What is SCN8A?

SCN8A is a gene that encodes a sodium channel in the brain known as $Na_V1.6$, which functions to regulate neuron excitability in the nervous system. SCN8A gene variants often cause disorders of the brain and are associated with epilepsy and related disorders that begin in early childhood. The spectrum of epilepsy and brain involvement may be quite variable.

Most SCN8A GOF variants result in a moderate-severe developmental and epileptic encephalopathy (DEE), which is the most common presentation of this genetic condition. DEE associated with SCN8A variants has been classified as Early Infantile Epileptic Encephalopathy type 13 (EIEE13.) Individuals affected by SCN8A DEE may present with developmental delay, difficult to control seizures of various types, intellectual disability, low muscle tone (hypotonia), autistic features, movement disorders, improper regulation of the autonomic nervous system (dysautonomia), and blindness due to cortical visual impairment.

Subjects carrying milder GOF variants may present with relatively benign infantile onset seizures and paroxysmal dyskinesia, which is characterized by intermittent involuntary abnormal movements that may look like seizures. Children with this type of presentation have normal cognition (BFIS5) and seizures are often outgrown. Some children may have seizures that are partially or fully controlled with typical neurocognitive development. Patients with LOF variants generally have mild cognitive impairment, movement disorders, and/or autistic features. While some patients may have mild seizures, seizures are often absent.

In most cases, the pathogenic SCN8A variant is not inherited. That is, it occurs as a new variant (*de novo*). This happens when the variant occurs in one of the parent's gametes (a sperm or egg) before the egg is fertilized at conception. Occasionally the pathogenic variant is inherited from a mildly affected or unaffected parent. The latter case may be the result of parental mosaicism in which the variant is present in a subset of the parent's cells.

Gene variants alter specific amino acids in the $Na_V1.6$ sodium channel protein. While most variants are unique to single patients, there are certain variants that have been found in more than one patient across the world. These variant hotspots affect approximately 30% of cases.

Other names for SCN8A: Early Infantile Epileptic Encephalopathy type 13 (EIEE13.)

What types of seizures (and epilepsies) are associated with variants in SCN8A?

Children with SCN8A-related epilepsy may develop different types of seizures, including focal seizures or focal seizures that evolve to generalized tonic-clonic seizures, infantile or epileptic spasms, tonic seizures, absence seizures, and myoclonic seizures. Febrile seizures are infrequent. Spontaneous non-febrile, prolonged seizures or status epilepticus, with or without visible convulsions, may occur in some cases.

Seizure frequency is variable ranging from many seizures a day to a few seizures a month. Although some children may have seizure free periods, the seizures are typically difficult to control with medical therapy and may evolve over time. The main type of epilepsy in subjects with LOF variants is absence seizures.

What are non-seizure symptoms seen in individuals with variants in SCN8A?

Non-seizure symptoms that occur with SCN8A variants include intellectual disability, autism spectrum disorder, or movement disorders.

How is SCN8A-related epilepsy diagnosed?

Symptoms that may suggest SCN8A-related epilepsy include seizures beginning in infancy or early childhood, especially when combined with intellectual disability, autism spectrum disorder, or movement disorders. Seizure onset is typically from birth to 18 months with an average age of onset of 4-5 months. However, there is a range of onset times with nearly 20% of patients experiencing a first seizure in the neonatal period, and about 12% with an onset time at >10 months. Another possible sign of SCN8A-related epilepsy is a delay in achieving developmental milestones in infancy or early childhood. However, because there are other multiple genetic disorders with similar symptoms, clinical findings alone may not establish a firm diagnosis.

The diagnosis of SCN8A-related disorder is established by identification of a pathogenic variant in the SCN8A gene through molecular genetic testing, included in multi-gene epilepsy panels or whole exome sequencing (WES). Additional diagnosis testing by electroencephalogram (EEG) and magnetic resonance imaging (MRI) may yield evidence of abnormalities and may lead to additional diagnoses defined on EEG patterns (e.g., Lennox-Gastaut syndrome) or seizure types (e.g., West Syndrome.)

How is SCN8A-related epilepsy treated?

The type and severity of seizures guide treatment strategies, as does the type of variant carried by a patient. Unlike LOF variants, the GOF mechanism predicts that seizures are likely to respond to sodium channel blocking medications (SCB). SCBs are usually very effective in people with milder manifestations, while subjects with more severe GOF variants or seizure clusters tend to require combinations of medications, including anti-seizure medications that alter neuronal excitability by other mechanisms such as GABAergic drugs (e.g., clobazam). Favorable responses to SCBs such as carbamazepine, oxcarbazepine and phenytoin are common, while more variable responses have been reported with lacosamide, valproate, lamotrigine, topiramate, zonisamide, and rufinamide. Cannibidiol (CBD) may also be effective.

Epileptic spasms may respond favorably to high dose corticosteroids or adrenocorticotrophic hormone, or in some cases vigabatrin, but control of spasms may be difficult and may not be sustained. There is a growing consensus that seizures may be exacerbated with the use of levetiracetam, although ~10% of patients do well with this medication.

Rescue medications such as diazepam, clonazepam, and midazolam are often required to help stop or shorten clusters of seizures when they occur. When medications are not effective in controlling seizures, other options include implantable devices (e.g., vagus nerve stimulation (VNS) and dietary therapy (e.g., ketogenic diet or modified Atkins diet). Physical, occupational, and speech therapies are recommended in cases with cognitive and developmental delays or autism spectrum disorder.

How common is SCN8A?

SCN8A is estimated to comprise 1% of epileptic encephalopathies and incidence is estimated to be ~1/56,000 births.

What is the outlook for people with SCN8A-related epilepsy and related disorders?

Children with the typical form of SCN8A epileptic encephalopathy have significant developmental impairment and mild to severe intellectual disability and features of autism. Drug-resistant seizures will likely require ongoing treatment with the use of multiple medications. For subjects with moderate GOF variants, anti-seizure medications are more effective and fewer developmental delays and regressions are expected over time. Subjects may also be ambulatory and develop some speech and language function. For all patients with epileptic encephalopathy, developmental regression events may recur in association with increases in seizures, illnesses, vaccinations, changes in medication, or with unknown causes. While the overall mortality in SCN8A-related epilepsies is relatively high (estimated at 5.3%), the majority of these patients suffer a gradual

worsening of their neurologic and overall condition, and only a minority (estimated at 1.6%) experience sudden unexplained death in epilepsy (SUDEP).

Subjects with milder GOF variants are expected to have a more benign course as seizures are under better control. These patients often have relatively normal cognition and motor abilities. Although, language delays are more likely. Less is known about long term outcome in patients with LOF variants who show variable intellectual disability, movement disorder, ataxia, and seizure activity.

For more information

- A website devoted to SCN8A Epilepsy and Related Disorders was established in 2014 to provide scientific and medical information to families, clinicians, and researchers. It also serves as a portal to an online registry for families who want to participate in SCN8A research.
- Wishes for Elliott, Advancing SCN8A Research
- The Cute Syndrome Foundation

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