SCN5A gene

sodium voltage-gated channel alpha subunit 5

Normal Function

The *SCN5A* gene belongs to a family of genes that provide instructions for making sodium channels. These channels open and close at specific times to control the flow of positively charged sodium atoms (sodium ions) into cells. The sodium channels containing proteins produced from the *SCN5A* gene are abundant in heart (cardiac) muscle cells and play key roles in these cells' ability to generate and transmit electrical signals. These channels play a major role in signaling the start of each heartbeat, coordinating the contractions of the upper and lower chambers of the heart, and maintaining a normal heart rhythm.

Health Conditions Related to Genetic Changes

Brugada syndrome

More than 400 mutations in the *SCN5A* gene have been identified in people with Brugada syndrome, which is a heart condition characterized by an irregular heart rhythm (arrhythmia). *SCN5A* gene mutations also cause sudden unexpected nocturnal death syndrome (SUNDS), which was originally described in Southeast Asian populations. Researchers have since determined that SUNDS and Brugada syndrome are the same disorder.

Some *SCN5A* gene mutations associated with Brugada syndrome change single protein building blocks (amino acids) in the SCN5A protein. These mutations alter the structure of ion channels made with the SCN5A protein and disrupt the flow of sodium ions into cardiac muscle cells. Other mutations prevent the *SCN5A* gene from producing any functional ion channels, which also reduces the inward flow of sodium ions. A disruption in ion transport changes the way the heart beats, leading to the arrhythmia often found in Brugada syndrome and SUNDS.

Progressive familial heart block

A few mutations in the *SCN5A* gene have been found to cause progressive familial heart block. This condition alters the normal beating of the heart and can lead to fainting (syncope) or sudden cardiac arrest and death. The *SCN5A* gene mutations change single amino acids in the SCN5A protein. Channels made with this altered protein allow

little or no sodium to enter the cell. Cardiac cells with these altered channels have difficulty producing and transmitting electrical signals that coordinate normal heartbeats. Interruption of this signaling is known as heart block. The impaired cardiac cells die, leading to a buildup of scar tissue (fibrosis) over time that worsens the heart block.

Romano-Ward syndrome

At least 238 mutations in the *SCN5A* gene are known to cause Romano-Ward syndrome, which is the most common form of an arrhythmia called long QT syndrome. Mutations in this gene account for five to 10 percent of cases of Romano-Ward syndrome. In individuals with this condition the cardiac muscle takes longer than usual to recharge between beats.

The *SCN5A* gene mutations that cause Romano-Ward syndrome include changes in single amino acids and deletions or insertions of a small number of amino acids in the SCN5A protein. Channels made with these altered SCN5A proteins stay open longer than usual, which allows sodium ions to continue flowing into cardiac muscle cells abnormally. This delay in channel closure alters the transmission of electrical signals in the heart, increasing the risk of an irregular heartbeat that can cause syncope or sudden death.

Sick sinus syndrome

At least 16 mutations in the *SCN5A* gene have been found to cause another heart condition called sick sinus syndrome. This condition affects the function of the sino-atrial (SA) node, which is an area of specialized cells in the heart that functions as a natural pacemaker. The *SCN5A* gene mutations that cause sick sinus syndrome lead to the production of nonfunctional sodium channels or abnormal channels that cannot transport ions properly. The flow of these ions is essential for creating the electrical impulses that start each heartbeat and spread these signals to other areas of the heart. Mutations reduce the flow of sodium ions, which alters the SA node's ability to create and spread electrical signals. These changes increase the risk of abnormally fast or slow heartbeats, which can cause dizziness, light-headedness, syncope, and related symptoms.

Familial atrial fibrillation

MedlinePlus Genetics provides information about Familial atrial fibrillation

Familial dilated cardiomyopathy

MedlinePlus Genetics provides information about Familial dilated cardiomyopathy

Left ventricular noncompaction

MedlinePlus Genetics provides information about Left ventricular noncompaction

Other disorders

Variations in the *SCN5A* gene are associated with several other heart conditions. These include potentially life-threatening forms of arrhythmia called atrial fibrillation and ventricular fibrillation. The genetic variations associated with these conditions alter the flow of sodium ions through the channel, which can lead to abnormal heart rhythms and affect the heart's ability to pump blood.

SCN5A gene mutations have also been identified in some cases of sudden infant death syndrome (SIDS). SIDS is a major cause of death in babies younger than 1 year. It is characterized by sudden and unexplained death, usually during sleep. Researchers are working to determine how changes in the *SCN5A* gene could contribute to SIDS. Other genetic and environmental factors, many of which have not been identified, also play a part in determining the risk of this disorder.

Certain drugs, including medications used to treat arrhythmias, infections, seizures, and psychotic disorders, can lead to an abnormal heart rhythm in some people. This drug-induced heart condition, which is known as acquired long QT syndrome, increases the risk of cardiac arrest and sudden death. A small percentage of cases of acquired long QT syndrome occur in people who have an underlying change in the *SCN5A* gene.

Other Names for This Gene

- HH1
- LQT3
- Nav1.5
- SCN5A_HUMAN
- Sodium channel protein, cardiac muscle alpha-subunit
- sodium channel, voltage gated, type V alpha subunit
- sodium channel, voltage-gated, type V, alpha (long QT syndrome 3)
- sodium channel, voltage-gated, type V, alpha subunit
- SSS1

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of SCN5A (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=6331[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28SCN5A%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+720+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- SODIUM VOLTAGE-GATED CHANNEL, ALPHA SUBUNIT 5; SCN5A (https://omim.org/entry/600163)
- CARDIOMYOPATHY, DILATED, 1E; CMD1E (https://omim.org/entry/601154)
- SUDDEN INFANT DEATH SYNDROME (https://omim.org/entry/272120)
- VENTRICULAR FIBRILLATION, PAROXYSMAL FAMILIAL, 1; VF1 (https://omim.org/entry/603829)
- ATRIAL FIBRILLATION, FAMILIAL, 10; ATFB10 (https://omim.org/entry/614022)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/6331)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=SCN5A[gene])

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Genomic Location

The *SCN5A* gene is found on chromosome 3 (https://medlineplus.gov/genetics/chromosome/3/).

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