SCN1A-RELATED SEIZURE DISORDERS

GENETIC TESTING

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What are *SCN1A*-related seizure disorders?

***SCN1A* is a gene. Genes are present in every cell of the body. They carry the instructions for making proteins that control how each cell functions. The *SCN1A* gene makes a protein that controls the movement of sodium in and out of cells in the brain. This flow of sodium is how brain cells send signals to each other. When there is a defect in the *SCN1A* gene, the normal signaling pathway of brain cells may be cut off. This can result in a seizure disorder. An *SCN1A*-related seizure disorder may be mild and short-lived, like the seizures that affect some young children when they have fevers (febrile seizures), or it may be a condition like severe myoclonic epilepsy of infancy (SMEI) that causes recurrent, difficult-to-control seizures.**[1]

What is SMEI?

Severe myoclonic epilepsy of infancy (SMEI) is a rare childhood brain disorder. It affects about 1 in 40,000 children.[2] Other names for SMEI are Dravet syndrome and polymorphic myoclonic epilepsy of infancy (PMEI).

A child with SMEI will start having seizures before 1 year of age, typically when he or she has a fever.

- These seizures may be tonic (causing the arm, leg, and head muscles to stiffen), clonic (causing the muscles to twitch and jerk), or tonic-clonic.[2,3]
- The seizures may affect the muscles on just one side of the body or both sides.[2,4]
- The seizures tend to be long lasting and can lead to status epilepticus, which is the name for a seizure that lasts longer than 30 minutes or several seizures that occur one right after the other. Status epilepticus is a medical emergency.
- The seizures usually do not respond well to treatment.[3]

Starting at about 2 years of age, a child with SMEI will start having seizures when his or her body temperature is normal.[2] Other types of seizures may occur at this stage, including the following[2-4]:

- Myoclonic (causing the muscles to jerk)
- Complex partial (causing decreased awareness and responsiveness to one's surroundings and involuntary behaviors, such as lip smacking or purposeless hand movements)
- Atypical absence (causing "staring spells" with eye blinking and jerking movements of the lips)

Many children with SMEI also experience speech and developmental delays, as well as loss of muscle coordination (ataxia).[2,4] Additionally, affected children may develop attention deficit hyperactivity disorder (ADHD)-like symptoms such as difficulty controlling behavior and difficulty staying focused and paying attention.[1] They may also develop a brain disease called epileptic encephalopathy.[1]

There is no cure for SMEI at this time; however, when the disorder is correctly diagnosed, a treatment plan can be created to help manage seizures.

What causes *SCN1A*-related seizure disorders?

SCN1A-related seizure disorders are caused by a defective gene. Normally, each of your cells carries 2 copies of all your genes. You inherit 1 copy of a gene from each of your parents. Genes can undergo abnormal changes (mutations) that may lead to cells not working properly. This can result in health and developmental disorders that can be passed from parent to child (inherited).

- More than 100 different *SCN1A* mutations have been found in people with SMEI.[5] Studies show that as many as 95% of *SCN1A* mutations are *de novo*.[1-3,5] This means the gene mutation is not inherited but occurs for the first time in the affected child.
- About 10 different mutations have been found in children with febrile seizures and 8 mutations in children with generalized epilepsy febrile seizures plus (GEFS+).[1] GEFS+ causes febrile and other types of seizures that can last beyond childhood.

In cases in which *SCN1A* mutations are passed from parent to child, it happens in an autosomal dominant

manner.[1] This means a child needs to inherit just 1 copy of the *SCN1A* gene mutation to be at risk for an *SCN1A*-related seizure disorder. However, because of a feature of autosomal dominant inheritance called reduced penetrance, not all children who inherit defective *SCN1A* genes will develop a seizure disorder.[1]

Knowing whether the parents of a child with signs and symptoms of an *SCN1A*-related seizure disorder carry an *SCN1A* mutation may help a doctor diagnose such a disorder and find out whether other family members are at risk for the disorder.

How is an *SCN1A*-related seizure disorder diagnosed?

The diagnosis of an *SCN1A*-related seizure disorder can be quite challenging because many conditions cause seizures. Symptoms can vary from mild to severe among patients and within families. Your doctor may consider the following factors when determining whether your child has an *SCN1A*-related seizure disorder:

- History of seizures including age of onset, type of seizures, and how often seizures occur
- Details about the child's development
- Results of electroencephalogram (EEG), a procedure that records electrical activity in the brain
- Whether one or more family members have been diagnosed with epilepsy

If there is reason to believe your child may have an *SCN1A*-related seizure disorder, his or her doctor may order a blood test to find out if your child has an *SCN1A* gene mutation.

What possible gene sequencing test results can be reported and what do they mean?

- **Negative:** After scanning the *SCN1A* gene, no detectable mutations were found. This test does not detect all possible mutations in the *SCN1A* gene. For this reason, a negative result cannot completely rule out an *SCN1A* mutation or a mutation in another gene as the cause of a child's epilepsy.
- **Positive**: After scanning the *SCN1A* gene, a mutation was found. Along with the child's signs and symptoms, a positive genetic test result may confirm a diagnosis of an *SCN1A*-related seizure disorder.
- **Variant of unknown significance:** After scanning the *SCN1A* gene, a mutation was found that has not been reported before. It is unclear if this mutation is the cause of the child's symptoms. In some cases it may be helpful to test the child's parents to find out if 1 or both of them carry the same mutation. If either parent tests positive for the mutation and does not have epilepsy, then it is unlikely that the mutation is the cause of the child's symptoms.

Gene sequencing test results should be combined with clinical findings and reviewed by a heath professional who specializes in medical genetics.

Where can I find more information?

If you have questions or want more information about genetic testing for *SCN1A*-related seizure disorders, ask your doctor or genetic counselor. You may search for a genetic counselor in your area using an online address book provided by the National Society of Genetic Counselors at **www.nsgc.org**.

Other information resources include:

- American Epilepsy Society (AES)
  Telephone: 860-586-7505
  Home page: **www.aesnet.org**
- Epilepsy Foundation
  Telephone: 800-332-1000
  Home page: **www.epilepsyfoundation.org**
- National Institute of Neurological Disorders and Stroke
  Telephone: 800-352-9424
  Home page: **www.ninds.nih.gov**
- Dravet.org
  Telephone: 866-828-1843
  Home page: **www.dravet.org**

Note: This material is provided for general information purposes only. It is not intended as a substitute for medical advice and/or consultation with a physician or technical expert.

References

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