Establishing the genetic heterogeneity of familial hemiplegic migraine

In this issue of Brain Thomsen and colleagues present data representing several important developments in the field of familial hemiplegic migraine (FHM) with their investigation of the genetic spectrum and prevalence of this disorder (Thomsen et al., 2006). The authors have performed the first population-based sampling strategy to obtain complete case ascertainment of this rare disease (Lykke Thomsen et al., 2002) and followed this initial effort with a complete genetic molecular analysis of the collected samples, both by searching for mutation at the three identified FHM loci (Ophoff et al., 1996; De Fusco et al., 2003; Dichgans et al., 2005) and also by performing a genome wide linkage scan. These data allow expansion and refinement of the genetic etiology of FHM within the relatively homogenous Danish population. Specifically, they clarify the penetrance of each mutation, population prevalence of mutations in genes known to cause this disorder, identify novel mutations and also show data that suggest additional as yet unidentified genetic lesions underlying this disorder. From a clinical perspective the study provides valuable data on the potential contribution of these mutations in defining the phenotypic (clinical) spectrum of this disorder. The hope is that these innovations will someday be extended to FHM’s highly prevalent cousin, the common migraine.

The extent of sampling in this study distinguishes it from others since the aim was to capture every FHM family in Denmark by systematic selection through the national patient registry, headache clinics, and advertising in national journals to physicians and headache patients. Sampling for families from the population for rare disorders [FHM is estimated to occur in ~1/20,000 individuals in Denmark (Lykke Thomsen et al., 2002)] is uncommon as it typically requires massive screening of samples to obtain sufficient cases for case control or linkage studies, but once accomplished, findings are more representative for the full spectrum of genetic contribution and phenotypic expression. Thus, although this survey initially relies on diagnostic sensitivity of physicians outside of the study to detect all cases, it is a remarkably complete approach.

The success of this sampling also assumes that the clinical diagnostic criteria on which the selection occurs are also valid. Previous findings (i.e. the three FHM loci) from much smaller sampling frames provide this evidence of biological validity (Ophoff et al., 1996; De Fusco et al., 2003; Dichgans et al., 2005). Results from this study can help further validate the original phenotype definition of FHM and potentially be informative for the definition of migraine in general. The highly variable clinical expression described among the families (ranging from fully affected with no mutation to the opposite, mutation but no symptoms) demonstrates the complexity and difficulty of placing rigid emphasis and importance on diagnostic definitions without some sort of pathological validation. However, following such a pathological anchor, specificity (and non-specificity) of mutations to clinical symptom profiles (i.e. genotype–phenotype correlations) can be considered. The R583Q mutation in CACNA1A of family 6034 seems to demonstrate specificity to persistent, potentially permanent, cerebellar ataxia with some relatives never even having migraine; whereas in contrast, the T666M mutation of family 6002 has a more atypical non-specific profile, not associated with persistent cerebellar ataxia. Both observations are consistent with previous reports (Ducros et al., 1999). The new mutations do not appear to follow any clear clinical pattern, perhaps due to the small size of the families. But as new mutations from other families emerge clinical associations can be made, contributing to further phenotypic refinements.

Following ascertainment of patients and their families as described above, the authors embarked on a series of experiments designed to identify the known and novel mutations underlying FHM. They performed a complete sequence-based screening of the coding exons of CACNA1A and ATP1A2, and a more focused analysis of SCN1A typing the patients for a single mutation. From the first two known genes, the investigators identified six mutations, three within CACNA1A (designated as the locus FHMI; R583Q, T666M and C1369Y) and three within ATP1A2 (designated FHM2; V138A, R202Q and R763C). The mutation C1369Y in CACNA1A and all three mutations in ATP1A2 are novel. Thus, while there is good reason to suspect these as causative of disease, the identification of additional families with these mutations or functional evidence of an unequivocal pathogenic effect are needed to prove pathogenicity. Also of interest regarding these loci is the relative penetrance of...
mutations—in contrast to previous reports of 80–90% penetrance for mutation of \textit{CACNA1A} or \textit{ATP1A2} genes, the authors show a lower rate of disease in mutations carriers (~65%). This often occurs in a population-based analysis, as family based studies have inherent selection bias towards larger kindreds with many affected members.

For the third known gene, \textit{SCN1A}, the authors did not identify any patients with the Q1489K mutation. Although the occurrence of \textit{SCN1A} mutations in this population cannot be completely ruled out, the lack of a linkage signal at this locus suggests that this is not a major cause of FHFM in this population. The fact that less than one-fifth of the 43 families studied had mutations at these two genes suggests that other, as yet unidentified genetic variants are contributing to this disorder in the Danish population. In general, the mutation negative families had fewer affected members than those with an identified mutation which may reflect: a more complex mode of inheritance; a genetic lesion or risk factor that has a lower penetrance than mutations at \textit{CACNA1A} or \textit{ATP1A2} (in terms of expressivity of hemiplegic migraine); or, less likely, simply chance clustering of hemiplegic migraine cases within families.

In addition to clarifying known genes that underlie FMH, another clear goal of this research was to define novel genetic loci. To this end, the authors carried out a complete genome wide linkage screen of families without mutations at \textit{CACNA1A} or \textit{ATP1A2}; although this did not identify any additional unequivocally linked genomic regions they did show suggestive linkage at chromosomes 3p, 10p, 10q, 14q and Xp. These regions will be of interest to others working in the field and clearly pursued by those with the requisite family material.

Outside of identifying new genes, where will this work go next? A critical aim of any genetic investigation of disease is to understand the molecular processes that underlie the disorder, ultimately leading to the development of etiology-based therapies for this and related disorders. Thus, follow up of the biological mechanisms of the genetic mutations should be pursued with future targets of treatment and prevention in mind. Not only will these clues be useful in understanding the pathogenesis and treatment of migraine with and without aura, but also they may offer potential insight into the commonly associated disorders of migraine such as stroke, epilepsy, allergies, and mood and anxiety disorders (Low and Merikangas, 2003; Scher et al., 2005; Sacco et al., 2006). Additionally, the identification of large families with genetic lesions underlying the disease presents the opportunity to study influences on penetrance, clinical expression and attack triggers, as well as the chance to examine and follow apparently asymptomatic mutation positive individuals to define the presence or absence of any related phenotype outside of FHFM.

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