Familial hemiplegic migraine: A model for the genetic studies of migraine

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FHM3 is a rare subtype of familial hemiplegic migraine (FHM) caused by mutations in the neuronal sodium channel gene SCN1A (1). Only five FHM3 mutations have been described in a few families since the identification of SCN1A as the third FHM gene in 2005 (1–4). In the present issue of Cephalalgia, Weller et al. (5) report the identification of two novel SCN1A FHM3 mutations in two families with pure FHM. This study is important for clinicians managing patients with FHM, and should also encourage geneticists to consider or reconsider FHM as one of the major targets in the continuing quest for migraine genes.

Despite extensive studies, migraine genes remain difficult to identify (6). The common migraines (migraine without aura and migraine with aura) are characterized by high prevalence in the general population, high phenotypic variability, absence of any objective diagnosis marker and polygenic inheritance. Therefore, a successful approach in the search for migraine genes has been the study of FHM, a rare autosomal dominant subform of migraine with aura characterized by the presence of a motor weakness during the aura phase. However, studies of FHM have shown that being monogenic does not imply being a “simple” model. Indeed, FHM is genetically heterogeneous, i.e. mutations in different genes can cause the same phenotype of recurrent migraine attacks with complex aura. From 1996 to 2005, three FHM genes have been identified that all encode ion transporters: a neuronal calcium channel (CACNA1A, FHM1) (7), a glial sodium/potassium pump (ATP1A2, FHM2) (8) and a neuronal sodium channel (SCN1A, FHM3) (1). In 2012, the proline-rich transmembrane protein 2 gene (PRRT2), encoding a protein associated with the exocytosis complex, was proposed as the fourth FHM gene (9,10). Mutations in CACNA1A, ATP1A2 and PRRT2 have also been found in patients with sporadic hemiplegic migraine (SHM) and are often de novo mutations (9,11–13). Study of cellular and murine models have shown that FHM mutations in CACNA1A and ATP1A2 facilitated the initiation of cortical spreading depression waves, the mechanism underlying the migraine aura, and increased neuronal excitability with an excess of glutamatergic neurotransmission (11,13). A proportion of cases with FHM or SHM do not harbor a mutation in the four known genes, indicating that other FHM genes are still to be discovered. Furthermore, genotype-phenotype correlations studies have described the wide clinical spectrum of FHM and the high clinical variability among patients with the same mutation (13). While most cases have so-called “pure” hemiplegic migraine, a small subset of familial and sporadic cases have associated manifestations including permanent cerebellar signs (nystagmus and/or ataxia), epilepsy, cognitive impairment, elicited repetitive daily blindness and paroxysmal dyskinesia. Some patients can present with early-onset severe attacks with coma, prolonged hemiplegia, fever and brain edema (13). Moreover, different mutations in FHM genes induce other monogenic neurological disorders, CACNA1A mutations can cause episodic ataxia type 2 and spinocerebellar ataxia type 6 (7,13). PRRT2 mutations are associated with benign familial infantile convulsions, infantile convulsions with choreoathetosis, and paroxysmal dyskinesias (10). SCN1A was already known as an epilepsy gene previous to its identification as the FHM3 gene (1).

Diagnosing HM might be a challenge. The first step relies on a detailed description of the aura (13). Apart from the presence of a motor weakness during the aura and the frequency of prolonged auras, most HM attacks are similar to attacks of migraine with typical or with brain stem aura. Single cases are diagnosed as sporadic HM, while at least two affected first- and/or

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second-degree relatives in a family are diagnosed as familial HM. Obtaining a reliable family history may sometimes be difficult. A long-term follow-up study showed that some patients reassessed a few years after cessation of HM attacks had forgotten that they once had a motor weakness during their auras (14). Diagnosis difficulties can also arise from the clinical variability of HM. In such cases, screening of the known FHM genes is of great help, notably in severe sporadic cases with or without associated neurological signs (12), and in familial cases when the severity of attacks or permanent neurological features is different compared to the other affected relatives (13). The identification of a disease mutation confirms the clinical diagnosis and may avoid repeated unnecessary investigations.

Once genetic testing has been decided, the detailed clinical phenotype observed in the proband and the other family members can help to determine the order of FHM gene’s scanning. Mutations in \textit{CACNA1A} and \textit{ATP1A2} seem to account for the majority of cases running in large families and also for the majority of early-onset SHM cases (12,13). \textit{SCN1A} and \textit{PRRT2} are more rarely implicated. “Usual” HM attacks are similar in patients with mutations in any of the FHM genes, and epilepsy can be associated with FHM1, 2, 3 and 4 (2,9,10,13). Comatose attacks are frequent in FHM1 and FHM2, while they have not been described yet in FHM3. Permanent ataxia and nystagmus suggests FHM1; elicited repetitive daily blindness indicates FHM3 (4), whereas paroxysmal dyskinesia has been described only in patients with HM and a \textit{PRRT2} mutation (9,10). Finally, learning disabilities and mental retardation have been described in FHM1 and FHM2 (13).

The likelihood of identifying a mutation increases when HM attacks started before 16 years old, as in both families reported by Weller et al. (5), and in the presence of associated manifestations such as ataxia, epilepsy or cognitive impairment (12,13). Although pure FHM can be associated with mutations in any of the four known FHM genes, cases with pure FHM or SHM often have a negative screening. The study by Weller et al. (5) should encourage clinicians and geneticists to perform genetic testing in pure FHM, and to systematically scan all four known genes.

Most FHM mutations are missense mutations, which introduce a single amino-acid substitution in the protein (1–5,7–9,11–13). In the absence of functional studies that are not routinely feasible, the identification of a novel missense mutation will often leave the question whether the mutation is disease causing or a non-pathogenic variant. In SHM, analyzing both parents can prove that the variant is a de novo mutation, which is most likely pathogenic (12). The study by Weller et al. (5) clearly details the methods permitting a conclusion that a novel inherited missense mutation is most likely pathogenic. By sequencing the coding sequence of \textit{CACNA1A}, \textit{ATP1A2} and \textit{PRRT2}, the authors excluded a causal mutation in the other known FHM genes. They demonstrated that each novel \textit{SCN1A} variant co-segregated with FHM3 in the affected family, was absent in a large control panel, affected an important domain of the protein, and changed a highly conserved amino acid in homologous and orthologous sodium channel \(\alpha_1\) subunits. Finally, they used three different in silico bioinformatics prediction programs, which consistently indicated that the novel mutations likely were pathogenic (5). Since FHM mutations can be recurrent, like the \textit{CACNA1A} mutation T666M, which accounts for 40% of FHM1 families (13), it is important to publish novel mutations. When genetic scanning in a subject with FHM or SHM yields a mutation previously identified in an unrelated proband, this variant can be considered as pathogenic.

Contrary to FHM, the initial attempts to identify the common migraine genes by candidate gene approaches or linkage studies were deceiving, and most publications are now recognized as being false-positive findings (6). A great hope has risen since 2010, thanks to four large genome-wide association studies (GWAS) followed by a meta-analysis, which yielded 12 variants associated with common migraine (6,15). These variants might be better considered as genetic risk factors, as each has only a modest contribution to the overall risk of migraine (6,15). Moreover, these variants are also present in a proportion of the control population, meaning that they exert only a low pathogenic effect. Because functional analysis is not actually feasible, the mechanisms by which these variants contribute to migraine attacks are speculative. Three of these variants affect genes involved in glutamate homeostasis (15), and it is tempting to say that these findings fit into the glutamatergic FHM hypothesis (6,11). However, other neurotransmitters, synaptic effects, or functions could also be involved. Furthermore, the majority of the migraine variants are still to be identified. Future directions in migraine genetics include GWAS on larger cohorts of patients and controls, and extensive new generation whole genome sequencing (6). Several recent publications about other hereditary neurological conditions, such as epilepsy, have described the pitfalls of GWAS, which are designed to identify frequent variants with a low pathological effect (6,16). Central nervous system (CNS) disorders are over-represented in the Online Mendelian Inheritance in Man (OMIM) database of monogenic
conditions. This, together with other arguments, led some authors to suggest that an important proportion of hereditary CNS disorders might be due to rare variants with a strong effect (17), which cannot be identified by GWAS but by extensive sequencing in patients and small families, after careful phenotyping (6,16). For all these reasons, the experience gained in clinical and genetic studies of patients and families with FHM is important in the overall field of migraine genetics.

Conflict of interest
None declared.

References