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Novel mutation confirms seizure locus *SCN1A* is also *FHM3* migraine locus

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Abstract

While the gene encoding the neuronal voltage-gated sodium channel, type 1A is a well-recognized target of mutations underlying a spectrum of epilepsy syndromes, and lies within an extended 12 megabase disease-associated haplotype at the Familial Hemiplegic Migraine, type 3 locus, it remains to be confirmed that mutations within this gene itself cause syndromes that include migraine phenotypes. This report presents a family segregating the novel T1174S missense mutation of this gene detected in a heterozygous female child who presented with myoclonus and an abnormal EEG, and in her mother who has an ataxic migraine syndrome similar to that of her own mother. This three-generation family exhibits the broad phenotypic spectrum of the dominant neuronal hyper-excitability syndromes produced by even a given allele of this sodium channel gene. It also exhibits the second allele of this sodium channel gene associated with a migraine syndrome similar to those caused at the two other Familial Hemiplegic Migraine loci, confirming that this gene itself, not some linked gene, is the Familial Hemiplegic Migraine, type 3 locus.

Introduction

Migraine is an extremely common complex polygenic trait into which a window has recently been opened by studies on rare inherited Mendelian dominant forms of migraine, Familial Hemiplegic Migraine (FHM), providing important insights into migraine pathophysiology [1,2]. Analysis of the normal and pathogenic alleles of genes underlying such rare genetic syndromes is a promising route to the discovery of critical molecular targets that are involved in common disease and against which new drugs can be developed [3].

FHM has been clearly associated with missense mutations in at least two genes. *CACNA1A*, encoding the α1 subunit of the neuronal P/Q Ca^{++} channel, and *ATP1A2*, encoding the α2 isoform of the major subunit of the Na,K-ATPase, give rise to FHM1 [OMIM #141500] and FHM2 [OMIM #602481], respectively, and together account for most FHM patients [2,4,5]. The FHM2 mutations produce hypomorphic kinetic alterations in Na/K pump function [6,7],

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but it remains controversial whether FHM1 mutations are hypermorphic [8] or hypomorphic [9].

The range of disease phenotypes produced by alleles at both of these FHM loci is quite broad, but clearly includes seizures and ataxia as well as migraine [1-5,10-12], with the FHM1 *CACNA1A* locus having alleles that cause a spectrum of diseases that include Episodic Ataxia type 2 (EA2), Spinocerebellar Ataxia type 6, as well as many individuals comorbid with FHM, ataxia or seizures. Likewise alleles at the FHM2 *ATP1A2* locus cause a spectrum of diseases that includes comorbidity with Benign Familial Infantile Convulsions, and ataxia.

Recently, the neuronal voltage-gated sodium channel gene *SCN1A* has also been implicated as an FHM locus since an extended disease-associated haplotype covering over twelve million bases of chromosome 2q24 was detected in three, likely closely related, families segregating the classical FHM syndrome [13]. The *SCN1A* rare mutation G1489K was found within this extended disease haplotype, and the homologous mutation in a related gene, *SCN5A*, was shown to alter channel function, making this mutation a promising etiological candidate for FHM3 [13]. However, the large size of the shared haplotype, the inability to directly express the pathogenic allele for functional analysis, and the existence of only this single pathogenic haplotype that would be estimated to contain at least 10,000 additional polymorphic variants [taking the HapMap typical frequency of 1/1200 bp]), leave this to be proven.

SCN1A mutations, however, have been previously unambiguously shown to be pathogenic. They were first observed to cause the epilepsy syndrome Generalized Epilepsy with Febrile Seizures +, type 2 (GEFS+ type2) [OMIM #600235], and now at least a dozen pathogenic alleles causing variants of this syndrome have been recognized, all being missense mutations creating amino acid replacements that do not perturb the critical ion pore region of the channel [14,15]. Shortly thereafter a rare, very severe dominant seizure syndrome that is also initially associated with febrile seizures but progresses to a malignant myoclonic seizure phenotype, called Severe Myoclonic Epilepsy of Infancy (SMEI [OMIM #607208]), proved to be allelic with GEFS+ type 2 [16]. Dozens of alleles have now been identified, most being new mutations in *SCN1A*, and the vast majority being functional null alleles (e.g. frameshift, nonsense), but also including missense mutations within the critical pore domain of the channel [15]. This report presents a three-generation family exhibiting both the broad phenotypic spectrum of the dominant syndromes produced at this locus and also the second *SCN1A* allele associated with a migraine syndrome similar to those caused at the two other FHM loci, securing the assignment of *SCN1A* itself, not a linked gene, as the *FHM3* locus.

Patients and Methods

Patient 1

This female patient of nonconsanguineous mixed European, French Canadian, Native American and Mexican ancestry presented at four years of age with a history of uncontrolled jerking of the limbs and trunk. The movements were not noticed at birth, but had been observed by the family since at least two years of age. The jerking movements were exacerbated by fine motor activity and walking. She has had no recognized seizures. There was no delay of early developmental milestones, however she has been enrolled in special education classes and remains challenged in comprehension. Neurological examination was normal with the exception of impaired fine motor coordination, a broad based, clumsy gait, and multifocal action myoclonus. There was no opsoclonus. Video EEG telemetry was abnormal, with frequent spikes and polyspikes from the right occipital region, and multiple episodes of action tremor that did not correlate with the electrographic changes. Brain MRI was normal with the exception of an incidental pineal cyst. Over the next few months, increased myoclonus and gait deterioration were noted, prompting an extensive workup. Urinary VMA, HVA and

organic acids, lysosomal enzyme assays, CSF measles antibody and CSF neurotransmitters were all normal. Plasma pyruvate and lactate were slightly elevated (respectively, 0.13-0.16, normal upper limit 0.08, and 2.3 - 2.7 normal upper limit 2.1, all in mmol/l) and plasma amino acids and ammonia were normal. The patient started to receive intensive physical and occupational therapy. Coincident with this, her gait appeared to improve, and the myoclonus stabilized. While she had never previously had headaches, at 9 yrs of age she began to develop frequent “band-like” headaches weekly that were moderately severe, but lasted less than one hour. The headaches have never been accompanied by aura, photophobia, phonophobia, nausea, vomiting or ataxia, but she reports frequent periodic colorful visual distortions unassociated with the headache.

Patient 2

Patient 2 is a 39-year old woman of nonconsanguineous European, Native American and Mexican ancestry who is the mother of Patient 1. She additionally has a healthy 4 year-old son. She has a twelve year history of episodic migraine that includes symptoms of vertigo, ataxia, nausea, photophobia, phonophobia and non-pulsatile tinnitus (despite otherwise normal hearing). The headaches typically last 1-2 days, one episode 10 years ago severe enough to result in prolonged hospitalization. She experiences a prodromal “skunk” odor one day or more before onset of symptoms, but never visual aura. She then experiences a sensation of pressure at the back of her head. She has episodes of oscillopsia, lasting seconds, and at times feels light-headed. She additionally experiences episodes of abdominal cramping and diarrhea independent of the migraine. Neurological examination is normal except for an abnormal Romberg. There is no nystagmus or oscillopsia. MRI of the brain showed patchy areas of increased signal in the left frontal region on long T2 sequences. These did not enhance following administration of gadolinium.

Patient 2’s mother also has similar attacks of periodic vertigo and ataxia, at least one sufficiently severe to result in an extended hospitalization over 20 yrs ago. She continues to have these attacks but has never had migraine, aura or significant headache. She had a total of two daughters and four sons, none of whom have symptoms except for Patient 2.

Genotype analysis

Sequence analysis of the *SCN1A* gene was a CLIA-approved diagnostic test performed by Athena Diagnostics (Worcester, MA). It was carried out by routine PCR amplification of highly purified genomic DNA, followed by standard automated uni-directional DNA sequencing of the 26 exons and exon-intron splice junctions of the *SCN1A* gene. Variants were confirmed by bi-directional sequencing.

Results

Genotyping

Both Patient 1 and 2 were found to be heterozygous for the same novel DNA sequence variant of the *SCN1A* gene. The novel variant allele was a C to G transversion at nucleotide position 3521, resulting in a threonine to serine amino acid change encoded by codon 1174 (T1174S). This is a rare novel allele not present in the NCBI SNP database (http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?locusId=6323) and never previously reported. It occurs in a highly conserved region of the SCN1A protein, with the threonine residue completely conserved through phylogeny. The father of Patient 1 was healthy and homozygous for the normal allele. The maternal grandmother and asymptomatic brother of Patient 1 were not genotyped.

Discussion

The novel T1174S allele, and the range of disease phenotypes produced in this three-generation family, exhibits the broad phenotypic spectrum of dominant neuronal hyper-excitability syndromes even a given allele of this sodium channel gene can produce. The difference in phenotype of Patient 1 and 2, while potentially attributable to the well-recognized variant presentation of migraine in children [17], is substantial even though they share the same major pathogenic allele and half of the alleles at other, potentially modifying, loci. This family also presents the second *SCN1A* allele associated with a migraine syndrome that, while not itself strictly FHM, is similar to syndromes caused at the two other established FHM loci, confirming that the *SCN1A* gene itself is the *FHM3* locus, not some other gene in tight linkage disequilibrium. This is a critical observation since key to defining the underlying unifying pathogenesis of FHM is a definition of the vulnerable mechanisms able to produce the syndrome. For instance, with the addition of *SCN1A* as the third FHM locus, it can be readily recognized that the common nature of the genes mutated in FHM are ion transport proteins, making it likely that FHM, and perhaps other forms of migraine, are caused by impairment of cation transport. Furthermore, with the addition of this locus, it becomes clear that the two channels involved (encoded by the *CACNA1A* and *SCN1A* genes) are strictly neuronal, while *ATP1A2* has prominent expression in neurons, but is somewhat more broadly expressed in other excitable tissue. Based upon several prior paradigms of channelopathy phenotypes created at multiple loci [1,3] (i.e. Long QT, Benign Neonatal Febrile Convulsions, Hypokalemic Periodic Paralysis, Malignant Hyperthermia) the shared phenotype caused by mutations in these three genes most parsimoniously arises by a shared perturbation of one critical mechanism, and therefore suggests FHM is a *neuronal* disease. Finally, the finding that different mutations in all three of these FHM genes also cause seizures, the prototypical neuronal channelopathy phenotype [1,3], anchors the notion that FHM is a neuronal disease. The fact that FHM alleles at all three of these loci are only missense, never null, mutations suggests a pathogenesis based upon relatively subtle alterations in function.

The second point illustrated in this report is that there is a spectrum of diseases caused by mutations at the FHM loci, such that the apparently distinct diseases of migraine, ataxia and seizures differ more in a quantitative than qualitative nature [1,3]. This notion of an allelic spectrum raised for the *FHM1* and *FHM2* loci is echoed in the *SCN1A* mutations. While the most severe phenotype, SMEI, is associated with null alleles, similar in nature to the alleles of *CACNA1A* that cause EA2, weaker missense alleles produce the milder phenotype of GEFS+. Furthermore, while most of the GEFS+ amino acid replacements occur in the transmembrane segments of the channel protein, and those rare SMEI amino acid replacements occur within the pore, the novel allele we report alters an amino acid in the conserved cytoplasmic linker region between the pseudo-monomer repeats in the channel protein, specifically between the IIS6 domain and the IIIS1 domain. It's of note that the initial FHM3 allele [13] also alters an amino acid in a comparable position, but in that case between the next pair of pseudo-monomer repeats, between the IIIS6 domain and the IVS1 domain, perhaps beginning to suggest some degree of genotype – phenotype correlation within the allelic spectrum for *SCN1A* as well. Finally, it is intriguing that two of the three *SCN1A* missense alleles found in familial autism [18] also alter amino acids found in cytosolic domains between S6 and S1 segments; the third is found at the C-terminus.

The overarching question posed by the FHM loci, however, is how the mutations perturb physiological homeostasis in specific cells to create a meta-stable state susceptible to recurrent periodic decompensations leading to the phenotype recognized as migraine. Clearly this requires not only a definition of the range of molecular alterations caused by pathogenic alleles, but also a definition of the critical cell(s) affected and the nature of allele-specific perturbations of that cell, two major areas for future investigation.

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