SCN4A gene

sodium voltage-gated channel alpha subunit 4

Normal Function

The *SCN4A* gene belongs to a family of genes that provide instructions for making sodium channels. These channels, which transport positively charged sodium atoms (sodium ions) into cells, play a key role in a cell's ability to generate and transmit electrical signals.

The *SCN4A* gene provides instructions for making a critical part (the alpha subunit) of sodium channels that are abundant in muscles used for movement (skeletal muscles). For the body to move, these muscles must tense (contract) and relax in a coordinated way. Muscle contractions are triggered by the flow of ions, including sodium, into skeletal muscle cells. Channels made with the SCN4A protein control the flow of sodium ions into these cells.

Health Conditions Related to Genetic Changes

Hyperkalemic periodic paralysis

More than 14 variants (also known as mutations) in the *SCN4A* gene have been found to cause hyperkalemic periodic paralysis, a condition that causes episodes of extreme muscle weakness that are often associated with high levels of potassium in the blood (hyperkalemia). The variants change single building blocks (amino acids) in the SCN4A protein, which alters the structure and function of sodium channels in skeletal muscle cells. These changes delay the closing of channels made with the SCN4A protein or prevent the channels from staying closed. As a result, sodium ions continue flowing into muscle cells abnormally. This increase in sodium ions triggers the release of potassium from muscle cells, which causes more sodium channels to open and stimulates the flow of even more sodium ions into these cells. These changes in ion transport reduce the ability of skeletal muscles to contract, leading to episodes of muscle weakness or paralysis.

Hypokalemic periodic paralysis

At least nine variants in the *SCN4A* gene have been identified in people with hypokalemic periodic paralysis, a condition that causes episodes of extreme muscle weakness that are associated with low levels of potassium in the blood (hypokalemia).

Variants in the *SCN4A* gene account for about 10 percent of all cases of this condition. Each of the known variants changes a single amino acid in the SCN4A protein, which alters the structure and function of sodium channels in skeletal muscle cells. The abnormal channels change the normal flow of sodium ions, which prevents muscles from contracting normally. Low potassium levels also contribute to this problem. Because muscle contraction is needed for movement, these changes in ion transport lead to long-lasting episodes of severe muscle weakness.

Paramyotonia congenita

At least 28 variants in the *SCN4A* gene are known to cause paramyotonia congenita, a muscle disease characterized by episodes of sustained muscle tensing (myotonia) that prevent muscles from relaxing normally. The *SCN4A* gene variants that cause this condition each change a single amino acid in the SCN4A protein, which alters the structure and function of sodium channels in skeletal muscle cells. The most common genetic changes replace the amino acid arginine with one of several other amino acids at protein position 1448.

Variants delay the closing of channels made with the SCN4A protein and, once the channels are closed, cause them to open again too quickly. These changes increase the flow of sodium ions into skeletal muscle cells. An influx of extra sodium ions triggers prolonged muscle contractions, which underlie the episodes of myotonia characteristic of paramyotonia congenita. Muscles with sustained high levels of sodium ions may become unable to contract at all, resulting in attacks of muscle weakness. Additionally, the effects of *SCN4A* gene variants on the altered ion channels may be increased by cold temperatures, which may help explain why signs and symptoms can be triggered by exposure to cold.

Potassium-aggravated myotonia

Several variants in the *SCN4A* gene result in potassium-aggravated myotonia, a condition that causes episodes of myotonia that prevent muscles from relaxing. The resulting muscle stiffness may be triggered (aggravated) by eating potassium-rich foods, such as bananas and potatoes.

The most common genetic changes associated with potassium-aggravated myotonia replace the amino acid glycine with one of several other amino acids at position 1306 in the SCN4A protein. These variants delay the closing of channels made with the SCN4A protein, which increases the flow of sodium ions into skeletal muscle cells. When excess potassium is present in the body, which occurs after eating potassium-rich foods, even more sodium ions flow into skeletal muscle cells in order to maintain a proper balance of calcium and potassium. These changes in ion transport trigger prolonged muscle contractions, which underlie the muscle stiffness characteristic of potassium-aggravated myotonia.

Congenital myasthenic syndrome

MedlinePlus Genetics provides information about Congenital myasthenic syndrome

Other Names for This Gene

- Na(V)1.4
- Nav1.4
- SCN4A_HUMAN
- skeletal muscle voltage-dependent sodium channel type IV alpha subunit
- SkM1
- sodium channel, voltage gated, type IV alpha subunit
- sodium channel, voltage-gated, type IV, alpha
- sodium channel, voltage-gated, type IV, alpha subunit
- voltage-gated sodium channel type 4 alpha

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of SCN4A (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=6329[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28SCN4A%5BTIAB%5D%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- SODIUM VOLTAGE-GATED CHANNEL, ALPHA SUBUNIT 4; SCN4A (https://omim.org/entry/603967)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/6329)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=SCN4A[gene])

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Genomic Location

The *SCN4A* gene is found on chromosome 17 (https://medlineplus.gov/genetics/chromosome/17/).

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