CACNA1A

Patient Description:
EM, now 21 years old, presented early in life with global developmental disabilities and hypotonia. She developed a seizure disorder, which has been reasonably well managed with anticonvulsants, and ataxia, which has caused problems with her balance. Also, some dysmorphic facial features are present. Early on, work-up, including karyotype, microarray comparative genomic hybridization, electromyography, nerve conduction studies and muscle biopsy failed to reveal an etiology. In 2017, whole exome sequencing revealed a de novo mutation in CACNA1A. Review of the literature revealed that the point mutation is unique.

Disease/Syndrome Features:
Mutations in CACNA1A cause three autosomal dominant neurological disorders: familial hemiplegic migraine type 1 (FHM1), episodic ataxia type 2 (EA-2), and spinocerebellar ataxia type 6 (SCA6) [Ophoff 1996, Zhuchenko 1997]. FHM is a particular type of migraine with aura featuring headaches that follow bouts of transient hemiparesis. Around 80 percent of families with hemiplegic migraine have what is termed pure FHM and the remainder have FHM with cerebellar signs including progressive cerebellar atrophy. CACNA1A mutations account for about half of all FHM cases and all FHM cases associated with cerebellar signs [Ophoff 1996, Ducros 2001]. In EA-2, another paroxysmal cerebellar disorder, patients experience related symptoms including acetazolamide-responsive attacks of cerebellar ataxia, migraine, nystagmus, and cerebellar atrophy [Von Brederlow 1995, Ophoff 1996]. Finally, SCA6 is an insidious and late-onset motor disorder. The clinical features initially described include progressive cerebellar ataxia of the limbs and gait, nystagmus, and dysarthria. Patients may become wheelchair bound over a period of 20 to 30 years and choking has been observed in older patients [Zhuchenko 1997]. Interestingly, each of these disorders involves a distinct type of CACNA1A mutation. Patients with FHM are generally found to have missense mutations, patients with EA-2 harbor premature stop codons either as a result of frameshift mutations or aberrant splicing, and patients with SCA6 show expansion of a polymorphic CAG repeat at the 3’ end of the gene [Ophoff 1996, Zhuchenko 1997].

In addition to these autosomal dominant disorders, the phenotypic landscape of CACNA1A dysfunction includes associations with both epilepsy and cognitive impairments. For example, idiopathic generalized epilepsy (IGE) exhibits a complex pattern of inheritance but has been shown to display allelic association with a single nucleotide polymorphism on exon 8 of CACNA1A [Chioza 2001]. Additionally, several studies have identified patients who display features of FHM1 or EA-2 in addition to status epilepticus, complex partial seizures, absence seizures, tonic-clonic seizures, or other epilepsy disorders [Ducros 2001, Jouveneau 2001, Kors 2004, Beauvais 2004]. Most recently, CACNA1A loss-of-function mutations and missense mutations have been demonstrated to cause some epileptic encephalopathies, a group of severe childhood epilepsy disorders including infantile spasms and Lennox-Gastaut Syndrome [Auvin 2009, Consortium 2013, Damaj 2015, Myers 2016]. In addition to seizures, patients with
CACNA1A mutations and epileptic encephalopathies showed a variety of cognitive manifestations including psychomotor delay, mild to profound intellectual disability, ADHD, and/or autism spectrum disorders [Auvin 2009, Damaj 2015, Myers 2016].

Protein/Pathway:
CACNA1A is located on the short arm of chromosome 19 at position 13.13 and encodes the α1A subunit of the neuronal P/Q-type Ca++ channel termed CaV2.1 [Ophoff 1996]. The structure of this pore-forming subunit is well-described and consists of an intracellular N-terminal domain, four repeated domains (I-IV) consisting of six α-helical membrane spanning segments (S1-S6), and an intracellular C-terminal domain. The S5 and S6 segments, as well as their joining P-loops, form the inner pore of the calcium channel and the S4 segments serve as its voltage sensor [Ophoff 1996]. P/Q-type Ca++ channels are widely expressed in the mammalian CNS and major transcripts were detected by Northern blot in rhesus monkey cerebellum, cerebral cortex, thalamus and hypothalamus [Ophoff 1996, Jouvenceau 2001]. Within the brain, they are found on the presynaptic side of synapses where they regulate neurotransmitter release [Westenbroek 1995]. P/Q-type Ca++ channels are strongly expressed in Purkinje cells and cerebellar granule cells. The mouse ortholog of the α1A subunit of the P/Q-type Ca++ channel is mutated in tottering and leaner mice, two models of absence seizures [Fletcher 1995].

Publications:


Support Groups and Information:
International Hemiplegic Migraine Foundation (Facebook)
National Ataxia Foundation
19p13.13 Microdeletion Leaflet