

# Migraine Genetics: A Fascinating Journey Towards Improved Migraine Therapy

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*The study of migraine genetics promises to deliver significant changes to migraine therapy. Dr. Ferrari explores the emergence of the field and its importance to headache medicine.*

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Migraine is clinically and pathophysiologically so heterogeneous a neurovascular disorder that it probably would be better to speak of “the migraines.” Various combinations of genetic and nongenetic susceptibility factors are likely to underlie the different forms of the disorder. Dissecting the complex genetics of migraine undoubtedly will help to unravel the mechanisms that trigger migraine attacks, ultimately leading to much-needed improvements in prophylactic therapy. In what follows, I will attempt to recount the migraine genetics story to date [as perceived through my admittedly near-sighted glasses ( $-8.75 \pm 0.25$  dp)], and I apologize to those colleagues whose work could not be discussed here due to space restrictions.

## Unravelling the pathogenesis of familial hemiplegic migraine

### *From Families to Linkage*

For most clinicians, genetics remains a “black hole.” So it used to be for me as well . . . until early 1991. Then I saw, within the time frame of 2 weeks, 2 different patients from 2 supposedly distinct families with familial hemiplegic migraine (FHM). FHM is a rare, autosomal dominant subtype of migraine with aura associated with hemiparesis. Additional ictal and interictal neurological features may occur as well. There are

also sporadic cases (sporadic hemiplegic migraine: SHM). FHM and SHM are frequently misdiagnosed as epilepsy, stroke, encephalitis, or conversion disorder.

These 2 FHM families were living in a small area in the eastern part of the Netherlands (one of the few parts which is actually above sea level). Two different families with such a rare disease, in such a small, relatively isolated part of the country? Serendipity? Not surprising, then, the 2 families turned out to be related, making one big family. I discussed this family with Keith Campbell, and he kindly offered me access to an extended FHM family that he was following at the Mayo Clinic in Rochester. Coincidence? My PhD student, Dr. Caroline Grubben, subsequently spent over 3 weeks travelling through 9 different states across the USA to characterize this family clinically and to collect blood for DNA. Suddenly, we had 2 extended, multigenerational families with FHM: a “geneticist’s dream” for linkage analysis. Rune Frants, our geneticist, just had linked another rare neurological disorder, fascioscapulohumeral dystrophy. To do so, he had used microsatellites, a novel method in those days, and he was enthusiastic to repeat the same trick for FHM. The Leiden migraine genetics story had started.

Unfortunately, there also is a “geneticist’s nightmare”: *phenocopies*. These are family members

who present with the same clinical picture but actually do not have the same disease. Phenocopies are more common in diseases without objective symptoms and can prove disastrous for linkage analysis. Our FHM families had their fair share of phenocopies, and thus it took “just a tiny bit longer” than expected to find the disease locus. Sadly, we were scooped. The Leiden team had tested several thousands of (at that time) expensive DNA markers, without success, . . . and then, at the Paris International Headache Society meeting in 1993, the French team led by Marie-Germaine Bousser and Elizabeth Tournier-Lasserre announced the linkage of FHM to chromosome 19p13. Not long before, they had linked another neurovascular disorder with migraine, “cerebral autosomal dominant arteriopathy with subcortical infarcts and leuco-encephalopathy (CADASIL) to that chromosomal location. Because of the clinical similarities existing between FHM and CADASIL, they decided to have a go with only 3(!) of their CADASIL markers. Again . . . serendipity. A

major disappointment from the Leiden perspective, a major breakthrough for migraine science!”

#### *From Locus to Disease Gene*

Identifying the actual disease gene can prove challenging, as even a single locus may contain many genes. For example, for Huntington’s Disease it took 10 years from linkage to gene identification. We were luckier. Firstly, we had identified additional FHM families, and we could confirm linkage to 19p13 in several. Then in early 1996, by using the combined genetic information from these families, Roel Ophoff and Gisela Terwindt discovered the first gene for FHM: *CACNA1A*. The gene encodes the pore forming, ion-conducting  $\alpha_{1A}$  subunit of neuronal P/Q type  $Ca_v2.1$  calcium channels. Certain *CACNA1A* mutations may cause FHM1 of various degrees of severity, while other mutations are associated with a range of neurological disorders that includes episodic ataxia type 2 (which is often associated with migraine), progressive forms of ataxia, various forms of epilepsy, and fatal mild head trauma-triggered migraine (see below). In the subsequent years, 2 more genes were identified for FHM: the FHM2 *ATP1A2* gene on chromosome 1q23 (by Giorgio Casari’s Italian team in 2003) and the FHM3 *SCN1A* gene on chromosome 2q24 (by Martin Dichgans and colleagues in Germany). *ATP1A2* encodes the  $\alpha$  subunit of a glial cell  $Na^+, K^+$ -ATPase pump, and *SCN1A* codes for the  $\alpha$  subunit of a neuronal voltage-gated sodium ( $Na_v1.1$ ) channel. A prime example of heterogeneity: mutations in 3 different genes encoding 3 different proteins all cause FHM. Based on existing linkage data from other afflicted families, additional FHM genes are likely to exist.

#### *From Gene Mutations to Disease Mechanisms: Transgenic Mouse Models for Migraine*

Once a disease gene has been identified, the next challenge is to dissect the functional consequences of the

gene mutations so as to gain a better understanding of the underlying disease mechanisms.  $Ca_v2.1$  channels control  $Ca^{2+}$  influx and, through this mechanism, neurotransmitter release. In cellular models, FHM1 *CACNA1A* mutations were shown to increase  $Ca^{2+}$  influx, predicting an increase in neurotransmitter release *in vivo*. In order to characterize the functional changes *in vivo*, Arn van den Maagdenberg generated 2 knock-in mouse models carrying human FHM1 mutations. The first transgenic FHM1 mouse model carried the FHM1 R192Q mutation, which in humans is associated with phenotypically mild FHM. The second FHM1 mouse model carried the S218L *CACNA1A* mutation, which in humans is associated with what is

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probably the most extreme end of migraine’s clinical spectrum: fatal mild head trauma-triggered migraine. These unfortunate subjects may die after a trivial head injury which triggers a migraine attack that is associated with excessive cerebral oedema. We have hypothesized that changes that are truly relevant for a predominantly female disease such as migraine would show a correlation with gender and clinical severity. Although full characterization of both models is still underway, we believe this hypothesis to be largely correct.

Familial hemiplegic migraine 1 R192Q mutations enhanced  $Ca^{2+}$  influx, increased basal and evoked release of neurotransmitters, and reduced the triggering threshold for cortical spreading depression (CSD);

the effect on CSD was greater in female FHM1 mice and could be reversed by ovariectomy. There was also a gene–dosage relationship: greater abnormalities were observed in homozygous than in heterozygous FHM1 mice. The greatest increase in neurotransmitter release and susceptibility for CSD was found in the “severe” S218L FHM1 model. Remarkably, FHM1 mice also exhibited behavior common to migraine such as photophobia and an exaggerated adaptation to time zone shifts, and, in the S218L model, episodes of hemiparesis!

It should be emphasized that characterization of the mouse models would not have been possible without collaborations between electrophysiologists and neurobiologists in Leiden (Jaap Plomp and Joke Meijer), Rotterdam (Chris de Zeeuw), Italy (Daniela Pietrobon and Tommaso Pizzorusso), Boston (Mike Moskowitz and Cenk Ayata), and Montreal (Jeffrey Mogil and Mona Lisa Chanda). Many of these collaborations were funded by the European Commission (EUROHEAD).

#### *Different Genes, Yet the Same Disease Mechanism?*

The studies involving the 2  $Ca_v2.1$  calcium channel mouse models strongly suggest a pivotal role for CSD due to increased availability of glutamate within the synaptic cleft. This assumes particular relevance when one recalls that CSD is the mechanism underlying migraine aura and a putative trigger for activating the trigeminovascular system that contributes significantly to the signalling of head pain. Is it conceivable that similar mechanisms play a role in FHM2 and FHM3? An elegant hypothesis linking all parts together would hold that FHM3 mutations might cause hyperexcitability with increased release of glutamate and that FHM2 mutations reduce the reuptake of glutamate and  $K^+$  from the synaptic cleft into glial cells. The net result of FHM mutations in all 3 genes would thus be increased levels

of glutamate or K<sup>+</sup> in the synaptic cleft, which would increase the susceptibility to CSD.

### Step two: from FHM to common migraine types

#### *Monogenic Subtypes as “Pathway Guides” for Common Complex Diseases*

Skeptics will ask: how relevant are the FHM and mouse model findings to the “real thing”? To answer this question, it is important to consider the general research hypothesis that rare monogenic subtypes of common multifactorial disorders may serve as valid models to unravel the genetics and, even more important, the underlying mechanisms for the common complex forms. Examples include Alzheimers and Parkinson’s disease, where genes and, more importantly, mechanisms for rare monogenic subtypes were also found to be involved in the common complex forms. Genes for rare disorders may thus be regarded as “common pathway guides.”

#### *FHM as a Subtype of Migraine with or without Aura*

A number of clinical and genetic arguments strongly suggest that FHM indeed may serve as a valid model for migraine with and even without aura. Apart from the hemiparesis, the aura and headache features of attacks of FHM, SHM and the more common forms of migraine are identical, and the headaches of each respond equally well to triptans. The vast majority of FHM and SHM patients also have nonhemiplegic migraine attacks. Finally, all 3 forms share similar trigger factors and respond to similar prophylactic agents. FHM mutations also are found in patients with SHM or nonhemiplegic migraine (incomplete penetrance), suggesting a clinical and genetic spectrum that extends from FHM to SHM and to “typical” migraine with and without aura.

#### *Other Monogenic Subtypes of Migraine*

Typical migraine also can be associated with monogenic neurovascular

syndromes such as CADASIL (*NOTCH3* mutations), retinal arteriolar tortuosity and leucoencephalopathy (*COL4A1* mutations), retinal vasculopathy with cerebral leukodystrophy (RVCL: *TREX1* mutations) and familial advanced sleep phase syndrome (FASPS: CKI  $\delta$ -T44A mutation). The functional characterization of the disease gene mutations is underway.

#### *Migraine as a Multifactorial Disorder with Complex Genetics*

In the early 1990s, Michael Bjorn Russell, Jes Olesen, and, later, others convincingly demonstrated that migraine with and migraine without aura are *multifactorial* disorders. Complex genetic factors are estimated to account for up to 61% of the heritability, whereas nongenetic environmental factors may contribute for up to 39%. Although some believe that migraines with and without aura are different diseases, it is more likely that they simply are different clinical expressions of the same disorder. A wide range of candidate genes and loci have since been associated to migraine with or without aura, but in most cases replication has been lacking. The most promising and multiple replicated genetic associations include the *MTHFR* gene and loci at 4q24 and 5q21. The latter locus was found in unbiased, hypothesis-free genome wide analyses (GWA) using various methods for endophenotyping and novel trait component analyses performed in Finland (Aarno Palotie) and Australia (Dale Nyholt).

#### *Common Migraines as Genetic Ionopathies*

Familial hemiplegic migraine and SHM are clearly due to disturbances of ion transportation across cell membranes. The evidence that more common forms of migraine might also be ionopathies so far is only circumstantial but is accumulating. First, migraine shares strikingly similar clinical characteristics with established channelopathies such as

FHM and SHM (see above) and episodic neuromuscular disorders. These include an episodic clinical presentation, a similar distribution for attack duration and frequency, similar trigger factors for attacks (such as emotion, stress, food, alcohol, and weather changes), and similar gender-related expression (with onset mainly around puberty and amelioration after age 40 years). Second, FHM gene mutations have been found in patients with common nonhemiplegic migraine types, and linkage and association studies suggest a role for FHM genes in at least some common migraine types. Third, a neurophysiologic study from Jean Schoenen’s group in Liege revealed subclinical cerebellar dysfunction in migraineurs that likely reflect dysfunction of cerebellar P/Q-type Ca<sub>v</sub>2.1 channels. Finally, Peter Goadsby’s group in London and others have demonstrated that P/Q-type Ca<sub>v</sub>2.1 channels within the brainstem may modulate putative migraine mechanisms such as neurogenic inflammation, release of CGRP, and trigeminal activation.

#### *From Disease Mechanisms to Prophylactic Treatments*

Many people may experience just one or two auras or attacks of migraine headache throughout their lifetime. The attack itself thus may not be abnormal; rather the *repeated occurrence* of attacks is abnormal. There is growing evidence that the *disease* migraine (ie, experiencing recurrent attacks) might be due to a genetically determined reduced threshold for migraine triggers. Attacks may then occur: (1) when migraine triggers are particularly strong or frequent; (2) when there is temporarily a further reduction of the intrinsic (genetic) threshold due to endogenous factors (eg, menstruation, sleep deprivation, stress or relaxation after stress) that can facilitate the triggering of an attack; or (3) when there is a temporal coincidence of both triggering and facilitating factors. Prevention of attacks thus may be achieved by

increasing the trigger threshold, and to this end one need understand the mechanism involved in setting and modulating the trigger threshold. The findings described above would suggest that reduction of the trigger threshold for CSD is important in FHM and possibly also in at least some of the more common migraine forms. Agents that increase the trigger threshold for CSD are attractive candidates to serve as uniquely effective prophylactic therapies for migraine. Indeed, although derived from different pharmacological classes, the more demonstrably efficacious of the existing migraine pro-

phylactics share the ability to inhibit CSD, and tonabersat, a representative of a novel class of drugs known to block CSD, has shown promising results in a proof-of-concept trial involving migraine prophylaxis.

### **Conclusions and the future**

The quest for migraine genes has resulted in the identification of *multiple* susceptibility genes and, even more important, pathways by which migraine attacks may be triggered. It is not unreasonable to anticipate that the ultimate result of such research will be pharmacologically specific,

better tolerated, and more effective prophylactic agents. An additional outcome could be the availability of more objective tests for diagnosing migraine subtypes and even the exciting possibility of “gene profile-guided,” personalized treatment. It is quite likely that unbiased, hypothesis-free GWA and “omics” approaches may result in the identification of yet more and heretofore unsuspected migraine genes and pathways, similar to what is currently occurring for a wide range of other complex disorders.