CACNA1A

Tutorial with Parents (September 25, 2018)
The *CACNA1A* tutorial took place in the Rose F. Kennedy IDDRC office during the late afternoon of September 25, 2017. Both parents were present, as was the patient's former pediatrician, Dr. Bob Marion, along with a diverse science team consisting of Dr. Kamran Khodakhah and his postdoctoral fellow, Dr. Heather Snell (calcium channel experts); Dr. Aristea Galanopoulou (a seizure specialist); and Dr. Herb Lachman (an iPSC expert). In addition, a medical student (Adam Kopp) who had prepared the research summary for this gene also attended. The meeting was hosted by Dr. Walkley. Dr. Marion reviewed the clinical history of the patient and the parents added much detail about their daughter's experiences living with this condition. The main science tutorial was presented by Drs. Khodakhah and Snell, offering insights into the complex disease forms (see below) that emerge when this channel is absent or abnormal in the CNS. Drs. Galanopoulou and Lachman added further explanations about seizure issues in this condition and how iPSCs could be useful in sorting basic mechanisms of disease. Drs. Khodakhah and Snell also offered that they would undertake an effort to make a mouse model in which the patient's mutation would be knocked in, with this effort supported by funds available to Dr. Khodakhah. In addition, in 2019 Dr. Lachman received an IDDRC pilot grant award to study the underlying mechanisms of *CACNA1A*-associated intellectual disability using human cerebellar neurons derived from induced pluripotent stem cells from the patient.

In February, 2019, the entire family participated in Einstein's Rare Disease Day program in LeFrak auditorium, with Dr. Snell providing a brief research summary on the gene and her efforts to understand the disease.

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 wheel-chair 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, Jouvenceau 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 α_{1A} 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, these voltage-gated calcium channels (VGCC) are most often found on the presynaptic side of synapses where they regulate

neurotransmitter release [Westenbroek 1995]. More recently, VGCC containing CACNA1A have also been reported to be present in lysosomal membranes of cells where they function to facilitate (via Ca++ release) the fusion of lysosomes with endosomes and autophagosomes [Tian, et al.,2015]. CACNA1A channels are strongly expressed in Purkinje cells and cerebellar granule cells. The mouse ortholog of the α_{1A} subunit of the P/Q-type Ca^{++} channel is mutated in tottering and leaner mice, two models of absence seizures [Fletcher 1995]. In addition to synaptic abnormalities, these mice have also been shown to exhibit defects in lysosomal function and neuronal homeostasis [Tian, et al., 2015].

Publications:

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Support Groups and Information:

International Hemiplegic Migraine Foundation (Facebook)
National Ataxia Foundation
19p13.13 Microdeletion Leaflet
Multiple CACNA1A Facebook groups are also available.
Parents of kiddos with EA2 (Episodic Ataxia Type 2) (Facebook)
Episodic Ataxia Support Group (Facebook)
Spinocerebellar Ataxia Awareness and Research Support Group (Facebook)
Ataxia Caregiver Support Group (Facebook)

Last updated: 4/19/2020, MKR