RYR1 gene

ryanodine receptor 1

Normal Function

The *RYR1* gene provides instructions for making a protein called ryanodine receptor 1 (also called the RYR1 channel). This protein is part of a group of related proteins called ryanodine receptors, which form channels that, when turned on (activated), release positively charged calcium atoms (ions) from storage within cells. RYR1 channels play a critical role in muscles used for movement (skeletal muscles).

For the body to move normally, skeletal muscles must tense (contract) and relax in a coordinated way. Muscle contractions are triggered by an increase in the concentration of calcium ions inside muscle cells.

RYR1 channels are located in the membrane surrounding a structure in muscle cells called the sarcoplasmic reticulum. This structure stores calcium ions when muscles are at rest. In response to certain signals, the RYR1 channel releases calcium ions from the sarcoplasmic reticulum into the cell fluid. The resulting increase in calcium ion concentration in muscle cells stimulates muscles to contract, allowing the body to move. The process by which electrical signals trigger muscle contraction is called excitation-contraction (E-C) coupling.

Health Conditions Related to Genetic Changes

Central core disease

More than 100 mutations in the *RYR1* gene have been identified in people with central core disease. This condition is characterized by muscle weakness, primarily affecting the muscles near the center of the body (proximal muscles), such as the muscles in the upper legs and hips. Affected individuals also have an increased risk of malignant hyperthermia (described below).

Most of the *RYR1* gene mutations involved in central core disease affect single protein building blocks (amino acids) in critical regions of the ryanodine receptor 1 protein. These mutations change the structure of the RYR1 channel, which alters the normal flow of stored calcium ions within muscle cells. A disruption in calcium ion release prevents muscles from contracting normally, leading to the muscle weakness characteristic of central core disease.

Researchers have proposed two mechanisms to explain how *RYR1* gene mutations underlie muscle weakness in people with central core disease. Some genetic changes cause the RYR1 channel to be "leaky," allowing calcium ions to flow slowly but continually out of the sarcoplasmic reticulum. The leaky channels greatly reduce the amount of stored calcium ions. As a result, not enough calcium ions are available in the sarcoplasmic reticulum to trigger muscle contractions. Muscle weakness results from the inability of skeletal muscles to contract appropriately.

Other *RYR1* gene mutations change the structure of the RYR1 channel in a way that impedes the normal flow of calcium ions. Although the sarcoplasmic reticulum stores plenty of these ions, the receptor cannot release them in response to the usual signals. Without enough calcium ions flowing out of the sarcoplasmic reticulum at the appropriate time, muscles cannot contract normally and muscle weakness results. This mechanism is known as E-C uncoupling.

Congenital fiber-type disproportion

At least 11 mutations in the *RYR1* gene have been found to cause congenital fiber-type disproportion, a disorder that causes general muscle weakness that typically does not worsen over time. Some mutations change single amino acids in the ryanodine receptor 1 protein. Other *RYR1* gene mutations create a premature stop signal in the instructions for making the receptor, resulting in an abnormally short, nonfunctional protein. Researchers suspect that disruption of the RYR1 channel may play a role in the muscle weakness and other features of congenital fiber-type disproportion, although the role of *RYR1* gene mutations in this condition is unclear.

It is not yet clear whether people with congenital fiber-type disproportion caused by *RYR1* gene mutations have an increased risk of malignant hyperthermia (described below).

Malignant hyperthermia

RYR1 gene mutations are the most common genetic risk factor for 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 (tachycardia), 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.

At least 48 mutations in the *RYR1* gene are known to increase the risk of malignant hyperthermia in people without features of a muscle disorder (such as central core disease, described above, or multiminicore disease, described below). Most of these mutations change single amino acids in important regions of the ryanodine receptor 1 protein. These mutations alter the structure of the RYR1 channel, causing it to open more easily and close more slowly in response to certain drugs (particularly some anesthetic gases and a type of muscle relaxant used during surgery). As a result, large amounts of calcium ions are released from the sarcoplasmic reticulum inside 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 within muscle cells also causes skeletal muscles to contract abnormally, which leads to muscle rigidity.

Many other changes in the *RYR1* gene have been described in people with an increased risk of malignant hyperthermia. It is unclear, however, whether these variations are directly related to malignant hyperthermia risk.

Multiminicore disease

More than 20 mutations in the *RYR1* gene have been found to cause atypical forms of multiminicore disease. Multiminicore disease is characterized by muscle weakness, and the atypical forms can have additional features. The condition is also associated with an increased risk of malignant hyperthermia (described above).

RYR1 gene mutations involved in multiminicore disease change single amino acids in the ryanodine receptor 1 protein, which alters the structure and function of the protein. The effects of these changes are unclear. Some mutations may reduce the amount of ryanodine receptor 1 protein produced by the cell or lead to an unstable version of the protein. Other mutations may interfere with the normal regulation of the RYR1 channel. Researchers believe that some *RYR1* gene mutations change the shape of the channel in such a way that calcium ions cannot flow through properly. A disruption in calcium ion transport prevents muscles from contracting normally, leading to the muscle weakness characteristic of multiminicore disease.

Centronuclear myopathy

MedlinePlus Genetics provides information about Centronuclear myopathy

Other Names for This Gene

- CCD
- MHS
- MHS1
- PPP1R137
- ryanodine receptor 1 (skeletal)
- ryanodine receptor type1
- RYDR
- RYR
- RYR-1
- RYR1_HUMAN
- sarcoplasmic reticulum calcium release channel
- skeletal muscle ryanodine receptor
- Skeletal muscle-type ryanodine receptor

- SKRR

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of RYR1 (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=6261[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28%28RYR1%5BTIAB%5D%29+OR+%28ryanodine+receptor+1%5BTIAB%5D%29%29+AND+%28ryr1%5BMAJR%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+1080+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- RYANODINE RECEPTOR 1; RYR1 (https://omim.org/entry/180901)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/6261)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=RYR1[gene])

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Genomic Location

The *RYR1* gene is found on chromosome 19 (https://medlineplus.gov/genetics/chromosome/19/).

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