

SCN4A Gene

Subjects: **Genetics & Heredity**

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sodium voltage-gated channel alpha subunit 4

genes

1. 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 normally, these muscles must tense (contract) and relax in a coordinated way. One of the changes that helps trigger muscle contractions is the flow of positively charged atoms (ions), including sodium, into muscle cells. Channels made with the SCN4A protein control the flow of sodium ions into these cells.

2. Health Conditions Related to Genetic Changes

2.1. Hyperkalemic periodic paralysis

More than 10 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 mutations 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.

2.2. Hypokalemic periodic paralysis

At least seven mutations 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). Mutations in the SCN4A gene account for about 10 percent of all cases of this condition. Each of the known mutations 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.

2.3. Paramyotonia congenita

At least 18 mutations 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 mutations 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.

Mutations 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.

The effects of SCN4A gene mutations 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.

2.4. Potassium-aggravated myotonia

Several mutations in the SCN4A gene result in potassium-aggravated myotonia, a condition that causes episodes of myotonia that prevent muscles from relaxing normally. The resulting muscle stiffness may be aggravated by eating potassium-rich foods. The most common genetic changes associated with potassium-aggravated myotonia replace the amino acid glycine with one of several other amino acids at protein position 1306. These mutations delay the closing of channels made with the SCN4A protein, which increases the flow of sodium ions into skeletal muscle cells. The presence of excess potassium stimulates the flow of even more sodium ions into these cells. These changes in ion transport trigger prolonged muscle contractions, which underlie the muscle stiffness characteristic of potassium-aggravated myotonia.

2.5. Other disorders

A mutation in the SCN4A gene is also responsible for one form of congenital myasthenic syndrome, a muscle disorder that appears shortly after birth. People with this condition have general muscle weakness and recurrent attacks of paralysis that specifically affect muscles used for speaking and breathing. The SCN4A gene mutation associated with this condition replaces the amino acid valine with the amino acid glutamic acid at protein position

1442 (written as Val1442Glu or V1442E). This genetic change alters the structure and function of sodium channels in skeletal muscle cells. The channels stay closed abnormally after repeated muscle contractions, reducing the flow of sodium ions into muscle cells. This disruption in ion transport reduces further muscle contraction, leading to muscle weakness and episodes of paralysis.

3. 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

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