

## CACNA1S gene

calcium voltage-gated channel subunit alpha1 S

### Normal Function

The *CACNA1S* gene provides instructions for making the main piece (subunit) of a structure called a calcium channel. Channels containing the CACNA1S protein are found in muscles used for movement (skeletal muscles). These skeletal muscle calcium channels play a key role in a process called excitation-contraction coupling, by which electrical signals (excitation) trigger muscle tensing (contraction).

Calcium channels made with the CACNA1S subunit are located in the outer membrane of muscle cells, so they can transmit electrical signals from the cell surface to inside the cell. The channels interact with another type of calcium channel called ryanodine receptor 1 (RYR1) channels (produced from the *RYR1* gene). RYR1 channels are located in the membrane of a structure inside the cell that stores calcium ions. Signals transmitted by CACNA1S-containing channels turn on (activate) RYR1 channels, which then release calcium ions inside the cells. The resulting increase in calcium ion concentration within muscle cells stimulates muscles to contract, allowing the body to move.

### Health Conditions Related to Genetic Changes

#### Malignant hyperthermia

*CACNA1S* gene mutations account for a very small percentage of all cases of malignant hyperthermia. Malignant hyperthermia is a severe reaction to particular anesthetic drugs that are often used during surgery and other invasive procedures. The reaction involves a high fever (hyperthermia), a rapid heart rate, muscle rigidity, breakdown of muscle fibers (rhabdomyolysis), and increased acid levels in the blood and other tissues (acidosis). Complications can be life-threatening without prompt treatment. Researchers have identified several mutations in the *CACNA1S* gene that are associated with an increased risk of this condition. These mutations replace single amino acids in the CACNA1S protein.

Channels made with the altered CACNA1S proteins likely activate the RYR1 channel improperly in response to certain drugs (particularly some anesthetics and a type of muscle relaxant used during surgery). As a result, large amounts of calcium ions are released from storage within muscle cells. An overabundance of calcium ions activates

processes that generate heat (leading to increased body temperature) and produce excess acid (leading to acidosis). An increase in calcium ion concentration also causes skeletal muscles to contract abnormally, which leads to muscle rigidity.

### Hypokalemic periodic paralysis

At least 11 mutations in the *CACNA1S* gene have been identified in people with hypokalemic periodic paralysis, a condition that causes episodes of extreme muscle weakness, usually in the arms and legs. *CACNA1S* gene mutations cause up to 70 percent of all cases of this disorder.

Mutations in the *CACNA1S* gene change single protein building blocks (amino acids) used to make the *CACNA1S* protein, which alters the structure and function of calcium channels in skeletal muscle cells. The altered channels open more slowly than usual, reducing the flow of calcium ions into these cells. This disruption in calcium ion transport prevents muscles from contracting normally. It is unclear precisely how these changes lead to episodes of muscle weakness in people with hypokalemic periodic paralysis.

### **Other Names for This Gene**

- CAC1S\_HUMAN
- CACH1
- CACN1
- CACNL1A3
- calcium channel, voltage-dependent, L type, alpha 1S subunit
- Cav1.1
- CCHL1A3
- DHPR
- dihydropyridine receptor
- dihydropyridine-sensitive L-type calcium channel alpha-1 subunit
- HOKPP
- HypoKPP
- hypoPP
- MHS5
- Voltage-dependent L-type calcium channel subunit alpha-1S
- voltage-gated calcium channel subunit alpha Cav1.1

### **Additional Information & Resources**

#### Tests Listed in the Genetic Testing Registry

- Tests of *CACNA1S* ([https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=779\[geneid\]](https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=779[geneid]))

### Scientific Articles on PubMed

- PubMed (<https://pubmed.ncbi.nlm.nih.gov/?term=%28CACNA1S%5BTIAB%5D%29+OR+%28%28CACNL1A3%5BTIAB%5D%29+OR+%28CCHL1A3%5BTIAB%5D%29+OR+%28dihydropyridine+receptor%5BTIAB%5D%29+OR+%28HOKPP%5BTIAB%5D%29+OR+%28CACH1%5BTIAB%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

- CALCIUM CHANNEL, VOLTAGE-DEPENDENT, L TYPE, ALPHA-1S SUBUNIT; CACNA1S (<https://omim.org/entry/114208>)

### Gene and Variant Databases

- NCBI Gene (<https://www.ncbi.nlm.nih.gov/gene/779>)
- ClinVar ([https://www.ncbi.nlm.nih.gov/clinvar?term=CACNA1S\[gene\]](https://www.ncbi.nlm.nih.gov/clinvar?term=CACNA1S[gene]))

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## Genomic Location

The *CACNA1S* gene is found on chromosome 1 (<https://medlineplus.gov/genetics/chromosome/1/>).

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