KCNA2

Tutorial with Parents:
(pending)

Patient Description:
EK was referred for evaluation at 6 years of age. The product of an uncomplicated pregnancy and delivery, he was in excellent health until the age of 16 months, when he experienced a seizure with fever. Evaluation at that time was negative for an etiology, and a diagnosis of febrile seizure was made. A second seizure occurred with fever when EK was 21 months and a third when he was 23 months. EK has had a total of approximately eight seizures with fever, with no more than two seizures occurring per year. He has never been treated with anti-convulsant medication.

At two years of age, he was evaluated by a neurologist who was concerned about his delayed development. EK was diagnosed with speech delay, impaired fine and gross motor skills, and delays in executive planning. On physical exam, he was noted to have mildly dysmorphic facial features and diffuse hypotonia. His cognitive skills were judged to be appropriate for his age. He was felt to have features of an autism spectrum disorder.

Following this evaluation, EK received physical, occupational, and speech therapy. A course of Applied Behavioral Analysis (ABA) therapy was also begun. He has made tremendous progress.

Because of his history of developmental disabilities, autism spectrum disorder, and seizures associated with fever, and the findings of dysmorphic features and hypotonia, whole exome sequencing was ordered. Results revealed a de novo variant of unknown significance in *KCNA2* (T698C). Pathogenic variants in *KCNA2* are known to be associated with Early Infantile Epileptic Encephalopathy, type 32.

Disease/Syndrome Features:

The KCNA2 gene, located on chromosome 1p13.3, encodes K_v 1.2, a potassium voltage-gated channel expressed in the brain [Syrbe 2015]. Pathogenic variants in the gene have been found to cause epileptic encephalopathy, hereditary spastic paraplegia, ataxia, and milder types of epilepsy [Masnada 2017]. With epileptic encephalopathy, development may be normal prior to the beginning of seizures and severely affected after the onset of seizures. After the onset of seizures, individuals have been found to have delayed speech development and intellectual disability.

Three main phenotypes have been observed with KCNA2 encephalopathy. They include: (1) features associated with loss-of-function variants; (2) features associated with gain-of-function variants; and (3) features associated with a combination of both gain-and-loss-of-function. All three of these phenotypes share some features in common, including onset of seizure within the first two years of life, and developmental and cognitive impairment. Most patients with any pathogenic variants in *KCNA2* manifest delays in motor development, abnormalities in coordination, and/or ataxia. These changes appear to be due to abnormal functioning of the potassium channels in the cerebellum.

Overall, individuals with the loss-of-function phenotype have milder disease outcomes than those who have either gain-of-function or gain-and-loss-of-function phenotypes.

In individuals with both the gain-of-function and gain-and-loss-of-function groups, there is more cerebellar dysfunction and severe ataxia when compared with those who have the loss-of-function phenotype. This was consistent with MRI findings of greater cerebellar atrophy in individuals with these two classes of variants. Additional examples of cerebellar dysfunction in these groups include impaired coordination and dysarthria.

Though all groups displayed some degree of cognitive impairment, these issues were more severe in those individuals who had gain-of-function variants. Language impairment was observed in nearly all patients.

Types of seizure, as well as outcome of the seizure disorders also could be stratified according to types of variant identified in *KCNA2*. Individuals with loss-of-function variants more commonly experienced focal seizures. Some were observed to have significant epileptiform activity during non-REM sleep accompanied by additional decline in cognitive, behavioral and language functioning. This is concerning for the condition of electrical status epilepticus in sleep (ESES), which may require different treatment from typical seizure therapies to improve neurodevelopmental outcomes [Nickels 2008]. A large proportion of these patients eventually become seizure-free.

Nearly all subjects in the gain-of-function only group experienced generalized seizures, including absence, myoclonic, and generalized tonic-clonic seizures.

In the gain-and-loss-of function group, there were similar amounts of subjects who experienced focal versus generalized seizures. Some individuals in this group with the T364A mutation had the most severe phenotypes compared with the other groups; these patients had intractable epilepsy, profound intellectual disability, spastic tetraplegia, choreoathetosis, and optic atrophy. In contrast to the individuals with loss-of-function variants, those in the gain-of-function and gain-and-loss-of-functions groups mostly never became seizure-free, though the frequency and severity of their seizures generally decreased over time. Individuals in all groups - whether loss-of-function, gain-of-function, or gain-and-loss-of function groups, generally remain on antiepileptic medication [Masnada 2017].

Protein/Pathway:

The potassium channel $K_v1.2$ is part of the K_v1 family of proteins which are expressed in the central nervous system. These channels play a vital role in neurotransmitter release and neuronal excitability.

$K_v1.2$ is part of the delayed rectifier class of potassium channels that enable neuronal repolarization after an action potential. These channels permit the efflux of the potassium ion (K^+) after the initial influx of sodium ions (Na^+), repolarizing the neuronal membrane and limiting the firing and duration of the nerve impulse.

These channels have four subunits with six transmembrane segments each. Some of these segments sense voltage, while others comprise the pore region where ions pass through. Different K_v1 subunits can assemble in particular combinations to form various channels with distinct qualities that determine voltage dependence.

As noted above, various changes in the DNA sequence of *KCNA2* have been found to cause loss-of-function, gain-of-function, or gain-and-loss function variations in the expressions of the protein.

Pathogenic variants associated with loss-of-function include Q213* (truncation), I263T, G398C, and P405L. These variants decrease neuronal voltage amplitude, impair neuronal repolarization, and lead to neuronal hyperexcitability due to the decreased efflux of potassium.

Variants associated with gain-of-function include G157K, R297Q, and L298F. These variants increase the amplitude of the neuronal voltage, causing hyperpolarization of the membrane potential, and inhibit the firing of neurons due to the increased efflux of potassium.

Finally, those variants known to be associates of both a gain and loss of function include L298R, L293H, and T374A. The gain-and-loss-of-function mutations have mixed features due to shifts in voltage-gated activation and inactivation curves along with decreased amplitude [Masnada 2017].

Publications:

Masnada, S., Hedrich, U. B. S., Gardella, E., Schubert, J., Kaiwar, C. (2017). Clinical spectrum and genotype–phenotype associations of KCNA2-related encephalopathies. *Brain* , 140 (9), 2337–2354.

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Syrbe, S., Hedrich, U. B., Riesch, E., Djemie, T., Muller, S., Moller, R. S., et al. (2015). *De novo* loss- or gain-of-function mutations in KCNA2 cause epileptic encephalopathy. *Nature Genetics*, 47: 393- 9. https://www.nature.com/articles/ng.3239