reductase, an enzyme in folate metabolism, the large majority of reported genetic associations with candidate migraine genes have not been convincingly replicated. Genetic linkage studies using migraine subtypes as an end diagnosis did not yield gene variants thus far. Clinical heterogeneity in migraine diagnosis may have hampered the identification of such variants. Therefore, the recent introduction of more refined methods of phenotyping, such as latent-class analysis and trait component analysis, may be certainly helpful. Combining the new phenotyping methods with genome-wide association studies may be a successful strategy toward identification of migraine susceptibility genes. Likely the identification of reliable biomarkers for migraine diagnosing will make these efforts even more successful.

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Introduction

Genetic studies in familial hemiplegic migraine (FHM), a monogenic subtype of migraine with aura, have yielded several migraine genes. Studies in the common forms of migraine have had limited success. This review will address how molecular insight coming from studies in FHM can help understand the pathophysiology of migraine. In addition, we will provide a detailed overview of the most relevant linkage and association studies in common migraine. Emphasis will be given to clinical and genetic heterogeneity in common migraine and alternative strategies how these problems can be tackled in future studies. We envisage that these novel strategies will yield gene variants for the common forms of migraine and will increase our insight into the molecular pathways and mechanisms involved in common migraine.

Migraine is an episodic neurovascular disorder that is diagnosed according to the criteria of the International Classification of Headache Disorders (ICHD-II) from the International Headache Society (IHS) (HCC 2004).

Migraine attacks are characterized by severe, often unilateral, pulsatile headache that can be accompanied by nausea, vomiting, photo- and/or phonophobia, and which last several hours to days (migraine without aura, MO) (Table 1). One-third of migraine patients experience transient (e.g., lasting between 20 and 60 min) neurological aura symptoms before the headache phase (migraine with aura, MA). The aura symptoms almost always include visual symptoms, but sensory- or speech-related symptoms can also be involved (Russell and Olesen 1996). Migraine is a very prevalent disorder that affects about 15% of the adult general population and is about three times more prevalent in females than in males (Stewart et al. 1994; Launer et al. 1999; Stovner et al. 2006). Migraine can be very disabling with 10% of migraine patients having weekly attacks. Consequently, the World Health Organization (WHO) rated severe migraine among the most disabling chronic disorders (Menken et al. 2000). Current acute and prophylactic treatments are not optimal as they are effective only in about half of the patients (Ramadan et al. 1997). A better understanding of disease pathophysiology is needed to identify novel targets for better intervention. The identification of migraine genes will help pinpointing such targets and molecular pathways in migraine.

Table 1 International Headache Society (IHS) criteria for migraine without aura (MO) and migraine with aura (MA) (Headache Classification Subcommittee of the International Headache Society (HCC) 2004)

Migraine without aura
A. At least five attacks fulfilling criteria B–D
B. Headache attacks lasting 4–72 h (untreated or unsuccessfully treated)
C. Headache has at least two of the following characteristics: 1. Unilateral location 2. Pulsating quality 3. Moderate or severe pain intensity 4. Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
D. During headache at least one of the following; 1. Nausea and/or vomiting 2. Photophobia and phonophobia
E. Not attributed to another disorder
Migraine with aura
A. At least two attacks fulfilling criteria B–D
B. Aura consisting of at least one of the following, but no motor weakness: 1. Fully reversible visual symptoms including positive features (e.g., flickering lights, spots, or lines) and/or negative features (i.e., loss of vision) 2. Fully reversible sensory symptoms including positive features (i.e., pins and needles) and/or negative features (i.e. numbness) 3. Fully reversible dysphasic speech disturbance
D. Headache fulfilling criteria B–D for migraine without aura begins during the aura or follows aura within 60 min
E. Not attributed to another disorder

Migraine pathophysiological mechanisms

Although it was previously thought that migraine either had a vascular or a neurogenic origin, the current view is that migraine has a neurovascular origin (for review see Goadsby 2007). Headache is not merely the consequence of painful vasodilatation, but is due to the activation of the trigeminovascular system (TGVS) that consists of meningeal and superficial cortical blood vessels that are innervated by the trigeminal nerve. The TGVS projects to the trigeminal nucleus caudalis in the brainstem, which in turn, projects into higher-order pain centers giving rise to the headache. It is well accepted that the migraine aura is not due to reactive vasoconstriction, but is neurally driven and most likely caused by the human equivalent of the cortical spreading depression (CSD) of Leao (Leao 1944; Lauritzen 1994). In experimental animals, CSD is characterized by a short-lasting, intense wave of neuronal and glial cell depolarization that spreads slowly over the cortex at a rate of approximately 2–5 mm/min and that is accompanied by massive fluxes of ions (Ca^{2+}, Na^{+}, and K^{+}) followed by a long-lasting inhibition of spontaneous and evoked neuronal activity (for review see Somjen 2002). The electrophysiological changes are associated with changes in cerebral blood flow (CBF). Initially there is a small, brief reduction in CBF followed by a profound increase of CBF lasting minutes, after which blood flow is reduced again for up to an hour. There is a considerable body of clinical evidence that CSD is the likely basis of the migraine aura. Visual aura symptoms in humans (Lashley 1941; Milner 1958; Russell et al. 1994) typically spread from the center of the visual field to the periphery with a propagation rate comparable to CSD evoked in experimental animals. Positive (e.g., scintillations, paresthesias) and negative (e.g., scotomata, paresis) phenomena of the migraine aura can be explained by the initial transient hyperexcitation front of CSD followed by neuronal depression. Most importantly, however, functional neuroimaging studies in humans using blood-oxygen level dependent (BOLD) signals have convincingly demonstrated that CBF changes that occur during a migraine aura are very similar to those observed in experimental animals during CSD (Hadjikhani et al. 2001). Additional support for the importance of CSD in migraine pathophysiology comes from a study by Ayata and coworkers who demonstrated that chronic, but not acute, treatment of rats with migraine prophylactic drugs of different pharmacological classes (e.g., β-adrenergic receptor blockers, tricyclic antidepressants, anticonvulsants and serotonergic drugs) that are effective in reducing the frequency and/or

intensity of migraine headaches in patients, dose-dependently suppressed CSD frequency by 40–80% and increased the threshold for inducing CSD (Ayata et al. 2006).

Animal studies have shown that CSD can activate the TGVS, and thus might trigger headache mechanisms (Bolay et al. 2002). However, the connection between CSD and headache in patients remains an open question (Blau 1992; Goadsby 2001). For instance, it would not explain how the headache phase is triggered in the majority of migraine patients that never experience an aura. Also, the fact that ketamine treatment can reduce aura symptoms but fails to prevent the headache (Kaube et al. 2000) would argue against a key role of CSD in triggering the headache. Although one can hypothesize that spreading depression may occur in migraine without aura patients in clinically silent subcortical areas of the brain without propagating to the visual cortex (Goadsby et al. 2002; Haerter et al. 2005), this has never been demonstrated.

Migraine is a genetic disorder

Migraine has a strong genetic component. Many patients have first-degree relatives who also suffer from migraine (Russell and Olesen 1993). Population-based family studies showed that the familial risk of migraine is increased (Russell and Olesen 1995; Stewart et al. 1997). First-degree relatives of probands with MO had an almost twofold increased risk to suffer from this disorder, but had only 1.4 times the risk of MA compared with the general population. Instead, first-degree relatives of probands with MA had a nearly fourfold increased risk for MA, but no increased risk for MO (Russell and Olesen 1995). Studies of mono- and di-zygotic twin pairs are the classical method to investigate the relative importance of genetic and environmental factors. Migraine concordance rates are between 1.5 and 2 times higher in monozygotic twins than in dizygotic twins for both MO and MA (Ulrich et al. 1999; Gervil et al. 1999), indicating that genetic factors are important in migraine susceptibility. A large population-based twin study comprising of some 30,000 twin pairs revealed that genetic and environmental factors had an almost equally large contribution (Mulder et al. 2003). Shared environmental factors seemed to play a minor role as shown by studies comparing twins that were raised together or apart (Ziegler et al. 1998; Svensson et al. 2003).

For genetic study designs, it is important whether MO and MA should be seen as different disease entities. Evidence from Danish studies that show no increased co-occurrence of MO and MA compared to the product of the prevalence of MO and MA in the general population (Russell and Olesen 1995; Russell et al. 1996) or in twins (Russell et al. 2002) supports this view. Others belief that MO and MA are different expressions of the same disease with pure MO to pure MA at both ends of the clinical spectrum (Kallela et al. 2001; Nyholt et al. 2004; Ligthart et al. 2006). Clinical observations support this view as both migraine types share identical headache symptoms and frequently co-occur in an individual. Future studies will have to show whether at least some migraine susceptibility genes are shared by both migraine types suggesting that there is a migraine continuum.

Hemiplegic migraine: a monogenic form of migraine with aura

Genetic studies in FHM: genes encode ion transporters

The most straightforward approach to identify genes and unravel pathways for complex genetic disorders is the study of monogenetic subtypes of the disease. An example of a monogenic subtype of migraine is familial hemiplegic migraine (FHM), a rare form of migraine with aura. FHM can be considered a model for the common forms of migraine because the headache and aura features, apart from the hemiparesis, are identical (Thomsen et al. 2002) and two-thirds of the FHM patients have, in addition to attacks of FHM, also attacks of common non-hemiplegic migraine (Ferrari et al. 2007).

Three genes have been identified studying families with FHM. The first FHM gene that was identified is *CACNA1A* (FHM1), which is located on chromosome 19p13 (Ophoff et al. 1996). *CACNA1A* encodes the α1 subunit of neuronal $Ca_V2.1$ (P/Q-type) voltage-gated calcium channels that are widely expressed throughout the central nervous system (CNS) (Westenbroek et al. 1995). All the 21 known FHM1 mutations (Fig. 1a) are missense mutations. FHM1 mutations are associated with a broad spectrum of clinical features besides hemiplegic migraine (Ducros et al. 2001). Cerebellar ataxia (Ducros et al. 1999; Battistini et al. 1999; Kors et al. 2003; Alonso et al. 2004; Stam et al. 2008a) and epilepsy, both during severe FHM attacks (Vahedi et al. 2000) or independent of FHM attacks (Kors et al. 2004; Beauvais et al. 2004), are not uncommon. The phenotype in for instance FHM1 S218L mutation carriers can be very severe, even lethal, after mild head trauma (Kors et al. 2001; Curtain et al. 2006; Chan et al. 2008). The second FHM gene, *ATP1A2* (FHM2), is located on chromosome 1q23 (De Fusco et al. 2003). It encodes the α2 subunit of sodium–potassium pumps. There are now over 30 FHM2 mutations (Fig. 1b) that, with a few exceptions, are all found in single families. Almost all FHM2 mutations are amino acid changes, but there are also small deletions (Riant et al. 2005) and a mutation affecting the stop codon

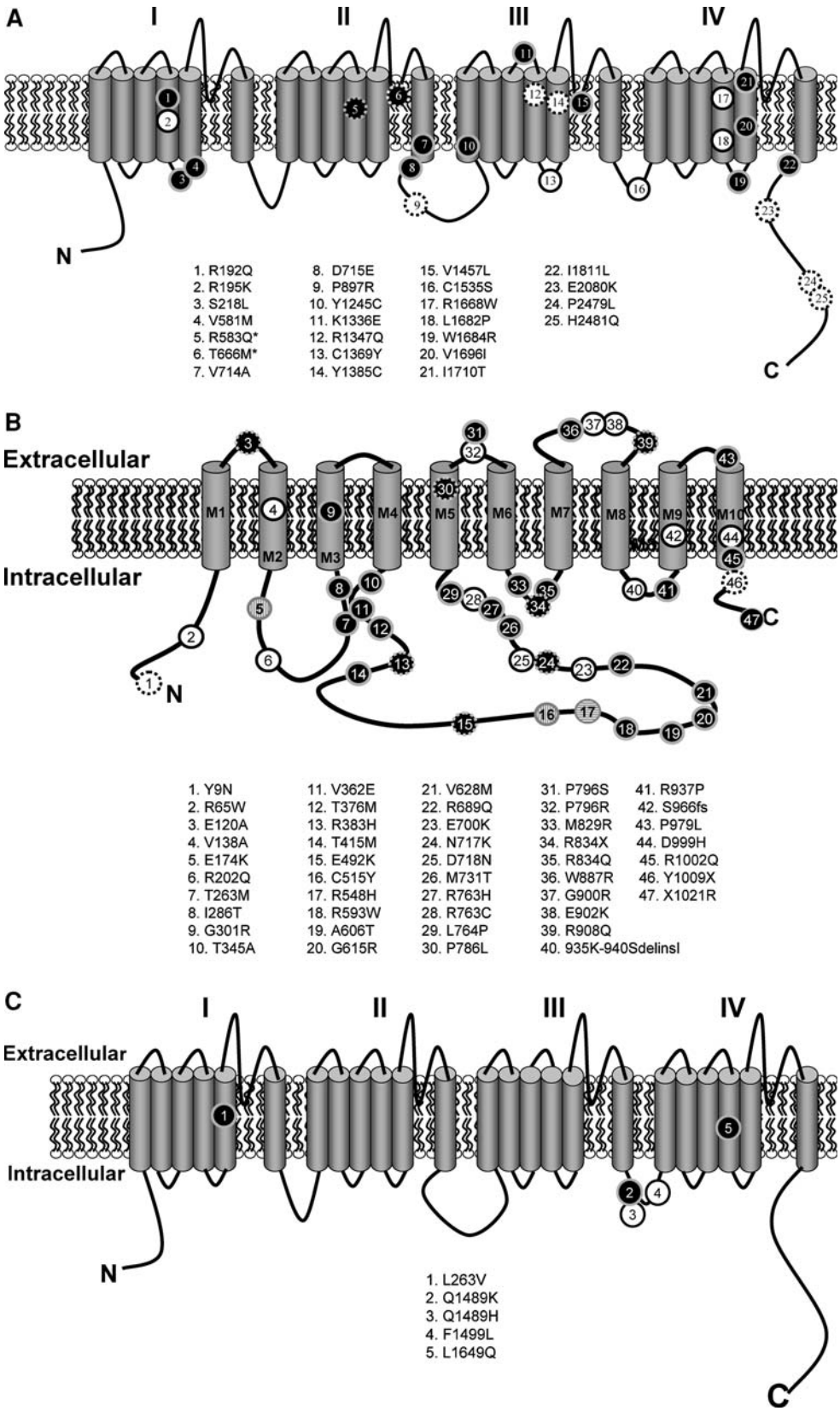

Fig. 1 Schematic representation of SHM and FHM mutations in FHM gene-encoded proteins. **a** Mutations in the α1A subunit of the voltage-gated $Ca_V2.1$ Ca^{2+} channel encoded by the FHM1 *CACNA1A* gene (Genbank Ac. nr. X99897). The protein is located in the plasma membrane and contains four repeated domains, each encompassing six transmembrane segments. **b** Mutations in the α2 subunit of the Na^+,K^+ ATPase encoded by the FHM2 *ATP1A2* gene (Genbank Ac. nr. NM_000702). The protein is located in the plasma membrane and contains ten transmembrane segments. **c** Mutations in the α1 subunit of the voltage-gated $Na_V1.1$ Na^+ channels encoded by the FHM3 *SCN1A* gene (Genbank Ac. nr. NM_006920). The protein is located in the plasma membrane and contains four repeated domains. Symbols: *Circle with solid line* FHM, *circle with dotted line* SHM, *circle with horizontal striped pattern* basilar-type migraine, *circle with vertical striped pattern* common migraine. *Asterisk* Mutation for which also SHM was reported, *black circles* mutation was tested for functional consequences, *white circle* mutation was not tested for functional consequences

causing an extension of the ATP1A2 protein by 27 amino acid residues (Jurkat-Rott et al. 2004). Most of the *ATP1A2* mutations are associated with pure FHM without additional clinical symptoms (De Fusco et al. 2003; Riant et al. 2005; Jurkat-Rott et al. 2004; Kaunisto et al. 2004; Pierelli et al. 2006). However, over the years, a number of FHM2

mutations (Fig. 1b) have been reported that are associated with FHM and cerebellar problems (Spadaro et al. 2004), childhood convulsions (BFIC) (Vanmolkot et al. 2003), epilepsy (Jurkat-Rott et al. 2004; Deprez et al. 2008), permanent mental retardation (Jurkat-Rott et al. 2004; Vanmolkot et al. 2006). Interestingly, certain *ATP1A2* mutations were shown to be associated with non-hemiplegic migraine phenotypes, such as basilar migraine (Ambrosini et al. 2005) and even common migraine (Todt et al. 2005), although causality has not been established for all mutations by functional testing. The most recently identified FHM gene is the *SCN1A* (FHM3) gene, which is located on chromosome 2q24 (Dichgans et al. 2005). *SCN1A* encodes the α1 subunit of neuronal $Na_V1.1$ voltage-gated sodium channels and is a well-known epilepsy gene with over 100 truncating and missense mutations that are associated with childhood epilepsy (i.e., severe myoclonic epilepsy of infancy (SMEI) or generalized epilepsy with febrile seizures (GEFS+)) (Meisler and Kearney 2005; Mulley et al. 2005). Only five FHM3 mutations (Fig. 1c) have been identified that all change amino acid residues (Dichgans et al. 2005; Vanmolkot et al. 2007a; Castro et al. 2009; Vahedi et al. 2009). Missense mutations Q1489K and L1649Q were identified in large families and are associated with pure FHM (Dichgans et al. 2005; Vanmolkot et al. 2007a). Notably, three out of five FHM carriers of the L263V mutation had generalized tonic–clonic epileptic attacks, occurring independently from their hemiplegic migraine attacks (Castro et al. 2009). Recently two novel FHM3 *SCN1A* mutations (i.e., Q1489H and F1499L) were reported (Vahedi et al. 2009). Four of five carriers of the FHM3 Q1489H mutation, in addition to having hemiplegic migraine, also suffered from 'elicited repetitive transient daily blindness' (ERDB) that was not associated with headache or other neurological symptoms (Le Fort et al. 2004). Moreover, both the proband and his daughter also suffered from childhood epilepsy. In the FHM3 family with the F1499L mutation, there was also a link with ERBD, but only in the proband.

The fact that not all FHM families are linked to one of the three known FHM loci implies that there are additional FHM genes. Recently, a novel FHM locus on chromosome 14q32 was proposed in a Spanish migraine family (Cuenca-León et al. 2009). However, genetic information of six FHM patients and seven patients with either MO or MA was combined to reach significant LOD scores. Therefore, future studies will have to show whether this locus contains a gene that can cause both FHM and common migraine.

Not all hemiplegic migraine patients are part of FHM families. The so-called sporadic hemiplegic migraine (SHM) patients do exist, and exhibit clinical symptoms that are similar to those of hemiplegic migraine patients (Thomsen et al. 2003). For instance, also SHM—like FHM—patients can have attacks of common migraine that are not associated with hemiparesis. Also the prevalence of familial and sporadic hemiplegic migraine in the population is similar; both are rare with a prevalence of approximately 0.01% (Thomsen and Olesen 2003). Several studies have tried to identify mutations in FHM genes in SHM patients (Terwindt et al. 2002; de Vries et al. 2007; Thomsen et al. 2008. Whereas about 15% of SHM patients in a Dutch clinic-based study had gene mutations (predominantly in the *ATP1A2* gene) (de Vries et al. 2007), hardly any mutations were identified in 100 patients from a Danish population-based study (Thomsen et al. 2008). SHM mutations are depicted in Fig. 1. Although mutations in known FHM genes have been identified in a proportion of SHM patients, and SHM thus, in part, belongs to the genetic migraine spectrum, other genetic factors likely play a role. Sporadic occurrence of disease can be explained by several genetic mechanisms; a de novo mutation, reduced penetrance of a hemiplegic migraine gene mutation, or an unfavorable combination of low-risk factors of common migraine gene variants that are present in a single patient.

There are no obvious clinical differences between mutation carriers of the three FHM genes, although patients with FHM1 mutations, more often exhibit cerebellar ataxia or trauma-triggered attacks (van den Maagdenberg et al. 2007; Ducros et al. 2001). Strikingly, for all three FHM genes, there are mutation carriers that have epilepsy (Haan et al. 2008). This is perhaps not so surprising given the epidemiological evidence that there is a bidirectional comorbidity of migraine and epilepsy (Ottman and Lipton 1994), suggesting that both disorders have, at least in part, a shared pathophysiology. The identification of gene mutations that can cause both FHM and epilepsy provides a unique opportunity to study these mechanisms.

Functional studies of FHM mutations

Functional consequences of FHM gene mutations have been studied in cellular and animal models. Not less than 12 FHM1 mutations have been tested in heterologous expression systems expressing recombinant $Ca_V2.1$ channels for their consequences on calcium channel functioning using whole cell or single channel electrophysiology (for review see Pietrobon 2007). At the single channel level, all eight investigated FHM1 mutations were shown to open at more negative voltages and have an enhanced channel open probability, compared to normal channels (Hans et al. 1999; Tottene et al. 2002, 2005). This gain-of-function effect results in increased Ca^{2+} influx, which would predict increased neurotransmission. At the whole cell level, however, neurons from $Ca_V2.1$-α1 knockout mice (Jun et al. 1999; Fletcher et al. 2001) transfected with either wildtype or mutant $Ca_V2.1$-α1 cDNA constructs, all seem to show a

loss-of-function effect (Hans et al. 1999; Tottene et al. 2002, 2005; Cao et al. 2004). Hippocampal neurons from $Ca_V2.1$-α1 knockout mice, that were transfected with wild-type or mutant $Ca_V2.1$-α1 cDNA constructs showed a reduced neurotransmitter release and a decreased contribution of P/Q-type channels in controlling neurotransmitter release (Cao et al. 2004). However, when mutant $Ca_V2.1$ channels are expressed at their normal level in their natural environment in knock-in mice that harbor the human FHM1 R192Q mutation that is associated with FHM in patients (Ophoff et al. 1996), electrophysiological analysis of cerebellar granule cells revealed a gain-of-function effect at the whole cell level. This is in line with gain-of-function effects observed at the single channel level in transfected neurons. The paradoxical loss-of-function effect on whole cell level in transfected cells is thought to be an artifact of overexpression (van den Maagdenberg et al. 2004), although others propose that a species differences (mice vs. humans) is the reason (Cao et al. 2004). Evoked and spontaneous neurotransmission was shown to be increased at the neuromuscular junction; a synapse in the peripheral nervous system where release of transmitter is predominantly determined by $Ca_V2.1$ calcium channels. Most relevant for migraine pathophysiology, in FHM1 R192Q mutant mice, the threshold for CSD was lowered and the propagation velocity for CSD was increased. These observations indicate that the FHM1 mutant mice are useful models to study the pathophysiology of migraine in vivo. Future studies have to reveal exactly how a lower activation threshold of mutated $Ca_V2.1$ Ca^{2+} channels can lead to an episodic disease. One may think that only when the stimulus is strong (for instance with repetitive firing) and the threshold is temporarily lowered (for instance by hormonal changes), hyperexcitability of neurons in a susceptible brain will lead to an attack. Decreased inhibition by G-protein modulation as exhibited by several FHM1 mutations (R192Q, S218L, Y1245C) (Melliti et al. 2003; Weiss et al. 2008; Serra et al. 2009) may contribute to this neuronal hyperactivity by promoting deinhibition. The complexity of $Ca_V2.1$ Ca^{2+} channel modulation is further demonstrated by the fact that the functionality of channels expressing certain FHM1 mutations (K1336E, W1684R, V1696I) can vary when combined with different auxillary β-subunits (Müllner et al. 2004). At this moment, it is still unclear to what extent such modulations play a role in disease pathophysiology.

The functional consequences of a large number of *ATP1A2* mutations causing either FHM or SHM have been investigated in various in vitro assays. Many were shown to be dysfunctional as they—unlike wildtype—were not (or only partially) able to rescue cell survival in assays in which endogenous sodium potassium pumps were inactivated by the drug ouabain (Koenderink et al. 2005). In these assays, wildtype or mutant α2 Na^+,K^+-ATPase cDNAs were insensitive to the ouabain challenge. Other studies investigated the consequences of *ATP1A2* mutations in more detail and revealed a wide variety of functional changes. FHM2 mutations G301R, T376M, L764P, W887R, led to non-functional proteins (Capendeguy and Horisberger 2004; Koenderink et al. 2005; Tavraz et al. 2008, 2009). Other FHM2 mutations resulted in sodium potassium pumps with partial activity with decreased (in the case of T345A and A606T) or increased (in the case of R689Q, M731T, R763H, and X1021R) affinity for potassium (Segall et al. 2004, 2005; Tavraz et al. 2008). For five FHM2 mutations (i.e., R383H, R689Q M731T, R763H, and R834Q) a reduced turn-over rate was identified. Since FHM2 mutations compromised pump function, *Atp1a2* knockout mice may serve as a good model for FHM. However, *Atp1a2* knockout mice that lack the α2-subunit have a very severe phenotype and die immediately after birth because of their inability to start breathing (Ikeda et al. 2003; James et al. 1999). Heterozygous mice are viable and exhibit enhanced fear and anxiety following conditioned fear stimuli (Ikeda et al. 2003). These mice have not been used as potential migraine mouse models.

Five FHM3 mutations have been identified so far (Dichgans et al. 2005; Vanmolkot et al. 2007a; Castro et al. 2009; Vahedi et al. 2009) and for three of them the functional consequences have been investigated. Early functional studies of the FHM3 Q1489K and L1649Q mutations used cardiac $Na_V1.5$ cDNA as the backbone for making mutant cDNAs and revealed various gain-of-function effects (Dichgans et al. 2005; Vanmolkot et al. 2007a). When expressed in the more appropriate $Na_V1.1$ protein, FHM3 mutations Q1489K and L1649Q revealed clear loss-of-function effects (Kahlig et al. 2008). The third FHM3 mutation L263V that in patients causes FHM and in the majority of carriers also generalized tonic–clonic epilepsy, essentially had gain-of-function effects (Kahlig et al. 2008). It was hypothesized that loss of sodium channel activity primarily disturbs the functioning of inhibitory neurons, where the $Na_V1.1$ are expressed normally (Ogiwara et al. 2007; Yu et al. 2006), whereas gain-of-activity has a predominant effect on excitatory neurons. From a recent in vitro study expressing FHM3 mutation Q1489K in cultured neurons, it is clear that the functional consequences of FHM3 mutations can be very complex. Depending on the test paradigm, the mutation had functional consequences fitting either hyperexcitability or hypoexcitability (self-limiting hyperexcitability capacity) (Cestele et al. 2008), but this has not been tested in for instance knock-in mice.

How do FHM mutations cause disease?

Can the molecular genetic findings of the three FHM genes (*CACNA1A*, *ATP1A2* and *SCN1A*) be integrated into one

common pathway? More specifically, can we link the functional consequences of the three genes to increased propensity for CSD (Moskowitz et al. 2004)? Mutant $Ca_V2.1$ calcium channels from FHM1 R192Q knock-in mice predict increased glutamate release in the cerebellar cortex and thereby can easier induce, maintain, and propagate CSD; this is in line with the observed decreased threshold for CSD in knock-in mice (van den Maagdenberg et al. 2004). FHM2 mutations in the sodium–potassium pump predict in vivo reduced glial uptake of K^+ and glutamate from the synaptic cleft. FHM3 mutations in the $Na_V1.1$ sodium channel predict in vivo hyperexcitability of excitatory neurons. Therefore, the predicted consequence for FHM1, FHM2, and FHM3 is that mutations seem to cause increased levels of glutamate and K^+ in the synaptic cleft and because both are facilitators of CSD, an increased propensity for CSD. The increased propensity for CSD could well explain the aura. As discussed earlier, it remains to be established whether this also would result in a more readily activated TGVS and thereby the headache.

Is it possible to translate genetic results from FHM to common migraine?

As the main clinical symptoms of headache and aura are similar in FHM and common migraine, it is thought that they may share a common pathophysiology (Ferrari et al. 2007). Several studies have investigated the role of FHM1 and FHM2 loci in the common forms of migraine. These studies led to conflicting results with some evidence in favor of the hypothesis (May et al. 1995; Nyholt et al. 1998; Terwindt et al. 2001; Todt et al. 2005), while others find no evidence for their involvement in common migraine (Hovatta et al. 1994; Jones et al. 2001; Jen et al. 2004). Some of the studies hypothesized that mutations found in FHM may cause common migraine, while it is more likely that 'milder', less penetrant, DNA variants are involved. A recent comprehensive study, including some 2,800 migraine patients from various European countries, tested whether common DNA variants in ion transport genes are involved in common migraine (Nyholt et al. 2008). Over 5,000 SNPs in 155 ion transport genes (including the 3 FHM genes) were studied, but none of the original significant SNPs (66 SNPs in 12 genes) was significant across all four replication cohorts. From this study it seems that common variants in ion transport genes do not play a major role in susceptibility for common migraine. Rarer variants or variants with a smaller effect size would not have been detected with this study design.

Other strategies for the genetic dissection of migraine?

In addition to investigating patients with rare monogenic FHM, what other options do we have to find gene variants for migraine? Several strategies have been tried. First of all, migraine can be part of other monogenic disorders. Identification of genes for these disorders possibly shed light on why migraine co-occurs in mutation carriers. Other strategies in common forms of migraine are candidate gene association studies and linkage approaches (Fig. 2). The various strategies and the results that came from them are discussed below.

Monogenetic syndromes associated with migraine

Migraine can be part of the clinical spectrum of certain monogenetic disorders. Perhaps the clearest example of migraine associated with a monogenic disease is cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) (Stam et al. 2008b). CADASIL is caused by mutations in the *NOTCH3* gene, which encodes the Notch3 receptor that plays a key role

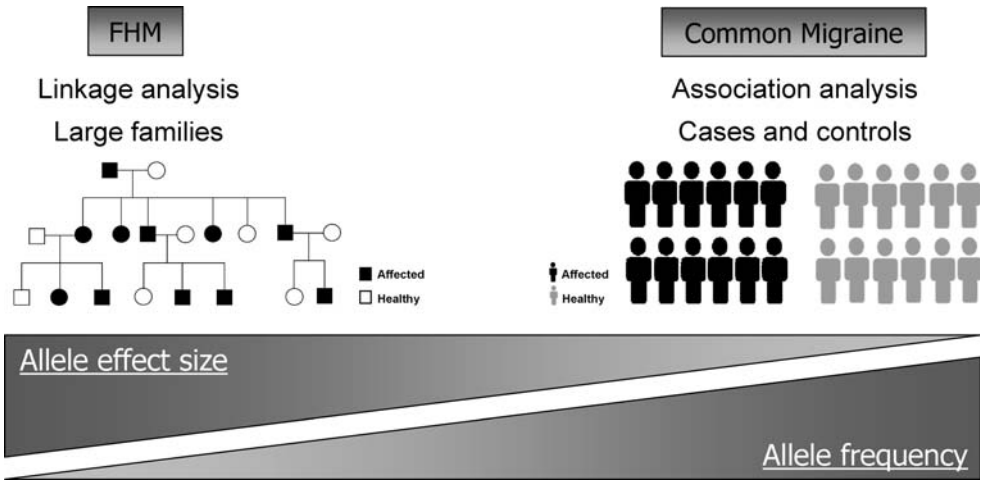

Fig. 2 Successful strategies for identification of genes in monogenic and complex forms of migraine. The linkage approach yielded genes in FHM that have a high effect size and a low population allele frequency, whereas candidate gene association studies tested potential migraine gene variants with a low effect size and relatively high allele frequencies in the population

vascular smooth muscle cell function in small arteries and arterioles of the brain (Joutel et al. 1996). Up to one-third of CADASIL patients suffer from migraine with aura, where migraine often is the presenting clinical symptom (Dichgans et al. 1998). The link with MA and not the more frequent MO, suggests that increased susceptibility for CSD is somehow caused by *NOTCH3* mutations, but this has not been investigated yet. A second example is retinal vasculopathy with cerebral leukodystrophy (RVCL), which is caused by mutations in the *TREX1* gene that encodes the major 3′–5′ DNA exonuclease TREX1 (Richards et al. 2007). RVCL is primarily characterized by progressive blindness due to vascular retinopathy and can be associated with a wide range of systemic and cerebral symptoms, including cerebral infarcts and white matter hyperintensities, vascular dementia, liver and kidney dysfunction, Raynaud's phenomenon, and migraine. Particularly in a Dutch RVCL family, migraine and Raynaud's phenomenon is very prominent (Terwindt et al. 1998). Comorbidity of migraine with CADASIL and RVCL indicates that cerebral or meningeal vasculopathy and vascular dysfunction may play a role in migraine (Vanmolkot et al. 2008). The vascular role in migraine was also shown by altered functional arterial properties and abnormal endothelial progenitor cells in migraine patients (Vanmolkot et al. 2007b; Lee et al. 2008). Future research is needed to reveal the possible role of *NOTCH3* and *TREX1* in migraine.

Linkage studies in common migraine

Another major genetic strategy to identify migraine susceptibility genes is classical linkage analysis, which aims to find chromosomal loci using a family-based approach. Over the years, a number of chromosomal loci (Table 2) have been identified using either migraine without or with aura patients diagnosed according criteria of the International Classification of Headache Disorders (ICHD-II) (HCC 2004). Except for a few loci, replication successes have been scarce. A promising migraine susceptibility locus resides on chromosome 4. A linkage study of 50 Finnish MA families revealed a locus on chromosome 4q24 (Wessman et al. 2002). Subsequently, an Icelandic study identified a locus on chromosome 4q21, but using MO patients (Bjornsson et al. 2003). The Finnish and Icelandic migraine loci overlap and it is unclear whether they harbor different genes for MA and MO, or one gene that causes both migraine types. For none of the reported chromosomal loci, the causative gene variant has been identified. There are several possible explanations for this rather disappointing outcome. Probably, due to the high prevalence of migraine, it has been difficult to ascertain "clean" pedigrees for linkage where migraine genes from spouses do not interfere. However, it is well conceivable that a major reason for the lack of success is the way migraine patients are diagnosed. Diagnosis of migraine is mainly based on questionnaires and (sometimes) interviewing the patients. A more objective method of diagnosing patients, such as a biochemical test in blood is not available. It may well be that some of the published migraine susceptibility loci in fact are false positive findings.

Diagnostic issues; from endpoint to trait classifications

The ICHD criteria resulting in an end diagnosis of migraine with or without aura are well suited for clinical practice (that is to diagnose the attacks that patients have), but may not be very useful for genetic research. Why is that? The IHS diagnosis consists of a number of traits (e.g., the presence of pulsating quality of the headache, nausea, vomiting) that can occur in patients in different combinations and

Table 2 Summary of relevant linkage results performed for migraine using the International Headache Classification (IHS) classification guidelines

Chromosomal locus	Phenotype	Genotyping method	References
1q31	MA, MA/MO[a]	Regional microsatellite markers	Lea et al. 2002
4q21	MO	Genome-wide scan	Bjornsson et al. 2003
4q24	MA	Genome-wide scan	Wessman et al. 2002
6p12.2-p21.1	MA/MO	Genome-wide scan	Carlsson et al. 2002
10q22-q23	MA	Genome-wide scan	Anttila et al. 2008
11q24	MA	Genome-wide scan	Cader et al. 2003
14q21.2-q22.3	MO	Genome-wide scan	Soragna et al. 2003
15q11-q13	MA	Regional microsatellite markers	Russo et al. 2005
19p13	MA	Regional microsatellite markers	Jones et al. 2001
Xq25-q28	MA/MO	Regional microsatellite markers	Nyholt et al. 1998, 2000

MO Migraine without aura, *MA* migraine without aura

[a] Only suggestive linkage for MA/MO combined

it is the combination of these traits that is used to diagnose a patient with migraine with or without aura (although patients can also have both types of attacks). Consequently, an end diagnosis inevitably carries a lot of underlying heterogeneity, thereby complicating genetic research. However, knowledge of the traits in individual patients provides possibilities for new avenues of intermediary or endophenotyping, which can increase the power of the genetic analyses. Interestingly, for several other complex disorders such as attention-deficit/hyperactivity disorder (ADHD) and schizophrenia, it was shown that the heritability of the individual traits is higher than of the syndrome as a whole (i.e., combination of traits) (Rommelse et al. 2008; Tuulio-Henriksson et al. 2002). Recently, researchers investigating migraine genetics have adopted two alternative approaches that are based on the individual traits: "trait component analysis (TCA)" and "latent class analysis (LCA)". Whereas TCA is a rather straightforward analysis of the individual traits, LCA is a complex statistical empirical clustering approach based on factor analysis that combines the information of several migraine symptoms. In principle, TCA and to a certain degree LCA, reflects the underlying processes in migraine pathophysiology as they utilize the questionnaire-based information in a more optimal manner, compared to the dichotomous IHS end diagnosis (Anttila et al. 2008). It can be expected that by using TCA, the clinical heterogeneity will be reduced, since traits better reflect the biological pathways that are influenced by specific genetic variations.

Recent linkage studies in migraine using alternative phenotyping methods

Nyholt and colleagues were the first to use LCA, to identify subgroups of migraine patients (Nyholt et al. 2004, 2005). In their studies, patient subgrouping was based on the presence and clustering of individual migraine symptoms. This resulted in four classes of (1) asymptomatic individuals (CL0), (2) patients with a mild form of recurrent non-migrainous headache (CL1), (3) patients with a moderately severe form of migraine, often without visual aura (CL2), and (4) patients with a severe form of migraine, often with aura (CL3). This classification reflects disease severity and does not specifically separate MO from MA. The LCA strategy seems to provide support for migraine as a continuum caused by multiple factors contributing to migraine severity and susceptibility, and not so much separate migraine with and without aura. Although more individuals are labeled affected using the LCA approach, compared to traditional IHS classification, all individuals considered affected by the IHS criteria are also considered affected in the LCA classification.

The LCA approach yielded a novel migraine susceptibility locus on chromosome 5q21 (Table 3) (Nyholt et al. 2005). Subsequent trait analyses revealed that the 5q21 locus is associated predominantly with pulsating headache. Some evidence for linkage was reported for other chromosomes with certain migraine symptoms, but none passed the threshold for multiple testing. Another Australian study recently reported linkage for the LCA severe phenotype (CL3) to a locus on chromosome 18p11. The strength of the LCA approach, according to this study, was shown by the fact that using traditional IHS criteria, no linkage was found (Lea et al. 2005). A similar conclusion about LCAs potential to detect loci, came from a Dutch study that reported suggestive linkage to a locus on chromosome 10 (Lighthart et al. 2008).

Trait components analysis in migraine was introduced by Palotie and colleagues (Anttila et al. 2006), who later compared TCA with LCA and classical clinical end diagnoses (Anttila et al. 2008). The most prominent result of their studies was a highly significant LOD score to a locus on chromosome 10q22-q23 with the TCA unilaterality phenotype (Table 3). The same locus was identified with five other TCA phenotypes, the IHS MA end diagnosis, and the LCA migrainous headache class. This locus showed robust replication in an independent Australian sample (but only for the TCA pulsation trait) and in the Dutch study that was

Table 3 Summary of linkage results performed for migraine grouped for phenotyping methods latent class analysis (LCA) and trait components analysis (TCA)

Chromosomal locus	Phenotypic trait (analysis method)[a]	References
4q24	Age at onset, photophobia, phonophobia, photo- and phonophobia, pain intensity, unilaterality, pulsation (TCA)	Anttila et al. 2006
5q21	Pulsation (LCA)	Nyholt et al. 2005
10q22-q23	Migrainous headache (LCA)	Anttila et al. 2008
10q22-q23	Unilaterality, pain intensity, phonophobia, pulsation, photophobia, nausea/vomiting (TCA)	Anttila et al. 2008
17p13	Pulsation (TCA)	Anttila et al. 2006

IHS International Headache Society, *LCA* latent class analysis, *TCA* trait component analysis

[a] Order based on level of significance (most significant trait mentioned first)

Table 4 Summary of association studies performed for migraine that contained at least 275 cases and controls

Gene	DNA variant[a]	Cases (*n*)[b] Migraine (MA/MO)	Controls (*n*)	Associated allele with phenotype (*P* value)[c]	Remarks	References
5′,10′-Methylenetetrahydrofolate reductase (*MTHFR*)						
MTHFR	c.677C>T (C677T)	652 (465/187)	320	677T: NS ($P = 0.017$/–)	Combined single cases and families, *P* values based on initial cohort of 270 migraine cases and 270 controls, replication provided	Lea et al. 2004
MTHFR	c.677C>T (C677T)	413 (187/226)	1,212	677T: – ($P < 0.006$/NS)		Scher et al. 2006
MTHFR	c.677C>T (C677T)	898 (898/–)	900	677T: – (NS/–)		Kaunisto et al. 2006
MTHFR	c.677C>T (C677T)	2,961 (2,170/791)	3,844	677T: NS ($P = 0.0005$/NS)	Meta-analysis	Rubino et al. 2007
MTHFR	c.677C>T	4,577 (1,275/1951)	20,424	677T: $P = 0.03$ ($P = 0.02$/NS)	Protective effect of 677T	Schürks et al. 2008
Dopaminergic system; catechol-O-methyltransferase (*COMT*), dopamine β-hydroxylase (*DBH*), dopamine transporter (*DAT1*)						
COMT	c.472A>G (Val158Met)	305	1,468	NS		Hagen et al. 2006
DBH	−1021C>T	830 (588/242)	500	−1021T: $P = 0.004$ ($P = 0.011$/NS)	*P* values based on initial cohort of 275 migraine cases and 275 controls, replication provided, protective effect of T-allele	Fernandez et al. 2009
	+1603C>T			NS (NS/NS)		
DBH	c.1434 + 1579A>G (rs2097629; intron 9)	650 (650/–)	650	c.1434 + 1579G: – ($P = 0.01$/–)	Two-step design (haplotype-tagging), 35 SNPs tested in dopamine pathway, corrected *P* values based on total cohort	Todt et al. 2009
DRD2	c.-32+16024T>:G (rs7131056; intron 1)			c.-32 + 16024T – ($P = 0.006$/–)		
SLC6A3	c.1840-204G>A (rs40184; intron 14)			c.1840-204A: – ($P = 0.03$/–)		
SLC6A3	VNTR in intron 8	550 (401/149)	550	NS (NS/NS)	*SLC6A3* is also known as DAT1	McCallum et al. 2007
Serotonergic system						
HTR2C	c.69G>C (Cys23Ser)	275	275	NS		Johnson et al. 2003
	c.2831T>G (T2831G)			NS		
HTR2C	c.69G>C (Cys23Ser)	335 (184/151)	335	NS (NS/NS)		Oterino et al. 2007
HTR2C	c.69G>C (Cys23Ser)	561 (561/–)	1,235	NS (NS/–)	Meta-analysis	Oterino et al. 2007
Gamma-aminobutyric acid type A (GABA-A) receptor system; GABA-A receptor α5 (*GABRA5*), β3(*GABRB3*), receptor ε (*GABRE*), γ3 (*GABRG3*), receptor θ (*GABRQ*) subunits						
GABRA5	Multiple variants tested	898 (898/–)	900	– (NS/–)	34 SNPs in region 15q11-q13 (haplotype-tagging)	Oswell et al. 2008
GABRB3	Multiple variants tested			– (NS/–)		
GABRG3	Multiple variants tested			– (NS/–)		
GABRA5	Multiple variants tested	649 (649/–)	652	– (NS/–)	56 SNPs tested in region 15q11-q12 (haplotype-tagging), *P* values for two cohorts	Netzer et al. 2008b
GABRB3	Multiple variants tested			– (NS/–)		
GABRG3	Multiple variants tested			– (NS/–)		
GABRE	Multiple variants tested	384 (254/130)	275	NS (NS/NS)	3 SNPs tested in *GABRE*	Fernandez et al. 2008
GABRQ	c.1432T>A (I478F)			NS (NS/NS)		
Hormone receptor system; estrogen receptor 1 and 2 (*ESR1* and *ESR2*), follicle stimulating hormone receptor (*FSHR*), androgen receptor (*AR*), CYP19 aromatase polypeptide A1 (*CYP19A1*), nuclear receptor-interacting protein 1 (NRIP1), progesterone receptor (*PGR*)						
ESR1	c.594G>A (G594A)	484 (360/124)	484	594A: $P = 0.003$ ($P = 0.01$/$P = 0.02$)	Two cohorts combined, *P* values based on initial cohort of 224 migraine cases and 224 controls	Colson et al. 2004
ESR1	c.2014G>A (G2014A)	898 (898/–)	900	– (NS/–)		Kaunisto et al. 2006
ESR1	c.325G>C (G325C)	356 (198/158)	374	325C: $P = 0.03$ ($P = 0.045$/NS)		Oterino et al. 2008
ESR2	c.2100A>G (A2100G)			2100A: NS ($P = 0.03$/NS)		

Table 4 continued

Gene	DNA variant[a]	Cases (*n*)[b] Migraine (MA/MO)	Controls (*n*)	Associated allele with phenotype (*P* value)[c]	Remarks	References
FSHR	c.2039G>A (Ser680Asn)			2039G: NS (p = 0.01/NS)		
CYP19A1	c.1672C>T (C1672T)			NS (NS/NS)		
NRIP1	c.225G>A (Gly75Gly)			NS (NS/NS)		
AR	CAG repeat in exon 1	509 (371/138)	454	NS (NS/NS)	*P* values based on initial cohort of 275 migraine cases and 275 controls; PROGINS was replicated	Colson et al. 2005
PGR	PROGINS ins in intron 7			PROGINS ins: *P* = 0.02 (NS/*P* = 0.008)		
Inflammation related genes; tumor necrosis factor-α and -β (*TNFA* and *TNFB*) and lymphotoxin α (*LTA*)						
TNFA	c.308G>A (G308A)	299 (38/261)	306	308G: *P* < 0.001 (NS/*P* < 0.001)		Rainero et al. 2004
TNFA	Multiple variants tested	439 (65/327)	382	NS	15 SNPs were tested	Lee et al. 2007
LTA	−294T>C (rs2844482; promoter)			−294C: *P* = 0.0002 (*P* = 0.006/*P* = 0.0008)		
TNFA	c.308G>A (G308A)	299 (–/299)	278	– (–/NS)		Asuni et al. 2009
TNFB	c.252G>A (G252A)			252A: – (–/*P* = 0.018)		
Insulin receptor gene (*INSR*)						
INSR	c.2946-713C>A (SNP84; intron 15)	827 (377/450)	765	c.2946-713A: NS (*P* = 0.002/NS)	48 SNPs tested in region 19p13, SNP84: rs2860172, SNP90: rs2860174, SNP274: rs1799817/His1085His, *P* values based on 331 migraine cases and 466 controls	McCarthy et al. 2001
	c.2842 + 1451T>A (SNP90; intron 14)			c.2842 + 1451A: NS (*P* = 0.007/NS)		
	c.3255C>T (SNP274)			c.3255T: NS (*P* = 0.008/NS)		
INSR	c.2842 + 1451T>A (rs2860174; intron 14)	1,278 (1,278/–)	1337	c.2842 + 1451T: – (*P* = 0.005/–)	Two-step design (haplotype-tagging), 35 SNPs tested in region 19p13, *P* values based on total cohort	Netzer et al. 2008a
Angiotensin converting enzyme (ACE), angiotensin receptor 1 (*AGTR1*) and angiotensin (*AGT*)						
ACE	Ins/del (rs1799752; intron 15)	342 (187/155)	403	NS (NS/NS)		Tronvik et al. 2008
ACE	Ins/del (rs1799752; intron 15)	3,226 (1,275/1951)	20,423	NS (NS/NS)		Schürks et al. 2009a
AGTR1	c.1166A>C (A166C)	3,226 (1,275/1,951)	20,423	NS (NS/NS)		Schürks et al. 2009b
AGT	c.803T>C (Met235Thr)			NS (NS/NS)		
Association studies with other genes						
NOS3	c.-51-898G>A (rs1800779; intron 1)	337 (188/149)	341	NS (NS/NS)	*NOS3* encodes for endothelial nitric oxide synthase	Toriello et al. 2008
	c.894T>G (rs1799983)			NS (NS/NS)		
Ion transporter genes	Multiple variants tested	3676	3624	NS (NS/NS)	>5,000 SNPs (haplotype-tagging) in 155 ion transporter genes tested in initial cohort; replication cohorts included	Nyholt et al. 2008

MA Migraine with aura, *MA* migraine without migraine, *NS* not significant, – not tested/not available, *SNP* single nucleotide polymorphism, *Ins* insertion, *Del* deletion, *VNTR* variable number of tandem repeats

[a] Nomenclature of DNA variant in the original study; for intronic DNA variants, the respective intron number is indicated

[b] Number of cases

[c] *P* values are given for all migraine cases combined or, when specified between brackets, for migraine with aura cases only and/or migraine without aura cases only

mentioned earlier (Lighthart et al. 2008). Although TCA and LCA yielded a novel migraine susceptibility locus, these new phenotyping methods still need to show whether they will lead to identification of gene variants. Although, the field will certainly welcome the identification of variants for TCA traits, it remains to be determined how a gene variant that is associated with a specific trait such as nausea will increase our insight into migraine pathophysiology and/or patient's diagnosis.

Association studies: candidate genes and genome-wide approaches

Another commonly used strategy to identify gene variants in complex genetic disorders are case–control association studies. These studies test for significant differences in allele frequencies between cases and controls. Many candidate gene association studies have been performed; mainly of genes involved in the serotonin and dopamine pathways—but also in other genes with an already suspected function in migraine pathophysiology—have been studied (Table 4). Unfortunately, the majority of the associations could not be replicated, suggesting that many of the original findings may represent false positive findings. There are several reasons for the inconsistencies among which, small sample sizes, not taking into account LD blocks when choosing polymorphisms, inadequate correction for multiple testing, and phenotyping issues. Clearly more systematic approaches are needed to assess whether candidate genes are indeed involved in migraine. To give an example, it is surprising that despite the strong evidence from neuroanatomical, pharmacological, clinical studies that the dopamine system is involved in the etiology of migraine (for review see Akerman and Goadsby 2007), most of the association studies investigating genes in this pathway were negative and positive results could often not be replicated. A more optimal design was used in a recent German study systematically investigating genes of the dopamine system (Todt et al. 2009). Using a two-step design, testing 50 polymorphisms in that were selected using a haplotype-based strategy in an adequately sized sample identified several associated polymorphisms in the dopamine β-hydroxylase, dopamine D2 receptor and dopamine transporter genes.

The best example of a genetic association with migraine is the 5′,10′-methylenetetrahydrofolate reductase (*MTHFR*) gene. MTHFR is a key enzyme in folate and homocysteine metabolism (Goyette et al. 1994). Most studies found an association of the T-allele of the *MTHFR* C677T polymorphism with migraine (Kowa et al. 2000; Kara et al. 2003; Lea et al. 2004; Oterino et al. 2004, 2005; Scher et al. 2006), although negative findings have been reported as well (Todt et al. 2006; Kaunisto et al. 2006). A recent meta-analysis of over 2,000 migraine patients revealed that the T-allele that results in moderately increased levels of homocysteine, was not associated with migraine overall, but only with MA (Rubino et al. 2007). Increased homocysteine levels may cause migraine through a vascular endothelium dysfunction effect, but evidence for this hypothesis is still lacking.

Genome-wide association

Only very recently, genotyping techniques and platforms have greatly improved making massive genotyping in large patient cohorts feasible. For many complex disorders, genome-wide association studies (GWAS) have led to successes, where linkage and candidate gene-based associations fell short (Aulchenko et al. 2008; van Es et al. 2008). The unbiased way of testing for the involvement of common variants throughout the genome in GWAS turned out more powerful than testing variants in candidate gene association studies. Large study populations (ideally well over a thousand cases and controls are used, although recent studies use even much larger samples) are needed to have sufficient power to detect genetic effects after correction for multiple testing. A critical factor for GWAS is the quality of phenotyping the cases and, depending on the design, the controls. No GWAS results have been reported for migraine, but several studies are currently being performed. Important lessons from recent GWAS are that, with few exceptions, identified variants have a low relative risk (RR) (that is well below 2) and contribute little to the overall genetic load. One may ask whether it is worthwhile to invest in the identification of risk factors with a RR of around 1.1, as this require huge sample sizes and will in all likelihood provide only a marginal contribution to the population attributable risk. Other factors such as epistasis and copy number variation have to be included in forthcoming study designs. Furthermore, it cannot be excluded that much of the genetic load is carried by a large number of allelic variants that may have a high RR and a (very) low allele frequency. This genetic variation is usually not captured in GWAS, but requires large-scale deep sequencing approaches. Fortunately, the appropriate technology is now emerging. Although the clinical predictive value of low-risk factors will be limited, it is important to obtain novel insights into the pathology of disease. The next few years will have to show what this new technology can bring for migraine.

Some thoughts on epigenetic and trigger mechanisms in genetic research

One possibility that has not gained much attention is that epigenetic mechanisms may play a role in migraine

pathophysiology. Epigenetics is defined by (meiotic and mitotic) modifications in gene expression, due to methylation of cytosines in specific CpG dinucleotides and histone modifications that are heritable but are not encoded in the DNA sequence. These modifications decrease (or increase) gene expression and thus influence molecular pathways (Jirtle and Skinner 2007). Epigenetic effects occur in early development but may change over lifetime, by lifestyle and diet, and it has been suggested that changes for instance in development of the individual or triggers such has stress determine the 'epigenetic outcome' and thus may affect migraine susceptibility (Montagna 2008). It would be interesting to subgroup migraine patients for genetic and/or epigenetic studies according to their self-reported triggers. A complicating factor, however, may be that often-mentioned triggers such as stress, hormonal changes, sleeping and eating habits, are not very reliable and not well understood (Lambert and Zagami 2008). For instance, although stress-sensitive patients reported an increase in perceived stress in the days before an attack, this was not accompanied by objective signs indicating a biological stress response (such as morning or evening cortisol levels) (Schoonman et al. 2007).

Opportunities for biomarkers in genetic research

As mentioned earlier, an important drawback for genetic migraine research is the lack of biomarkers. No objective, reliable, quantitative measurements are available for diagnosis. This should trigger research initiatives to identify such markers in migraine patients using cerebrospinal fluid, blood, urine, and/or imaging (Loder and Rizzoli 2006). Biomarkers will help defining more homogeneous groups of patients for genetic studies. The identification of biomarkers may also be of direct use in patient care, as they may help monitoring drug response, disease prognosis, and/or disease progression.

Conclusion/summary

The identification of genetic factors conferring migraine susceptibility will be important for our understanding of pathophysiological disease mechanisms. Studies in FHM, a rare Mendelian form of migraine with aura, yielded three genes, which all play a role in controlling ion and neurotransmitter levels in the brain. Functional studies of gene mutations in various cellular and animal models point toward neuronal hyperexcitability as an important disease mechanism. No convincing evidence has been obtained that the same genes play a major role in the common forms of migraine, although there is convincing evidence that disturbed ion balances and neurotransmitter pathways play a role. Until now, genetic studies investigating the common forms of migraine were largely unsuccessful. However, the use of alternative phenotyping methods (i.e., LCA and TCA) and large-scale GWAS approaches hold all the promises that migraine susceptibility genes will be identified soon.

Acknowledgments This work was supported by grants of the Netherlands Organization for Scientific Research (NWO) (903-52-291, M.D.F, R.R.F., and Vici 918.56.602, M.D.F), the EU "EUROHEAD" grant (LSHM-CT-2004-504837; M.D.F, R.R.F, A.M.J.M.v.d.M), and the Centre for Medical System Biology (CMSB) established by the Netherlands Genomics Initiative/Netherlands Organisation for Scientific Research (NGI/NWO).

References

Akerman S, Goadsby PJ (2007) Dopamine and migraine: biology and clinical implications. Cephalalgia 27:1308–1314

Alonso I, Barros J, Tuna A, Seixas A, Coutinho P, Sequeiros J, Silveira I (2004) A novel R1347Q mutation in the predicted voltage sensor segment of the P/Q-type calcium-channel alpha-subunit in a family with progressive cerebellar ataxia and hemiplegic migraine. Clin Genet 65:70–72

Ambrosini A, D'Onofrio M, Grieco GS, Di Mambro A, Montagna G, Fortini D, Nicoletti F, Nappi G, Sances G, Schoenen J, Buzzi MG, Santorelli FM, Pierelli F (2005) Familial basilar migraine associated with a new mutation in the *ATP1A2* gene. Neurology 65:1826–1828

Anttila V, Kallela M, Oswell G, Kaunisto MA, Nyholt DR, Hamalainen E, Havanka H, Ilmavirta M, Terwilliger J, Sobel E, Peltonen L, Kaprio J, Farkkila M, Wessman M, Palotie A (2006) Trait components provide tools to dissect the genetic susceptibility of migraine. Am J Hum Genet 79:85–99

Anttila V, Nyholt DR, Kallela M, Artto V, Vepsäläinen S, Jakkula E, Wennerström A, Tikka-Kleemola P, Kaunisto MA, Hämäläinen E, Widén E, Terwilliger J, Merikangas K, Montgomery GW, Martin NG, Daly M, Kaprio J, Peltonen L, Färkkilä M, Wessman M, Palotie A (2008) Consistently replicating locus linked to migraine on 10q22-q23. Am J Hum Genet 82:1–13

Asuni C, Stochino ME, Cherchi A, Manchia M, Congiu D, Manconi F, Squassina A, Piccardi MP, Del Zompo M (2009) Migraine and tumour necrosis factor gene polymorphism. An association study in a Sardinian sample. J Neurol 256:194–197

Aulchenko YS, Hoppenbrouwers IA, Ramagopalan SV, Broer L, Jafari N, Hillert J, Link J, Lundström W, Greiner E, Dessa Sadovnick A, Goossens D, Van Broeckhoven C, Del-Favero J, Ebers GC, Oostra BA, van Duijn CM, Hintzen RQ (2008) Genetic variation in the KIF1B locus influences susceptibility to multiple sclerosis. Nat Genet 40:1402–1403

Ayata C, Jin H, Kudo C, Dalkara T, Moskowitz MA (2006) Suppression of cortical spreading depression in migraine prophylaxis. Ann Neurol 59:652–661

Battistini S, Stenirri S, Piatti M, Gelfi C, Righetti PG, Rocchi R, Giannini F, Battistini N, Guazzi GC, Ferrari M, Carrera P (1999) A new *CACNA1A* gene mutation in acetazolamide-responsive familial hemiplegic migraine and ataxia. Neurology 53:38–43

Beauvais K, Cavé-Riant F, De Barace C, Tardieu M, Tournier-Lasserve E, Furby A (2004) New *CACNA1A* gene mutation in a case of familial hemiplegic migraine with status epilepticus. Eur Neurol 52:58–61

Bjornsson A, Gudmundsson G, Gudfinnsson E, Hrafnsdóttir M, Benedikz J, Skúladóttir S, Kristjánsson K, Frigge ML, Kong A, Stefánsson K, Gulcher JR (2003) Localization of a gene for migraine without aura to chromosome 4q21. Am J Hum Genet 73:986–993

Blau JN (1992) Classical migraine: symptoms between visual aura and headache onset. Lancet 340:355–356

Bolay H, Reuter U, Dunn AK, Huang Z, Boas DA, Moskowitz MA (2002) Intrinsic brain activity triggers trigeminal meningeal afferents in a migraine model. Nat Med 8:136–142

Cader ZM, Noble-Topham S, Dyment DA, Cherny SS, Brown JD, Rice GP, Ebers GC (2003) Significant linkage to migraine with aura on chromosome 11q24. Hum Mol Genet 12:2511–2517

Cao YQ, Piedras-Renteria ES, Smith GB, Chen G, Harata NC, Tsien RW (2004) Presynaptic Ca^{2+} channels compete for channel type-preferring slots in altered neurotransmission arising from Ca^{2+} channelopathy. Neuron 43:387–400

Capendeguy O, Horisberger JD (2004) Functional effects of Na+, K+-ATPase gene mutations linked to familial hemiplegic migraine. Neuromol Med 6:105–116

Carlsson A, Forsgren L, Nylander PO, Hellman U, Forsman-Semb K, Holmgren G, Holmberg D, Holmberg M (2002) Identification of a susceptibility locus for migraine with and without aura on 6p12.2-p21.1. Neurology 59:1804–1807

Castro MJ, Stam AH, Lemos C, de Vries B, Vanmolkot KR, Barros J, Terwindt GM, Frants RR, Sequeiros J, Ferrari MD, Pereira-Monteiro JM, van den Maagdenberg AM (2009) First mutation in the voltage-gated Nav1.1 subunit gene *SCN1A* with co-occurring familial hemiplegic migraine and epilepsy. Cephalalgia 29:308–313

Cestele S, Scalmani P, Rusconi R, Terragni B, Franceschetti S, Mantegazza M (2008) Self- limited hyperexcitability: functional effect of a familial hemiplegic migraine mutation of the Nav1.1 (*SCN1A*) Na^+ channel. J Neurosci 16:7273–7283

Chan YC, Burgunder JM, Wilder-Smith E, Chew SE, Lam-Mok-Sing KM, Sharma V, Ong BK (2008) Electroencephalographic changes and seizures in familial hemiplegic migraine patients with the *CACNA1A* gene S218L mutation. J Clin Neurosci 15:891–894

Colson NJ, Lea RA, Quinlan S, MacMillan J, Griffiths LR (2004) The estrogen receptor 1 G594A polymorphism is associated with migraine susceptibility in two independent case/control groups. Neurogenetics 5:129–133

Colson NJ, Lea RA, Quinlan S, MacMillan J, Griffiths LR (2005) Investigation of hormone receptor genes in migraine. Neurogenetics 6:17–23

Cuenca-León E, Corominas R, Montfort M, Artigas J, Roig M, Bayés M, Cormand B, Macaya A (2009) Familial hemiplegic migraine: linkage to chromosome 14q32 in a Spanish kindred. Neurogenetics (in press)

Curtain RP, Smith RL, Ovcaric M, Griffiths LR (2006) Minor head trauma-induced sporadic hemiplegic migraine coma. Pediatr Neurol 34:329–332

De Fusco M, Marconi R, Silverstri L, Atorino L, Rampoldi L, Morgante L, Ballabio A, Aridon P, Casari G (2003) Haploinsufficiency of ATP1A2 encoding the Na+/K+ pump alpha2 subunit associated with familial hemiplegic migraine type 2. Nat Genet 33:192–196

de Vries B, Freilinger T, Vanmolkot KR, Koenderink JB, Stam AH, Terwindt GM, Babini E, van den Boogerd EH, van den Heuvel JJ, Frants RR, Haan J, Pusch M, van den Maagdenberg AM, Ferrari MD, Dichgans M (2007) Systematic analysis of three FHM genes in 39 sporadic patients with hemiplegic migraine. Neurology 69:2170–2176

Deprez L, Weckhuysen S, Peeters K, Deconinck T, Claeys KG, Claes LR, Suls A, Van Dyck T, Palmini A, Matthijs G, Van Paesschen W, De Jonghe P (2008) Epilepsy as part of the phenotype associated with *ATP1A2* mutations. Epilepsia 49:500–508

Dichgans M, Mayer M, Uttner I, Brüning R, Müller-Höcker J, Rungger G, Ebke M, Klockgether T, Gasser T (1998) The phenotypic spectrum of CADASIL: clinical findings in 102 cases. Ann Neurol 44:731–739

Dichgans M, Freilinger T, Eckstein G, Babini E, Lorenz-Depiereux B, Biskup S, Ferrari MD, Herzog J, van den Maagdenberg AM, Pusch M, Strom TM (2005) Mutation in the neuronal voltage-gated sodium channel SCN1A in familial hemiplegic migraine. Lancet 336:371–377

Ducros A, Denier C, Joutel A, Vahedi K, Michel A, Darcel F, Madigand M, Guerouaou D, Tison F, Julien J, Hirsch E, Chedru F, Bisgård C, Lucotte G, Després P, Billard C, Barthez MA, Ponsot G, Bousser MG, Tournier-Lasserve E (1999) Recurrence of the T666M calcium channel *CACNA1A* gene mutation in familial hemiplegic migraine with progressive cerebellar ataxia. Am J Hum Genet 64:89–98

Ducros A, Dernier C, Joutel A, Cecillon M, Lescoat C, Vahedi K, Darcel F, Vicaut E, Bousser MG, Tournier-Lasserve E (2001) The clinical spectrum of familial hemiplegic migraine associated with mutations in a neuronal calcium channel. N Engl J Med 354:17–24

Fernandez F, Esposito T, Lea RA, Colson NJ, Ciccodicola A, Gianfrancesco F, Griffiths LR (2008) Investigation of gamma-aminobutyric acid (GABA) A receptors genes and migraine susceptibility. BMC Med Genet 9:109

Fernandez F, Colson N, Quinlan S, Macmillan J, Lea RA, Griffiths LR (2009) Association between migraine and a functional polymorphism at the dopamine beta-hydroxylase locus. Neurogenetics 3:82–87

Ferrari MD, van den Maagdenberg AM, Frants RR, Goadsby PJ (2007) Migraine as a cerebral ionopathy with impaired central sensory processing. In: Waxman SG (ed) Molecular neurology. Elsevier, Amsterdam, pp 439–461

Fletcher CF, Tottene A, Lennon VA, Wilson SM, Dubel SJ, Paylor R, Hosford DA, Tessarollo L, McEnery MW, Pietrobon D, Copeland NG, Jenkins NA (2001) Dystonia and cerebellar atrophy in *Cacna1a* null mice lacking P/Q calcium channel activity. FASEB J 15:1288–1290

Gervil M, Ulrich V, Kyvik KO, Olesen J, Russell MB (1999) Migraine without aura: a population based twin study. Ann Neurol 46:606–611

Goadsby PJ (2001) Migraine, aura, and cortical spreading depression; why are we still talking about it. Ann Neurol 49:4–6

Goadsby PJ (2007) Recent advances in understanding migraine mechanisms, molecules and therapeutics. Trends Mol Med 13:39–44

Goadsby PJ, Lipton RB, Ferrari MD (2002) Migraine—current understanding and treatment. N Engl J Med 346:257–270

Goyette P, Sumner JS, Milos R, Duncan AM, Rosenblatt DS, Matthews RG, Rozen R (1994) Human methylenetetrahydrofolate reductase: isolation of cDNA mapping and mutation identification. Nat Genet 7:195–200

Haan J, Terwindt GM, van den Maagdenberg AM, Stam AH, Ferrari MD (2008) A review of the genetic relation between migraine and epilepsy. Cephalalgia 28:105–113

Hadjikhani N, Sanchez Del Rio M, Wu O, Schwartz D, Bakker D, Fischl B, Kwong KK, Cutrer FM, Rosen BR, Tootell RB, Sorensen AG, Moskowitz MA (2001) Mechanisms of migraine aura revealed by functional MRI in human visual cortex. Proc Natl Acad Sci USA 98:4687–4692

Haerter K, Ayata C, Moskowitz MA (2005) Cortical spreading depression: a model for understanding migraine biology and future drug targets. Headache Curr 2:97–103

Hagen K, Pettersen E, Stovner LJ, Skorpen F, Zwart JA (2006) The association between headache and Val158Met polymorphism in the catechol-O-methyltransferase gene: the HUNT Study. J Headache Pain 7:70–74

Hans M, Luvisetto S, Williams ME, Spagnolo M, Urrutia A, Tottene A, Brust PF, Johnson EC, Harpold MM, Stauderman KA, Pietrobon D (1999) Functional consequences of mutations in the human alpha1A calcium channel subunit linked to familial hemiplegic migraine. J Neurosci 19:1610–1619

Headache Classification Subcommittee of the International Headache Society (HCC) (2004) The international classification of headache disorders. 2nd edn. Cephalalgia:24:1–160

Hovatta I, Kallela M, Farkkila M, Peltonen L (1994) Familial migraine: exclusion of the susceptibility gene from the reported locus of familial hemiplegic migraine on 19p. Genomics 23:707–709

Ikeda K, Onaka T, Yamakado M, Nakai J, Ishikawa TO, Taketo MM, Kawakami K (2003) Degeneration of the amygdala/piriform cortex and enhanced fear/anxiety behaviors in sodium pump alpha2 subunit (*Atp1a2*)-deficient mice. J Neurosci 23:4667–4676

James PF, Grupp IL, Grupp G, Woo AL, Askew GR, Croyle ML, Walsh RA, Lingrel JB (1999) Identification of a specific role for the Na, K-ATPase alpha 2 isoform as a regulator of calcium in the heart. Mol Cell 3:555–563

Jen JC, Kim GW, Dudding KA, Baloh RW (2004) No mutations in *CACNA1A* and *ATP1A2* in probands with common types of migraine. Arch Neurol 61:926–928

Jirtle RL, Skinner MK (2007) Nat Rev Genet 8:253–262

Johnson MP, Lea RA, Curtain RP, MacMillan JC, Griffiths LR (2003) An investigation of the 5-HT2C receptor gene as a migraine candidate gene. Am J Med Genet B Neuropsychiatr Genet 117B:86–89

Jones KW, Ehm MG, Percak-Vance MA, Haines JL, Boyd PR, Peroutka SJ (2001) Migraine with aura susceptibility locus on chromosome 19p13 is distinct from the familial hemiplegic migraine locus. Genomics 78:150–154

Joutel A, Corpechot C, Ducros A, Vahedi K, Chabriat H, Mouton P, Alamowitch S, Domenga V, Cécillion M, Marechal E, Maciazek J, Vayssiere C, Cruaud C, Cabanis EA, Ruchoux MM, Weissenbach J, Bach JF, Bousser MG, Tournier-Lasserve E (1996) Notch3 mutations in CADASIL, a hereditary adult-onset condition causing stroke and dementia. Nature 383:707–710

Jun K, Piedras-Rentería ES, Smith SM, Wheeler DB, Lee SB, Lee TG, Chin H, Adams ME, Scheller RH, Tsien RW, Shin HS (1999) Ablation of P/Q-type Ca(2+) channel currents, altered synaptic transmission, and progressive ataxia in mice lacking the alpha(1A)-subunit. Proc Natl Acad Sci USA 96:15245–15250

Jurkat-Rott K, Freilinger T, Dreier JP, Herzog J, Göbel H, Petzold GC, Montagna P, Gasser T, Lehmann-Horn F, Dichgans M (2004) Variability of familial hemiplegic migraine with novel A1A2 Na+/K+-ATPase variants. Neurology 62:1857–1861

Kahlig KM, Rhodes TH, Pusch M, Freilinger T, Pereira-Monteiro JM, Ferrari MD, van den Maagdenberg AM, Dichgans M, George AL Jr (2008) Divergent sodium channel defects in familial hemiplegic migraine. Proc Natl Acad Sci USA 105:9799–9804

Kallela M, Wessman M, Havanka H, Palotie A, Färkkilä M (2001) Familial migraine with and without aura: clinical characteristics and co-occurrence. Eur J Neurol 8:441–449

Kara I, Sazci A, Ergul E, Kaya G, Kilic G (2003) Association of the C677T and A1298C polymorphisms in the 5, 10 methylenetetrahydrofolate reductase gene in patients with migraine risk. Brain Res Mol Brain Res 111:84–90

Kaube H, Herzog J, Käufer T, Dichgans M, Diener HC (2000) Aura in some patients with familial hemiplegic migraine can be stopped by intranasal ketamine. Neurology 55:139–141

Kaunisto MA, Harno H, Vanmolkot KR, Gargus JJ, Sun G, Hämäläinen E, Liukkonen E, Kallela M, van den Maagdenberg AM, Frants RR, Färkkilä M, Palotie A, Wessman M (2004) A novel missense *ATP1A2* mutation in a Finnish family with familial hemiplegic migraine type 2. Neurogenetics 5:141–146

Kaunisto MA, Kallela M, Hämäläinen E, Kilpikari R, Havanka H, Harno H, Nissilä M, Säkö E, Ilmavirta M, Liukkonen J, Teirmaa H, Törnwall O, Jussila M, Terwilliger J, Färkkilä M, Kaprio J, Palotie A, Wessman M (2006) Testing of variants of the *MTHFR* and *ESR1* genes in 1798 Finnish individuals fails to confirm the association with migraine with aura. Cephalalgia 26:1462–1472

Koenderink JB, Zifarelli G, Qiu LY, Schwarz W, De Pont JJ, Bamberg E, Friedrich T (2005) Na, K-ATPase mutations in familial hemiplegic migraine lead to functional inactivation. Biochim Biophys Acta 1669:61–68

Kors EE, Terwindt GM, Vermeulen FL, Fitzsimons RB, Jardine PE, Heywood P, Love S, van den Maagdenberg AM, Haan J, Frants RR, Ferrari MD (2001) Delayed cerebral edema and fatal coma after minor head trauma: role of the *CACNA1A* calcium channel subunit gene and relationship with familial hemiplegic migraine. Ann Neurol 49:753–760

Kors EE, Haan J, Giffin NJ, Pazdera L, Schnittger C, Lennox GG, Terwindt GM, Vermeulen FL, Van den Maagdenberg AM, Frants RR, Ferrari MD (2003) Expanding the phenotypic spectrum of the *CACNA1A* gene T666M mutation: a description of 5 families with familial hemiplegic migraine. Arch Neurol 60:684–688

Kors EE, Melberg A, Vanmolkot KR, Kumlien E, Haan J, Raininko R, Flink R, Ginjaar HB, Frants RR, Ferrari MD, van den Maagdenberg AM (2004) Childhood epilepsy, familial hemiplegic migraine, cerebellar ataxia, and a new *CACNA1A* mutation. Neurology 63:1136–1137

Kowa H, Yasui K, Takeshima T, Urakami K, Sakai F, Nakashima K (2000) The homozygous C677T mutation in the methylenetetrahydrofolate reductase gene is a genetic risk factor for migraine. Am J Med Genet 96:762–764

Lambert GA, Zagami AS (2008) The mode of action of migraine triggers: a hypothesis. Headache 49:253–275

Lashley KS (1941) Patterns of cerebral integration indicated by the scotomas of migraine. Arch Neurol Psychiatry 46:331–339

Launer LJ, Terwindt GM, Ferrari MD (1999) The prevalence and characteristics of migraine in a population-based cohort: the GEM study. Neurology 53:537–542

Lauritzen M (1994) Pathophysiology of the migraine aura. The spreading depression theory. Brain 17:199–210

Le Fort D, Safran AB, Picard F, Bouchardy I, Morris MA (2004) Elicited repetitive daily blindness: a new familial disorder related to migraine and epilepsy. Neurology 63:348–350

Lea RA, Shepherd AG, Curtain RP, Nyholt DR, Quinlan S, Brimage PJ, Griffiths LR (2002) A typical migraine susceptibility region localizes to chromosome 1q31. Neurogenetics 4:17–22

Lea RA, Ovcaric M, Sundholm J, MacMillan J, Griffiths LR (2004) The methylenetetrahydrofolate reductase gene variant C677T influences susceptibility to migraine with aura. BMC Med 2:3

Lea RA, Nyholt DR, Curtain RP, Ovcaric M, Sciascia R, Bellis C, Macmillan J, Quinlan S, Gibson RA, McCarthy LC, Riley JH, Smithies YJ, Kinrade S, Griffiths LR (2005) A genome-wide scan provides evidence for loci influencing a severe heritable form of common migraine. Neurogenetics 6:67–72

Leao AA (1944) Spreading depression of activity in the cerebral cortex. J Neurophysiol 7:359–390

Lee H, Sininger L, Jen JC, Cha YH, Baloh RW, Nelson SF (2007) Association of progesterone receptor with migraine-associated vertigo. Neurogenetics 8:195–200

Lee ST, Chu K, Jung KH, Kim DH, Kim EH, Choe VN, Kim JH, Im WS, Kang L, Park JE, Park HJ, Park HK, Song EC, Lee SK, Kim M, Roh JK (2008) Decreased number and function of endothelial progenitor cells in patients with migraine. Neurology 70:1510–1517

Lighthart L, Nyholt DR, Hottenga JJ, Distel MA, Willemsen G, Boomsma DI (2008) Genome-wide linkage scan provides evidence for both new and previously reported loci influencing common migraine. Am J Med Genet B Neuropsychiatr Genet 5:1186–1195

Ligthart L, Boomsma DI, Martin NG, Stubbe JH, Nyholt DR (2006) Migraine with aura and migraine without aura are not distinct entities: further evidence from a large Dutch population study. Twin Res Hum Genet 9:54–63

Loder E, Rizzoli P (2006) Biomarkers in migraine: their promise, problems, and practical applications. Headache 46:1046–1058

May A, Ophoff RA, Terwindt GM, Urban C, van Eijk R, Haan J, Diener HC, Lindhout D, Frants RR, Sandkuijl LA, Ferrari MD (1995) Familial hemiplegic migraine locus on 19p13 involved in the common forms of migraine with and without aura. Hum Genet 96:604–608

McCallum LK, Fernandez F, Quinlan S, Macartney DP, Lea RA, Griffiths LR (2007) Association study of a functional variant in intron 8 of the dopamine transporter gene and migraine susceptibility. Eur J Neurol 14:706–707

McCarthy LC, Hosford DA, Riley JH, Bird MI, White NJ, Hewett DR, Peroutka SJ, Griffiths LR, Boyd PR, Lea RA, Bhatti SM, Hosking LK, Hood CM, Jones KW, Handley AR, Rallan R, Lewis KF, Yeo AJ, Williams PM, Priest RC, Khan P, Donnelly C, Lumsden SM, O'Sullivan J, See CG, Smart DH, Shaw-Hawkins S, Patel J, Langrish TC, Feniuk W, Knowles RG, Thomas M, Libri V, Montgomery DS, Manasco PK, Xu CF, Dykes C, Humphrey PP, Roses AD, Purvis IJ (2001) Single-nucleotide polymorphism alleles in the insulin receptor gene are associated with typical migraine. Genomics 78:135–149

Meisler MH, Kearney JA (2005) Sodium channel mutations in epilepsy and other neurological disorders. J Clin Invest 115:2010–2017

Melliti K, Grabner M, Seabrook GR (2003) The familial hemiplegic migraine mutation R192Q reduces G-protein-mediated inhibition of P/Q-type (Ca(V)2.1) calcium channels expressed in human embryonic kidney cells. J Physiol 546:337–347

Menken M, Munsat TL, Toole JF (2000) The global burden of disease study. Implications for neurology. Arch Neurol 57:418–420

Milner PM (1958) Note on a possible correspondence between the scotomas of migraine and spreading depression of Leão. Electroencephalogr Clin Neurophysiol 10:705

Montagna P (2008) The primary headaches: genetics, epigenetics and a behavioural genetic model. J Headache Pain 9:57–69

Moskowitz MA, Bolay H, Dalkara T (2004) Deciphering migraine mechanisms: clues from familial hemiplegic migraine genotypes. Ann Neurol 55:276–280

Mulder EJ, Van Baal C, Gaist D, Kallela M, Kaprio J, Svensson DA, Nyholt DR, Martin NG, MacGregor AJ, Cherkas LF, Boomsma DI, Palotie A (2003) Genetic and environmental influences on migraine: a twin study across six countries. Twin Res 6:422–431

Mulley JC, Scheffer IE, Petrou S, Dibbens LA, Berkovic SF, Harkin LA (2005) SCN1A mutations and epilepsy. Hum Mutat 25:535–542

Müllner C, Broos LA, van den Maagdenberg AM, Striessnig J (2004) Familial hemiplegic migraine type 1 mutations K1336E, W1684R, and V1696I alter $Ca_V2.1$ Ca2+ channel gating: evidence for beta-subunit isoform-specific effects. J Biol Chem 279:51844–51850

Netzer C, Freudenberg J, Heinze A, Heinze-Kuhn K, Goebel I, McCarthy LC, Roses AD, Göbel H, Todt U, Kubisch C (2008a) Replication study of the insulin receptor gene in migraine with aura. Genomics 91:503–507

Netzer C, Freudenberg J, Toliat MR, Heinze A, Heinze-Kuhn K, Thiele H, Goebel I, Nürnberg P, Ptácek LJ, Göbel H, Todt U, Kubisch C (2008b) Genetic association studies of the chromosome 15 GABA-A receptor cluster in migraine with aura. Am J Med Genet B Neuropsychiatr Genet 147B:37–41

Nyholt D, Lea R, Goadsby P, Brimage PJ, Griffiths LR (1998) Familial typical migraine. Linkage to chromosome 19p13 and evidence for genetic heterogeneity. Neurology 50:1428–1432

Nyholt DR, Curtain RP, Griffiths LR (2000) Familial typical migraine: significant linkage and localization of a gene to Xq24-28. Hum Genet 107:18-23

Nyholt DR, Gillespie NG, Heath AC, Merikangas KR, Duffy DL, Martin NG (2004) Latent class and genetic analysis does not support migraine with aura and migraine without aura as separate entities. Genet Epidemiol 26:231–244

Nyholt DR, Morley KI, Ferreira MA, Medland SE, Boomsma DI, Heath AC, Merikangas KR, Montgomery GW, Martin NG (2005) Genomewide significant linkage to migrainous headache on chromosome 5q21. Am J Hum Genet 77:500–512

Nyholt DR, LaForge KS, Kallela M, Alakurtti K, Anttila V, Färkkilä M, Hämaläinen E, Kaprio J, Kaunisto MA, Heath AC, Montgomery GW, Göbel H, Todt U, Ferrari MD, Launer LJ, Frants RR, Terwindt GM, de Vries B, Verschuren WM, Brand J, Freilinger T, Pfaffenrath V, Straube A, Ballinger DG, Zhan Y, Daly MJ, Cox DR, Dichgans M, van den Maagdenberg AM, Kubisch C, Martin NG, Wessman M, Peltonen L, Palotie A (2008) A high-density association screen of 155 ion transport genes for involvement with common migraine. Hum Mol Genet 17:3318–3331

Ogiwara I, Miyamoto H, Morita N, Atapour N, Mazaki E, Inoue I, Takeuchi T, Itohara S, Yanagawa Y, Obata K, Furuichi T, Hensch TK, Yamakawa K (2007) Na(v)1.1 localizes to axons of parvalbumin-positive inhibitory interneurons: a circuit basis for epileptic seizures in mice carrying an Scn1a gene mutation. J Neurosci 27:5903–5914

Ophoff RA, Terwindt GM, Vergouwe MN, van Eijk R, Oefner PJ, Hoffman SM, Lamerdin JE, Mohrenweiser HW, Bulman DE, Ferrari M, Haan J, Lindhout D, van Ommen GJ, Hofker MH, Ferrari MD, Frants RR (1996) Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca^{2+} channel gene CACNL1A4. Cell 87:543–552

Oswell G, Kaunisto MA, Kallela M, Hämäläinen E, Anttila V, Kaprio J, Färkkilä M, Wessman M, Palotie A (2008) No association of migraine to the GABA-A receptor complex on chromosome 15. Am J Med Genet B Neuropsychiatr Genet 147B:33–36

Oterino A, Valle N, Bravo Y, Muñoz P, Sánchez-Velasco P, Ruiz-Alegría C, Castillo J, Leyva-Cobián F, Vadillo A, Pascual J (2004) MTHFR T677 homozygosis influences the presence of aura in migraineurs. Cephalalgia 24:491–494

Oterino A, Valle N, Pascual J, Bravo Y, Muñoz P, Castillo J, Ruiz-Alegría C, Sánchez-Velasco P, Leyva-Cobián F, Cid C (2005) Thymidylate synthase promoter tandem repeat and MTHFD1 R653Q polymorphisms modulate the risk for migraine conferred by the MTHFR T677 allele. Brain Res Mol Brain Res 139:163–168

Oterino A, Castillo J, Pascual J, Cayon A, Alonso A, Ruiz-Alegria C, Valle N, Monton F, Ruiz-Lavilla N (2007) Genetic association study and meta-analysis of the HTR2C Cys23Ser polymorphism and migraine. J Headache Pain 8:231–235

Oterino A, Toriello M, Cayón A, Castillo J, Colas R, Alonson-Arranz A, Ruiz-Alegria C, Quintela E, Monton F, Ruiz-Lavilla N, Gonzalez F, Pascual J (2008) Multilocus analyses reveal involvement of the ESR1, ESR2, and FSHR genes in migraine. Headache 48:1438–1450

Ottman R, Lipton RB (1994) Comorbidity of migraine and epilepsy. Neurology 44:2105–2110

Pierelli F, Grieco GS, Pauri F, Pirro C, Fiermonte G, Ambrosini A, Costa A, Buzzi MG, Valoppi M, Caltagirone C, Nappi G, Santorelli FM (2006) A novel *ATP1A2* mutation in a family with FHM type II. Cephalalgia 26:324–328

Pietrobon D (2007) Familial hemiplegic migraine. Neurotherapeutics 4:274–284

Rainero I, Grimaldi LM, Salani G, Valfrè W, Rivoiro C, Savi L, Pinessi L (2004) Association between the tumor necrosis factor-alpha -308 G/A gene polymorphism and migraine. Neurology 62:141–143

Ramadan NM, Schultz LL, Gilkey SJ (1997) Migraine prophylactic drugs: proof of efficacy, utilization and cost. Cephalalgia 17:73–80

Riant F, De Fusco M, Aridon P, Ducros A, Ploton C, Marchelli F, Maciazek J, Bousser MG, Casari G, Tournier-Lasserve E (2005) *ATP1A2* mutations in 11 families with familial hemiplegic migraine. Hum Mutat 26:281

Richards A, Van den Maagdenberg AM, Jen JC, Kavanagh D, Bertram P, Spitzer D, Liszewski MK, Barilla-Labarca ML, Terwindt GM, Kasai Y, McLellan M, Grand MG, Vanmolkot KR, de Vries B, Wan J, Kane MJ, Mamsa H, Schäfer R, Stam AH, Haan J, de Jong PT, Storimans CW, van Schooneveld MJ, Oosterhuis JA, Gschwendter A, Dichgans M, Kotschet KE, Hodgkinson S, Hardy TA, Delatycki MB, Hajj-Ali RA, Kothari PH, Nelson SF, Frants RR, Baloh RW, Ferrari MD, Atkinson JP (2007) Truncations in the carboxyl-terminus of human 30–50 DNA exonuclease TREX1 cause retinal vasculopathy with cerebral leukodystrophy. Nat Genet 39:1068–1070

Rommelse NN, Altink ME, Martin NC, Buschgens CJ, Buitelaar JK, Sergeant JA, Oosterlaan J (2008) Neuropsychological measures probably facilitate heritability research of ADHD. Arch Clin Neuropsychol 23:579–591

Rubino E, Ferrero M, Rainero I, Binello E, Vaula G, Pinessi L (2007) Association of the C677T polymorphism in the MTHFR gene with migraine: a meta-analysis. Cephalalgia (in press)

Russell MB, Olesen J (1993) The genetics of migraine without aura and migraine with aura. Cephalalgia 13:245–248

Russell MB, Olesen J (1995) Increased familial risk and evidence of genetic factor in migraine. Br Med J 311:541–544

Russell MB, Olesen J (1996) A nosographic analysis of the migraine aura in a general population. Brain 119:355–361

Russell MB, Rasmussen BK, Fenger K, Olesen J (1996) Migraine without aura and migraine with aura are distinct clinical entities: a study of four hundred and eighty-four male and female migraineurs from the general population. Cephalalgia 16:239–245

Russell MB, Iversen HK, Olesen J (1994) Improved description of the migraine aura by a diagnostic aura diary. Cephalalgia 14:107–117

Russell MB, Ulrich V, Gervil M, Olesen J (2002) Migraine without aura and migraine with aura are distinct disorders. A population-based twin survey. Headache 42:332–336

Russo L, Mariotti P, Sangiorgi E, Giordano T, Ricci I, Lupi F, Chiera R, Guzzetta F, Neri G, Gurrieri F (2005) A new susceptibility locus for migraine with aura in the 15q11-q13 genomic region containing three GABA-A receptor genes. Am J Hum Genet 76:327–333

Scher AI, Terwindt GM, Verschuren WM, Kruit MC, Blom HJ, Kowa H, Frants RR, van den Maagdenberg AM, van Buchem M, Ferrari MD, Launer LJ (2006) Migraine and MTHFR C677T genotype in a population-based sample. Ann Neurol 59:372–375

Schoonman GG, Evers DJ, Ballieux BE, de Geus EJ, de Kloet ER, Terwindt GM, van Dijk JG, Ferrari MD (2007) Is stress a trigger factor for migraine? Psychoneuroendocrinology 32:532–538

Schürks M, Zee RY, Buring JE, Kurth T (2008) Interrelationships among the MTHFR 677C>T polymorphism, migraine, and cardiovascular disease. Neurology 71:505–513

Schürks M, Zee RY, Buring JE, Kurth T (2009a) ACE D/I polymorphism, migraine, and cardiovascular disease in women. Neurology 72:650–656

Schürks M, Zee RY, Buring JE, Kurth T (2009b) Polymorphisms in the renin–angiotensin system and migraine in women. Headache 49:292–299

Segall L, Scanzano R, Kaunisto MA, Wessman M, Palotie A, Gargus JJ, Blostein R (2004) Kinetic alterations due to a missense mutation in the Na, K-ATPase alpha2 subunit cause familial hemiplegic migraine type 2. J Biol Chem 279:43692–43696

Segall L, Mezzetti A, Scanzano R, Gargus JJ, Purisima E, Blostein R (2005) Alterations in the alpha2 isoform of Na, K-ATPase associated with familial hemiplegic migraine type 2. Proc Natl Acad Sci USA 102:11106–11111

Serra SA, Fernàndez-Castillo N, Macaya A, Cormand B, Valverde MA, Fernández-Fernández JM (2009) The hemiplegic migraine-associated Y1245C mutation in *CACNA1A* results in a gain of channel function due to its effect on the voltage sensor and G-protein-mediated inhibition. Pflugers Arch 3:82–87

Somjen GG (2002) Ion regulation in the brain: implications for pathophysiology. Neuroscientist 8:254–267

Soragna D, Vettori A, Carraro G, Marchioni E, Vazza G, Bellini S, Tupler R, Savoldi F, Mostacciuolo ML (2003) A locus for migraine without aura maps on chromosome 14q21.2-q22.3. Am J Hum Genet 72:161–167

Spadaro M, Ursu S, Lehmann-Horn F, Veneziano L, Antonini G, Giunti P, Frontali M, Jurkat-Rott K (2004) A G301R Na+/K+-ATPase mutation causes familial hemiplegic migraine type 2 with cerebellar signs. Neurogenetics 5:177–185

Stam AH, Vanmolkot KR, Kremer HP, Gärtner J, Brown J, Leshinsky-Silver E, Gilad R, Kors EE, Frankhuizen WS, Ginjaar HB, Haan J, Frants RR, Ferrari MD, van den Maagdenberg AM, Terwindt GM (2008a) *CACNA1A* R1347Q: a frequent recurrent mutation in hemiplegic migraine. Clin Genet 74:481–485

Stam AH, Maagdenberg AM, Haan J, Terwindt GM, Ferrari MD (2008b) Genetics of migraine: an update with special attention to genetic comorbidity. Curr Opin Neurol 21:288–293

Stewart WF, Shechter A, Rasmussen BK (1994) Migraine prevalence. A review of population-based studies. Neurology 44(Suppl 4):S17–S23

Stewart WF, Staffa J, Lipton RB, Ottman R (1997) Familial risk of migraine: a population-based study. Ann Neurol 41:166–172

Stovner LJ, Zwart JA, Hagen K, Terwindt GM, Pascual J (2006) Epidemiology of headache in Europe. Eur J Neurol 13:333–345

Svensson DA, Larsson B, Waldenlind E, Pedersen NL (2003) Shared rearing environment in migraine: results from twins reared apart and twins reared together. Headache 43:235–244

Tavraz NN, Friedrich T, Durr KL, Koenderink JB, Bamberg E, Freilinger T, Dichgans M (2008) Diverse functional consequences of mutations in the Na^+/K^+-ATPase alpha2-subunit causing familial hemiplegic migraine type 2. J Biol Chem 283:31097–31106

Tavraz NN, Dürr KL, Koenderink JB, Freilinger T, Bamberg E, Dichgans M, Friedrich T (2009) Impaired plasma membrane targeting or protein stability by certain ATP1A2 mutations identified in sporadic or familial hemiplegic migraine. Channels (Austin) 3:82–87

Terwindt GM, Haan J, Ophoff RA, Groenen SM, Storimans CW, Lanser JB, Roos RA, Bleeker-Wagemakers EM, Frants RR, Ferrari MD (1998) Clinical and genetic analysis of a large Dutch family with autosomal dominant vascular retinopathy, migraine and Raynaud's phenomenon. Brain 121:303–316

Terwindt GM, Ophoff RA, van Eijk R, Vergouwe MN, Haan J, Frants RR, Sandkuijl LA, Ferrari MD, Dutch Migraine Genetics Research Group (2001) Involvement of the P/Q type calcium channel α1A-subunit (*CACNA1A*) gene region on 19p13 in migraine with and without aura. Neurology 56:1028–1032

Terwindt GM, Kors EE, Haan J, Vermeulen FL, van den Maagdenberg AM, Frants RR, Ferrari MD (2002) Mutation analysis of the *CACNA1A* calcium channel subunit gene in 27 patients with sporadic hemiplegic migraine. Arch Neurol 59:1016–1018

Thomsen LL, Olesen J (2003) Sporadic hemiplegic migraine. Cephalalgia 24:1016–1023

Thomsen LL, Eriksen MK, Roemer SF, Andersen I, Olesen J, Russell MB (2002) A population-based study of familial hemiplegic migraine suggests revised diagnostic criteria. Brain 125:1379–1391

Thomsen LL, Ostergaard E, Olesen J, Russell MB (2003) Evidence for a separate type of migraine with aura: sporadic hemiplegic migraine. Neurology 60:595–601

Thomsen LL, Oestergaard E, Bjornsson A, Stefansson H, Fasquel AC, Gulcher J, Stefansson K, Olesen J (2008) Screen for *CACNA1A* and *ATP1A2* mutations in sporadic hemiplegic migraine patients. Cephalalgia 28:914–921

Todt U, Dichgans M, Jurkat-Rott K, Heinze A, Zifarelli G, Koenderink JB, Goebel I, Zumbroich V, Stiller A, Ramirez A, Friedrich T, Göbel H, Kubisch C (2005) Rare missense variants in *ATP1A2* in families with clustering of common forms of migraine. Hum Mutat 26:315–321

Todt U, Freudenberg J, Goebel I, Netzer C, Heinze A, Heinze-Kuhn K, Göbel H, Kubisch C (2006) MTHFR C677T polymorphism and migraine with aura. Ann Neurol 60:621–622

Todt U, Netzer C, Toliat M, Heinze A, Goebel I, Nürnberg P, Göbel H, Freudenberg J, Kubisch C (2009) New genetic evidence for involvement of the dopamine system in migraine with aura. Hum Genet 125:265–279

Toriello M, Oterino A, Pascual J, Castillo J, Colás R, Alonso-Arranz A, Ruiz-Alegría C, Quintela E, Montón F, Ruiz-Lavilla N (2008) Lack of association of endothelial nitric oxide synthase polymorphisms and migraine. Headache 48:1115–1119

Tottene A, Fellin T, Pagnutti S, Luvisetto S, Striessnig J, Fletcher C, Pietrobon D (2002) Familial hemiplegic migraine mutations increase Ca(2+) influx through single human $Ca_V2.1$ channels and decrease maximal $Ca_V2.1$ current density in neurons. Proc Natl Acad Sci USA 99:13284–13289

Tottene A, Pivotto F, Fellin T, Cesetti T, van den Maagdenberg AM, Pietrobon D (2005) Specific kinetic alterations of human $Ca_V2.1$ calcium channels produced by mutation S218L causing familial hemiplegic migraine and delayed cerebral edema and coma after minor head trauma. J Biol Chem 280:17678–17686

Tronvik E, Stovner LJ, Bovim G, White LR, Gladwin AJ, Owen K, Schrader H (2008) Angiotensin-converting enzyme gene insertion/deletion polymorphism in migraine patients. BMC Neurol 8:4

Tuulio-Henriksson A, Haukka J, Partonen T, Varilo T, Paunio T, Ekelund J, Cannon TD, Meyer JM, Lönnqvist J (2002) Heritability and number of quantitative trait loci of neurocognitive functions in families with schizophrenia. Am J Med Genet 114:483–490

Ulrich V, Gervil M, Kyvik KO, Olesen J, Russell MB (1999) Evidence of a genetic factor in migraine with aura: a population-based Danish twin study. Ann Neurol 45:242–246

Vahedi K, Denier C, Ducros A, Bousson V, Levy C, Chabriat H, Haguenau M, Tournier-Lasserve E, Bousser MG (2000) *CACNA1A* gene de novo mutation causing hemiplegic migraine, coma, and cerebellar atrophy. Neurology 55:1040–1042

Vahedi K, Depienne C, Le Fort D, Riant F, Chaine P, Trouillard O, Gaudric A, Morris MA, Leguern E, Tournier-Lasserve E, Bousser MG (2009) Elicited repetitive daily blindness: a new phenotype associated with hemiplegic migraine and *SCN1A* mutations. Neurology 72:1178–1183

van den Maagdenberg AM, Pietrobon D, Pizzorusso T, Kaja S, Broos LA, Cesetti T, van de Ven RC, Tottene A, van der Kaa J, Plomp JJ, Frants RR, Ferrari MD (2004) A *Cacna1a* knockin migraine mouse model with increased susceptibility to cortical spreading depression. Neuron 41:701–710

van den Maagdenberg AM, Haan J, Terwindt GM, Ferrari MD (2007) Migraine: gene mutations and functional consequences. Curr Opin Neurol 20:299–305

van Es MA, van Vught PW, Blauw HM, Franke L, Saris CG, Van den Bosch L, de Jong SW, de Jong V, Baas F, van't Slot R, Lemmens R, Schelhaas HJ, Birve A, Sleegers K, Van Broeckhoven C, Schymick JC, Traynor BJ, Wokke JH, Wijmenga C, Robberecht W, Andersen PM, Veldink JH, Ophoff RA, van den Berg LH (2008) Genetic variation in DPP6 is associated with susceptibility to amyotrophic lateral sclerosis. Nat Genet 40:29–31

Vanmolkot KR, Kors EE, Hottenga JJ, Terwindt GM, Haan J, Hoefnagels WA, Black DF, Sandkuijl LA, Frants RR, Ferrari MD, van den Maagdenberg AM (2003) Novel mutations in the Na^+, K^+-ATPase pump gene *ATP1A2* associated with familial hemiplegic migraine and benign familial infantile convulsions. Ann Neurol 54:360–366

Vanmolkot KR, Stroink H, Koenderink JB, Kors EE, van den Heuvel JJ, van den Boogerd EH, Stam AH, Haan J, De Vries BB, Terwindt GM, Frants RR, Ferrari MD, van den Maagdenberg AM (2006) Severe episodic neurological deficits and permanent mental retardation in a child with a novel FHM2 *ATP1A2* mutation. Ann Neurol 59:310–314

Vanmolkot KRJ, Babini E, de Vries B, Stam AH, Freilinger T, Terwindt GM, Norris L, Haan J, Frants RR, Ramadan NM, Ferrari MD, Pusch M, van den Maagdenberg AM, Dichgans M (2007a) The novel p.L1649Q mutation in the *SCN1A* epilepsy gene is associated with familial hemiplegic migraine: genetic and functional studies. Hum Mutat 28:522

Vanmolkot FH, van Bortel LM, de Hoon JN (2007b) Altered arterial function in migraine of recent onset. Neurology 68:1563–1570

Vanmolkot KR, Terwindt GM, Frants RR, Haan J, van den Maagdenberg AM, Ferrari MD (2008) A gene for a new monogenic neurovascular migraine syndrome: a next step in unravelling molecular pathways for migraine? Cephalalgia 28:471–473

Weiss N, Sandoval A, Felix R, Van den Maagdenberg A, De Waard M (2008) The S218L familial hemiplegic migraine mutation promotes deinhibition of Ca(v)2.1 calcium channels during direct G-protein regulation. Pflugers Arch 457:315–326

Wessman M, Kallela M, Kaunisto MA, Marttila P, Sobel E, Hartiala J, Oswell G, Leal SM, Papp JC, Hämäläinen E, Broas P, Joslyn G, Hovatta I, Hiekkalinna T, Kaprio J, Ott J, Cantor RM, Zwart JA, Ilmavirta M, Havanka H, Färkkilä M, Peltonen L, Palotie A (2002) Susceptibility locus for migraine with aura, on chromosome 4q24. Am J Hum Genet 70:652–662

Westenbroek RE, Sakurai T, Elliott EM, Hell JW, Starr TV, Snutch TP, Catterall WA (1995) Immunochemical identification and subcellular distribution of the alpha 1A subunits of brain calcium channels. J Neurosci 15:6403–6418

Yu FH, Mantegazza M, Westenbroek RE, Robbins CA, Kalume F, Burton KA, Spain WJ, McKnight GS, Scheuer T, Catterall WA (2006) Reduced sodium current in GABAergic interneurons in a mouse model of severe myoclonic epilepsy in infancy. Nat Neurosci 9:1142–1149

Ziegler DK, Hur YM, Bouchard TJ Jr, Hassanein RS, Barter R (1998) Migraine in twins raised together and apart. Headache 38:417–422