
Clinical Care Guidelines

**WHAT PATIENTS & FAMILIES
NEED TO KNOW ABOUT
RYR-1-RELATED DISEASES**





Disclaimer, please read:

The information and advice published or made available in the “Clinical Care Guidelines” are not intended to replace the services of a physician, nor does it constitute a physician-patient relationship. It is for educational purposes only. This advice should be taken in conjunction with medical advice from your medical clinician whom you should consult in all matters relating to your health, in particular with respect to symptoms that may require diagnosis or medical attention. Any action on your part in response to the information provided in this booklet is at your own discretion. Ultimately, if you have concerns about your health, including RYR-1-related diseases, you should consult your healthcare provider.

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Please note:

Throughout the Clinical Care Guidelines, there is text in **red bold font**. These items are hyperlinked to various chapters, graphics, and text throughout this document, as well as to additional outside resources. Please click on the items in this text to be redirected to additional resources within and outside of the Clinical Care Guidelines.

Most chapters begin with a table of terms that your doctors and/or providers may use. When these terms first appear within the chapter, they will be ***bold and italicized***.

In addition, most chapters conclude with “Additional Resources” for the topics that have been addressed. To access these resources, simply click on the laptop image, the phone image, or the red bold link for more information.



For additional resources, please click on the above image or visit:
www.ryr1.org/ccg-introduction

At the end of this handbook, there is an “**Index**” with important terms; page numbers where these terms appear are listed and are also **hyperlinked**.

Introduction

Your doctor may have just told you that you and/or your child has an **RYR-1-Related Disease** (RYR-1-RD). This guide is meant to help you understand the different symptoms you may see and the types of care that you and/or your family might need. Understanding this information will help you be a helpful partner in your and/or your family's care.

Words Your Doctor May Use

CCD: Central core disease - **Please see Chapter 2, "Clinical Features of RYR-1-RD."**

CFTD: Congenital fiber type disproportion - **Please see Chapter 2, "Clinical Features of RYR-1-RD."**

CNM: Centronuclear myopathy - **Please see Chapter 2, "Clinical Features of RYR-1-RD."**

Congenital: Present from birth.

MmD: Multi-minicore disease - **Please see Chapter 2, "Clinical Features of RYR-1-RD."**

Myopathy: Muscle disease where the muscle fibers do not work normally.

RYR-1-Related Diseases: Muscle disease due to a mutation in the *RYR1* gene. Similar terms include "RYR-1-Related Myopathy" and "RYR-1 Muscle Disease."

RYR-1-RD is a group of genetic diseases in which the muscles do not work properly. Another equivalent term you might hear is RYR-1 **myopathy**. In general, people with RYR-1-RD have muscle weakness or poor muscle tone. In some cases, children with RYR-1-RD might take longer to sit up, crawl, and walk. People with RYR-1-RD can also have problems with their spine, eye muscles, chewing, swallowing, and breathing. In addition, RYR-1-RD can cause a wide range of symptoms from mild weakness to severe weakness (at times requiring wheelchair assistance and breathing support) to a potentially fatal reaction to certain forms of anesthesia known as malignant hyperthermia (MH). Certain forms of RYR-1-RD can lead to heat intolerance, exertional heat stroke, and a severe form of muscle breakdown, called rhabdomyolysis.

Some Signs and Symptoms of RYR-1-RD

- Long, narrow face
 - Drooping eyelids (ptosis)
 - Restricted movements of the eye muscles
 - Muscle weakness:
 - Facial muscles and muscles of the arms and legs
 - Delays in sitting, walking, etc.
 - Difficulties getting up from the floor or out of a chair
 - Difficulties walking or running
 - Difficulties with stairs
 - Muscle wasting (muscles get smaller over time)
 - Fixed or stiff joints
 - Changes in the shape of the chest
 - Hip dislocation
 - Eating difficulties
 - Breathing difficulties, including sleep apnea
 - Fatigue, especially in warm weather
 - Malignant hyperthermia (MH)
 - Exertional heat stroke
 - Rhabdomyolysis (a severe form of muscle breakdown)
-

There are several types of RYR-1-RD. They can be hard to tell apart, and they can be hard to distinguish from other muscle diseases. To diagnose RYR-1-RD, doctors may perform the following:

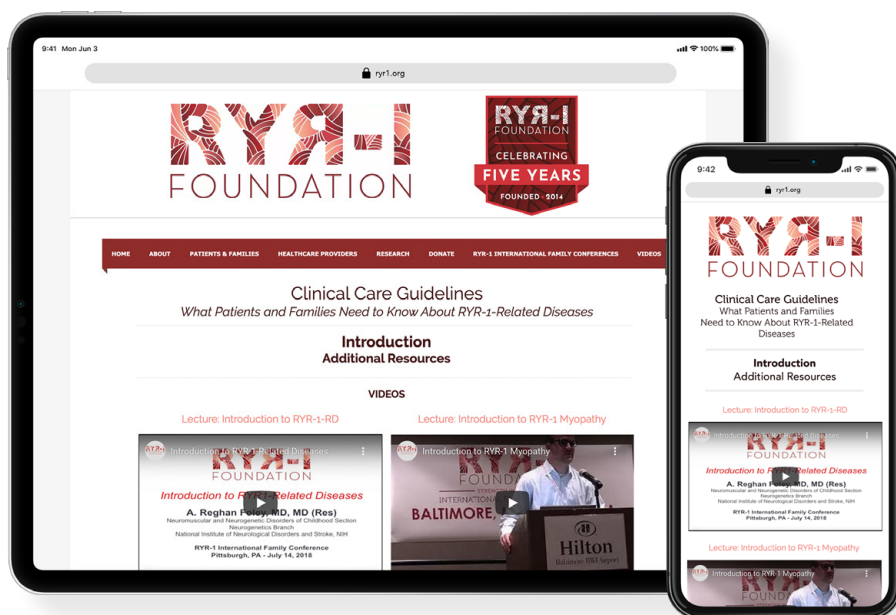
- Lab tests to rule out other diseases
- A muscle biopsy, where they take a tissue sample and look at changes in the muscle tissue under the microscope
- An MRI or an ultrasound scan to take a closer look at the muscle
- Genetic testing

To receive an official diagnosis of RYR-1-RD, the results from genetic testing must show changes in the *RYR1* gene. Previous terminology, based solely on a muscle biopsy (for example, central core disease and others), is no longer considered sufficient.

Currently, there are no treatments or cures for RYR-1-RD. There are no standard guidelines for managing RYR-1-RD, but the disease can be managed. The type of care and support you or your child receive will depend on the severity of symptoms. Your doctors will build a plan based on your and/or your child's genetic background and specific symptoms.

This guide provides information about RYR-1-RD and its potential complications. The next chapter will discuss genetics and the *RYR1* gene. **Chapter 2** will talk about overall clinical features of the disease. **Chapter 3** discusses how the nerves and muscles usually work together and what happens with RYR-1-RD. Later chapters will discuss other symptoms and complications and ways to manage them.

This guide is not meant to replace discussions with your doctor or a qualified professional. It is not meant to help you diagnose your disease. Instead, it will help you understand the disease so you and your doctor can work together on types of care.



For additional resources, please click on the above image or visit:
www.ryr1.org/ccg-introduction

Chapter 1

The Genetics of RYR-1-RD

Words Your Doctor May Use

Autosomal dominant: One abnormal copy of the *RYR1* gene is enough for someone to have the disease (RYR-1-RD).

Autosomal recessive: Both copies of the *RYR1* gene must have mutations for someone to have the disease (RYR-1-RD).

Carrier: Someone who carries a single recessive mutation and does not have the disease. In the case of RYR-1-RD, carriers may be at-risk for malignant hyperthermia (MH). Carriers have a 50% chance of passing down their mutation to each of his/her children.

Chromosome: A threadlike structure of DNA found in the nucleus of most living cells, carrying genetic information in the form of genes. All cells within your body have the same set of chromosomes.

Compound heterozygous: When someone has two bad copies of the same gene, but the location/type of the mutation within each copy of the gene is *different*.

De novo: A new mutation in the DNA sequence of an individual which was not inherited from either parent.

DNA: Hereditary material that makes up genes and is present in all organisms.

Gene: DNA unit or segment that determines a characteristic. Genes carry instructions for building proteins. There are thousands of genes on each chromosome.

Heterozygous: When someone has one normal copy of a gene and one bad copy of a gene.

Homozygous: When someone has two bad copies of the same gene.

Words Your Doctor May Use (continued)

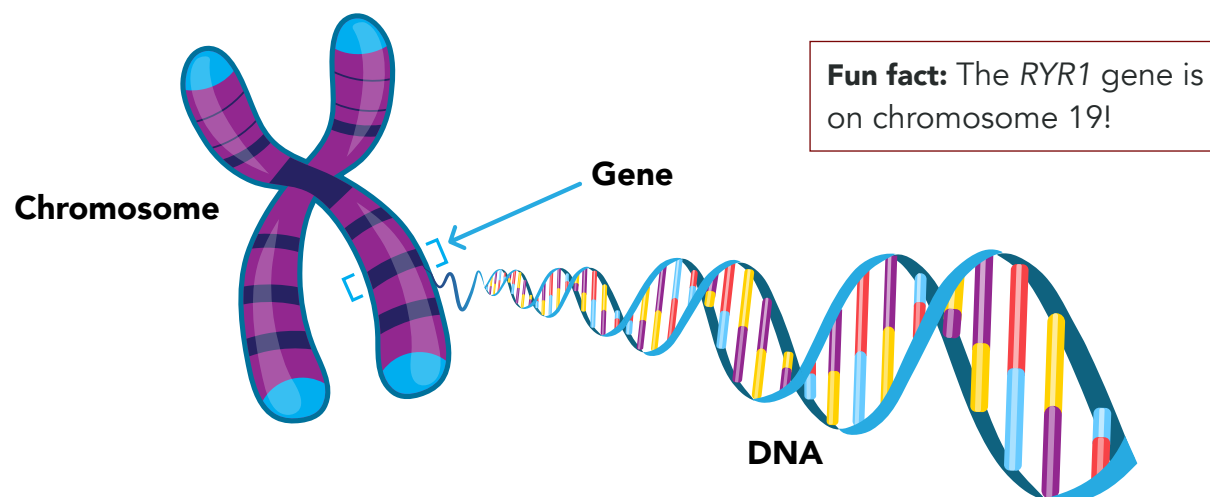
Mutation: Pathogenic (i.e., disease-causing) changes in the DNA sequence of a gene that affect the function of that gene and its corresponding protein (e.g., *RYR1* gene and RyR1 receptor).

The Evolving Definition of “Mutation”

Please note: The classic term “mutation” is being phased out. Doctors, genetic counselors, and scientists are starting to use an alternative term, “pathogenic variant” or “likely pathogenic variant,” as recommended by various national professional societies. This change in terminology is being done to better reflect the reality that everyone’s genes are full of “changes” or “variations,” most of which are benign or inconsequential. However, some of these “variants” will cause disease; these have historically been referred to as “mutations,” but, as mentioned above, are now being called “pathogenic variant” or “likely pathogenic variant.” For some “variants,” it is not known whether or not the variant is disease-causing. These are referred to as a “variant of unknown significance” or “VUS.” Because the term “mutation” is still commonly used, the Clinical Care Guidelines will continue its use.

RYR-1-RD is a genetic disease, which means you were born with it. RYR-1-RD is caused by changes in your **DNA**. DNA carries all of your genetic information. It is a “blueprint” for your body. All your DNA is tightly packaged into structures called **chromosomes**, which are present in all your cells. Chromosomes are passed on from parents to children.

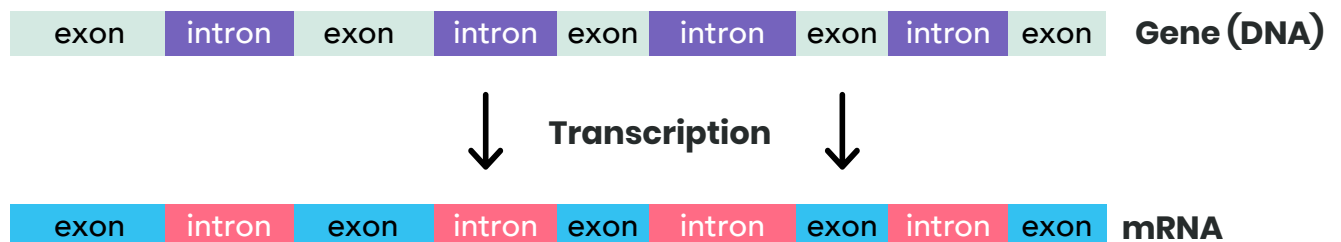
A **gene** is a piece of DNA within a chromosome that carries instructions for creating particular characteristics of each individual. Since genes are made up of DNA, they are part of chromosomes. Children inherit all their genes from their biological parents.



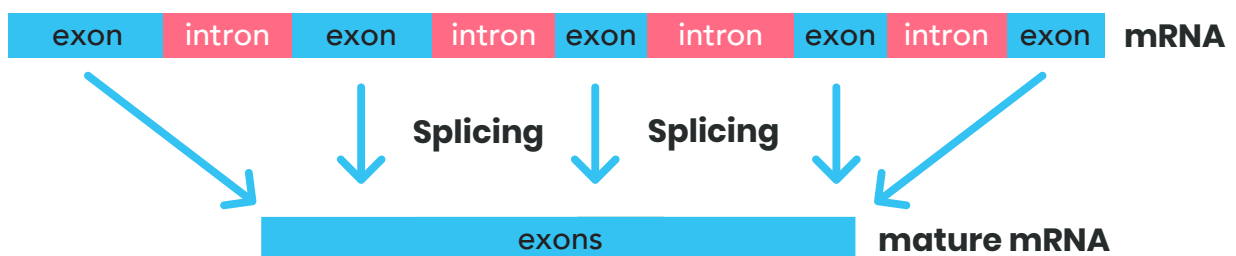
Scientists estimate that human beings have approximately 20,000 genes. If you think of DNA as a blueprint, and the body as a house, a single gene carries instructions for building one small part of the house, like a chimney. In biology, that small part of the “house” is a molecule, often a protein. The *RYR1* gene carries information for a specific protein called the ryanodine receptor type 1 (sometimes referred to as the “RyR1 receptor” or “RyR1 protein;” these terms are synonymous). The RyR1 receptor is a special kind of protein that is a “channel” (or “tunnel”) for the movement of calcium within muscle cells. This movement of calcium within a muscle cell is critically important for your muscles to function normally. For more detailed information on the role of the RyR1 receptor, **please see Chapter 3, “The Role of Calcium and the Ryanodine Receptor in RYR-1-RD.”**

How Does a Gene Lead to a Protein?

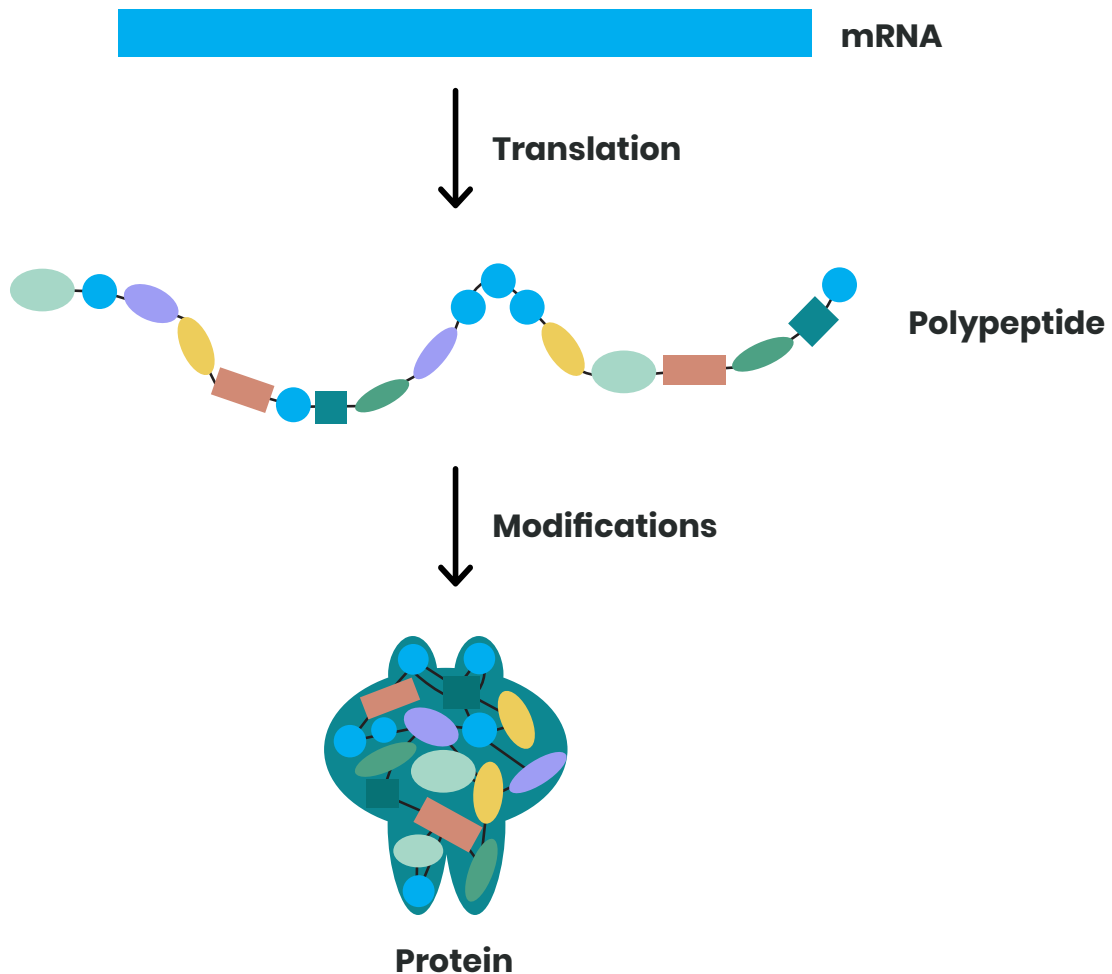
Cells use several steps to build a protein from a gene. First, they copy the instructions contained on the DNA in the gene into a message they can understand. That step is called **transcription**, and the message is called **messenger RNA** (mRNA). The message contains important instructions for building the protein from segments of the gene called exons. But the instructions also carry DNA segments, called introns, that are not important and are not needed to build a protein.



Therefore, to make the message easier to read, the introns are cut out. Once the introns are removed, the exons join together to form mature mRNA. This process is called **splicing**.



With the introns removed from the mRNA, the cell can read the message and build the protein. Almost like a recipe, the mRNA lists the ingredients the cell needs to build the protein. The main ingredients of the protein are called amino acids. Amino acids are the “building blocks” of a protein. The cell reads the mRNA to determine which amino acids to create and in which order they should be linked. When multiple amino acids are joined together, it creates a chemical chain called a peptide or a polypeptide. This process is called **translation**. Finally, the peptide chain folds up, and other modifications occur for it to become the fully formed protein.



What Does This Have to Do With RYR-1-RD?

RYR-1-RD is caused by **mutation(s)** in the *RYR1* gene. Mutations are changes in the DNA (contained within a gene) that ultimately result in an abnormal protein. They are often inherited. Mutations are faulty instructions that can cause problems at any step of protein production. In the case of RYR-1-RD, the mutation(s) in the *RYR1* gene can result in: 1) An RyR1 protein that does not work properly and/or 2) A reduction in the amount of RyR1 protein that is produced by the muscle cell. Scientists have found more than 200 *RYR1* mutations that cause RYR-1-RD. The report you receive from genetic testing may refer to mutation(s) in your DNA in a specific exon of the *RYR1* gene, which can result in a change in amino acids in the RyR1 receptor. Your genetic testing result may also refer to a “variant of unknown significance (VUS).” A VUS is a mutation in your *RYR1* gene, but scientists are not sure if this mutation actually causes RYR-1-RD.

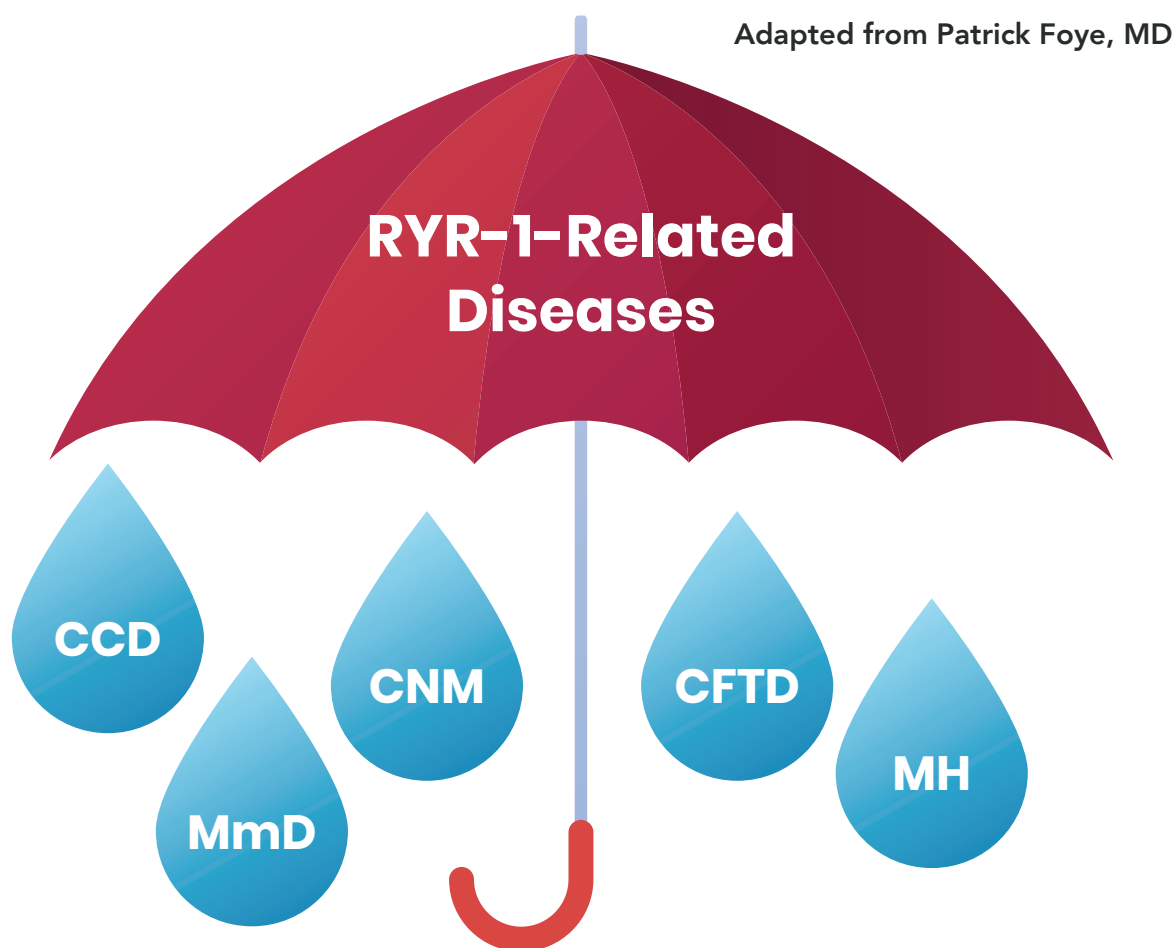
There are several types of mutations that are most commonly seen in RYR-1-RD. These include:

- 1) Missense - This is a mutation in the DNA that results in the wrong amino acid being incorporated into the RyR1 receptor. This can result in abnormal function of the RyR1 receptor, which can result in RYR-1-RD.
- 2) Nonsense - This is a mutation in the DNA that tells the cell to stop making the RyR1 receptor before it is completed. This results in a shortened mRNA, which can result in a reduced size of the RyR1 receptor and/or reduced amount of RyR1 receptor produced by the cell. This will likely result in abnormal function of the RyR1 receptor, which can result in RYR-1-RD.

There are several types of RYR-1-RD. These have historically been characterized by the appearance of the muscle cell taken from a muscle biopsy. However, it is important to remember that the most definitive way to make a diagnosis of RYR-1-RD is through genetic testing, and you may not need a muscle biopsy if you have already received a diagnosis via genetic testing. These disease types vary in symptoms and how severe they are. Some forms of RYR-1-RD are congenital, meaning that clinical symptoms appear from birth or during infancy. Other forms can present in childhood, during teenage years, or even in adulthood. For some otherwise healthy people, medical issues only show up under certain conditions, such as anesthesia or exercise (**please see Chapter 4, “Malignant Hyperthermia (MH)”**). The type of RYR-1-RD you have depends on:

- The type of *RYR1* mutation(s) you have
- The specific location of the mutation(s) in the *RYR1* gene
- The specific effect of the gene change on the structure, function, and/or amount of RyR1 protein

Types of RYR-1-RD



Central core disease (CCD)

Multi-minicore disease (MmD)

Centronuclear myopathy (CNM)

Congenital fiber type disproportion (CFTD)

Malignant hyperthermia (MH)

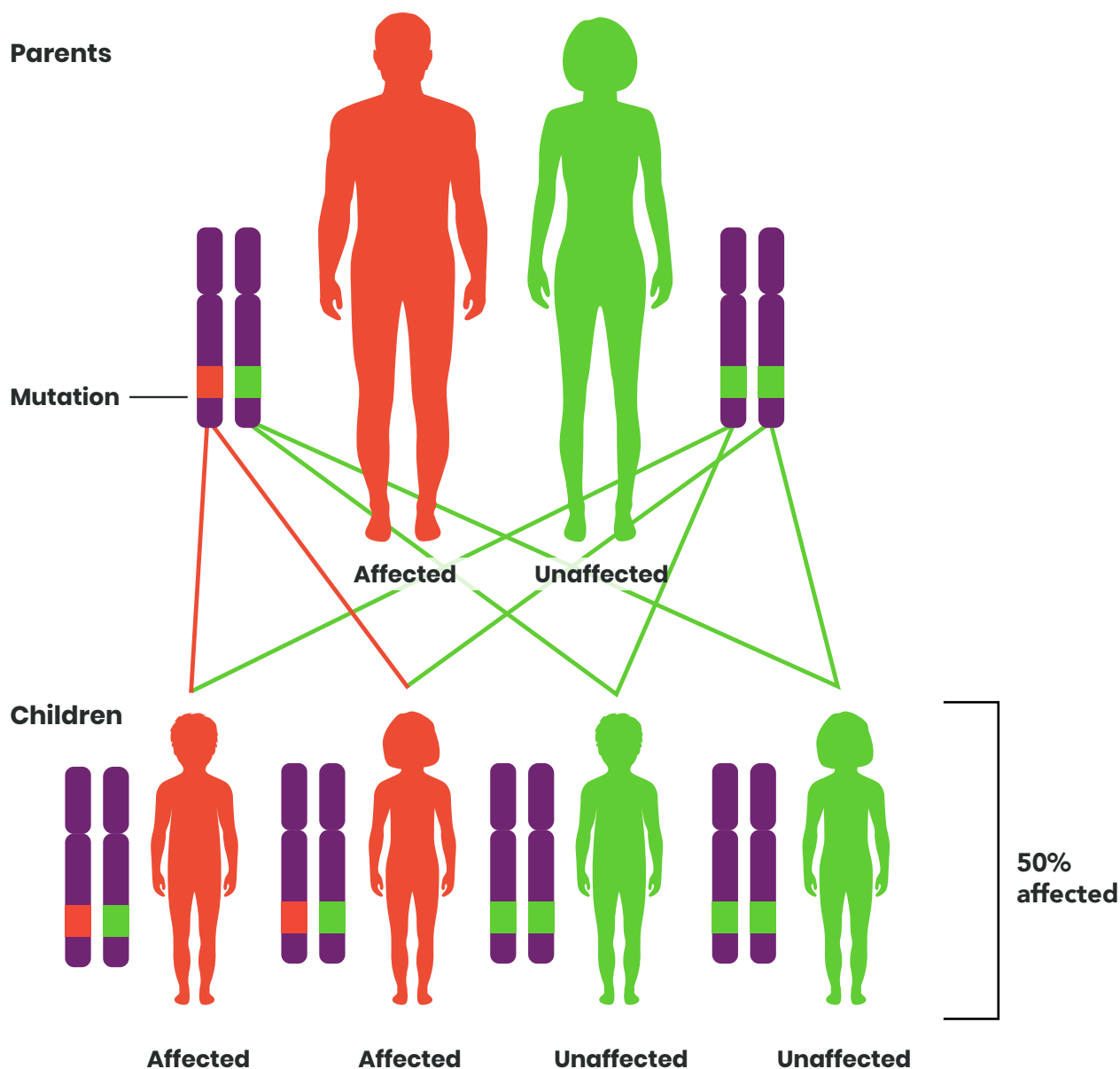
RYR-1-Related Diseases (RYR-1-RD) is an “umbrella” term that encompasses muscle conditions that occur as a result of mutations in the *RYR1* gene. These include conditions that historically received their names based on histopathologic classification, i.e., how the muscle biopsy appeared under a microscope (e.g., central core disease, multi-minicore disease, centronuclear myopathy, and congenital fiber type disproportion). In addition, many cases of malignant hyperthermia (MH) are due to a mutation in the *RYR1* gene.

How Can I Inherit RYR-1-RD?

You inherit two copies of each gene, one from each biological parent. You have two copies of the *RYR1* gene.

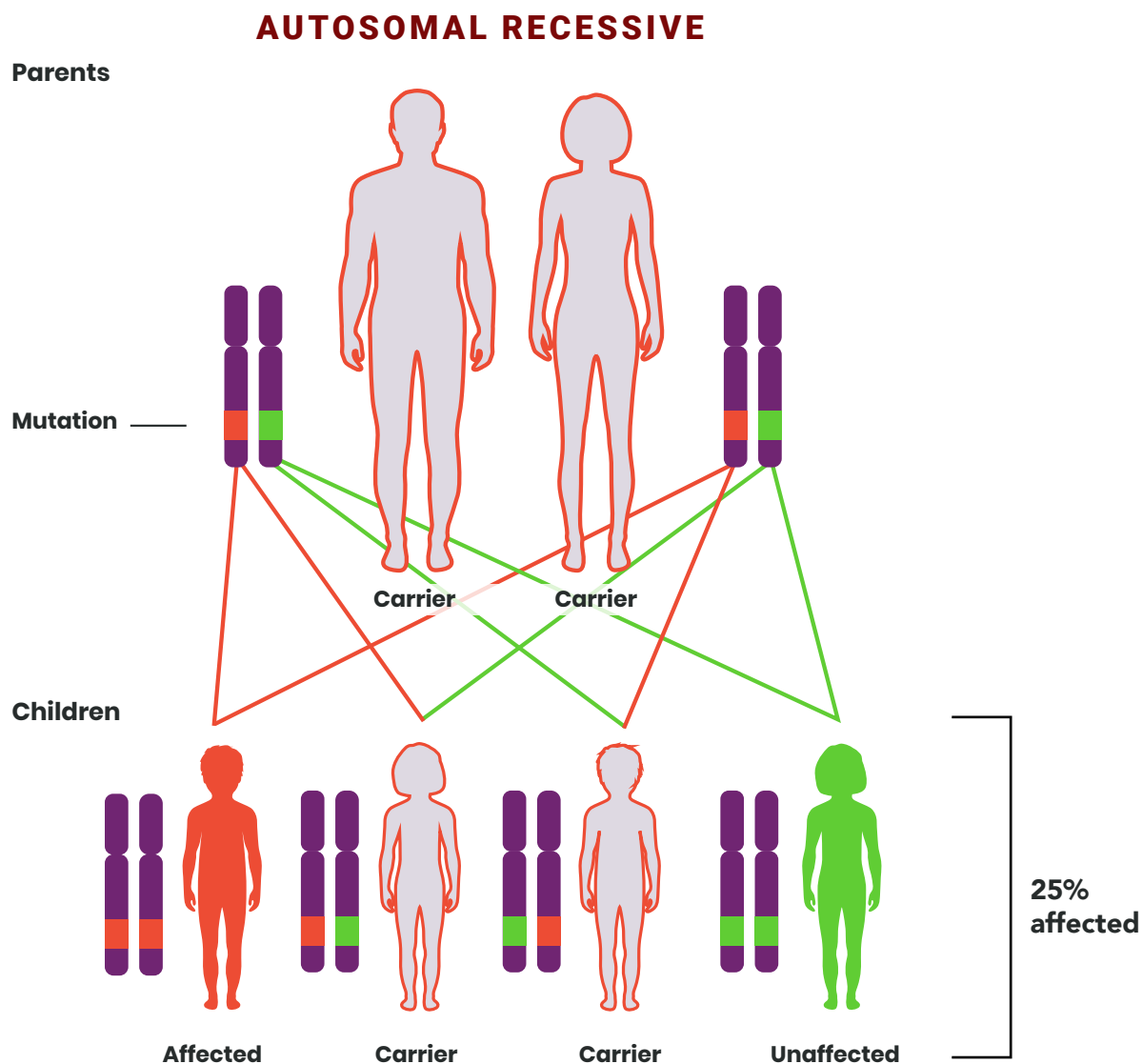
Types of Inheritance for RYR-1-RD	
<i>Autosomal dominant</i>	In autosomal dominant inheritance, one mutated copy of the gene in each cell is sufficient for a person to be affected. In many cases, an affected person inherits the condition from an affected parent. In others, the condition may result from a new mutation (<i>de novo</i>) in the gene and occur in people with no history of the disorder in their family.
<i>Autosomal recessive</i>	In autosomal recessive inheritance, both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition. Autosomal recessive disorders are typically not seen in multiple generations of an affected family.
<i>De novo</i>	A mutation that is present for the first time in one family member (and not present in either biological parent) is called <i>de novo</i> . This mutation occurs in either the egg or sperm of the individual's mother or father respectively.

AUTOSOMAL DOMINANT



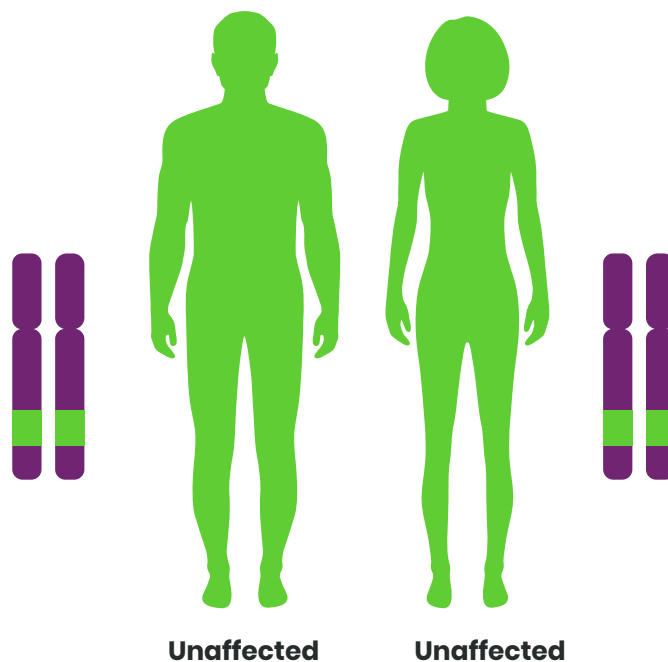
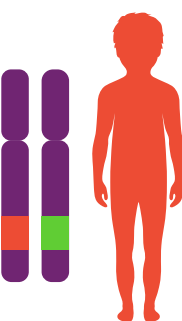
Some *RYR1* mutations are passed on through **autosomal dominant** inheritance. That means one mutant copy of the *RYR1* gene is enough for someone to have RYR-1-RD. If one parent with autosomal dominant RYR-1-RD conceives a child with a parent who does not have RYR-1-RD (and is not a carrier of a recessive mutation of *RYR1*), there is a 50% chance that the child will have RYR-1-RD.

Source - ghr.nlm.nih.gov/primer/inheritance/inheritancepatterns



Other *RYR1* mutations are passed on through **autosomal recessive** inheritance patterns. In this case, a person shows RYR-1-RD symptoms only if both copies of the *RYR1* gene have mutations. When someone has two bad copies of a gene, this is called **homozygous**. When someone has one normal copy of a gene and one bad copy of a gene, this is called **heterozygous**. In the case of an autosomal recessive form of RYR-1-RD, a person with only one bad copy of the *RYR1* gene (i.e., heterozygous) would not be affected by RYR-1-RD.

If two people who each carry one bad copy of the *RYR1* gene (i.e., heterozygous carriers) have a child, there is a 25% chance that the child will be homozygous for the mutation and have RYR-1-RD. There is also a 50% chance that the child will be heterozygous for the mutation and therefore not have RYR-1-RD; but this child will be a **carrier** of the mutant *RYR1* gene. There is a 25% chance that the child will get a normal copy of the *RYR1* gene from each parent, and therefore will not have the disease; this person would also not be at increased risk for malignant hyperthermia.

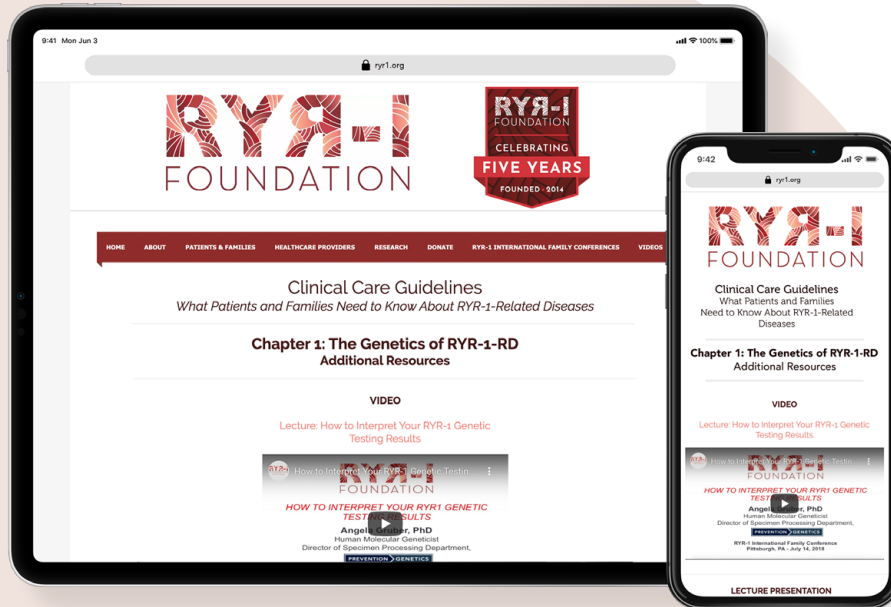
DE NOVO**Parents****Child****Affected**

Occasionally, an autosomal dominant mutation happens “brand new” or spontaneously and is not inherited from either parent. This is called a **de novo** mutation, and there is nothing from either parent to cause that DNA sequence change in the *RYR1* gene. The parents’ chance to have another child with RYR1-RD is very small (1% or less). The affected child, however, would then pass on the disease to approximately 50% of his or her children.

Different types of RYR-1-RD are passed on through different types of inheritance. For example, a common RYR-1-RD, called central core disease (CCD), typically follows autosomal dominant inheritance. Another type, multi-minicore disease (MmD), typically follows autosomal recessive inheritance. The types of symptoms that are present can also depend on whether the *RYR1* gene change is autosomal dominant or autosomal recessive, although this can be highly variable.

INHERITANCE AND DISEASE FEATURES

Feature	Dominant <i>RYR1</i> Mutations	Recessive <i>RYR1</i> Mutations
<i>Signs/Symptoms first occur in infancy</i>	Uncommon	Very common
<i>Signs/Symptoms first occur in childhood</i>	Common	Common
<i>Signs/Symptoms first occur in adulthood</i>	Common	Rare
<i>Affects eye muscles</i>	Rare	Very common
<i>Affects speech, swallowing, and chewing</i>	Rare	Very common
<i>Affects hands and feet</i>	Rare	Rare



For additional resources, please click on the above image or visit:
www.ryr1.org/ccg-genetics

Chapter 2

Clinical Features of RYR-1-RD

Words Your Doctor May Use

Anesthesia: Medication (drugs) you receive to help with surgery or medical procedure(s). General anesthesia puts you to sleep. Local anesthesia numbs a part of the body without putting you to sleep.

Congenital: Present from birth.

Distal muscle weakness: Weakness in the small muscles in the limbs, furthest away from your torso.

Histopathologic: How muscle tissue appears under a microscope after a biopsy.

Hypotonia: Low muscle tone - babies with hypotonia appear “floppy.”

Myopathy: Muscle disease where there is abnormal muscle function.

Neonatal: Related to newborns.

Neuromuscular disease: A disease that affects the muscles, the **nerve/muscle junction**, and/or the nerves that control them.

Pharmacogenetic condition: The condition is a genetic trait that is activated by a drug trigger.

Prognosis: The likely course of a disease.

Proximal muscle weakness: Weakness in the muscles around the torso or in the larger muscles in the limbs.

Ptosis: Drooping of the upper eyelids.

Quadriceps: Large muscles in the front of the thigh in the leg.

Words Your Doctor May Use (continued)

Sign: Objective, clinical evidence of a disease, which can be observed by others (e.g., ptosis, long/narrow face, restricted movement of the eyes, etc.).

Smooth muscle: Muscles that you do not control. These muscles can be found in organs such as the stomach, intestines, bladder, uterus, and blood vessels.

Static symptoms: Symptoms that occur all the time.

Symptom: Subjective evidence of disease, experienced by the patient (e.g., fatigue, back pain, anxiety, etc.).

RYR-1-RD is called a **neuromuscular disease**, because it affects your muscles. This chapter focuses mainly on the clinical features affecting your muscles. Later chapters will discuss other clinical characteristics of RYR-1-RD.

Muscle Types	
Skeletal muscles	The muscles attached to bones. These are the muscles that you use when you move.
Smooth muscles	The muscles that you do not control. These muscles appear in organs like the stomach, intestine, bladder, uterus and blood vessels.
Cardiac muscles	The muscles in your heart.
RYR-1-RD predominantly affects the skeletal muscles , but may also affect the smooth muscles .	

In general, people with RYR-1-RD often have static muscle weakness; that is, the symptoms of muscle weakness are always present. This weakness typically affects the muscles closest to the torso (**proximal muscle weakness**) and those controlling eye movements (ophthalmoparesis).

The different types of RYR-1-RD vary widely in:

- The types of signs and symptoms the person has
- When those signs and symptoms start
- Severity of those signs and symptoms
- How muscle tissue from a biopsy looks (**histopathologic** appearance) on a microscopic slide
- Which *RYR1* mutation(s) the person has

Some people with RYR-1-RD have muscle cramping and pain. Some cannot tolerate heat or too much exercise. These are referred to as dynamic symptoms. The signs and symptoms of many types of RYR-1-RD first occur in infancy. Others begin to occur in early childhood, adolescence, or even adulthood. Still others occur suddenly in otherwise healthy people. Some RYR-1-RD progress slowly and some types do not progress at all.

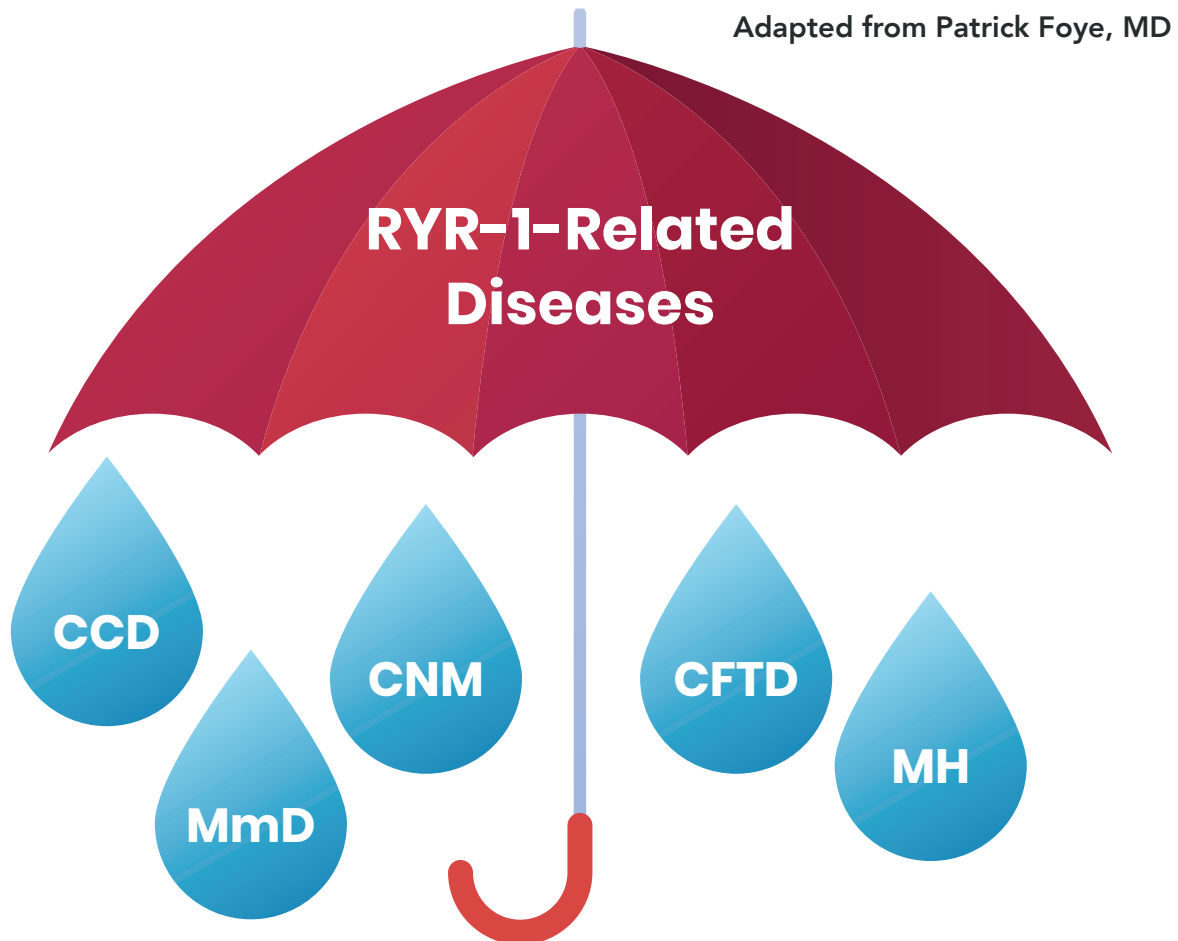
RYR-1-RD can be associated with skeletal (bone) abnormalities, including chest wall deformity, scoliosis, and hip dysplasia. **Chapter 6, "The Bones and Joints/Orthopedics,"** will discuss those problems.

Autosomal dominant and autosomal recessive forms of RYR-1-RD may share similar clinical characteristics. Genetic testing can determine which type you have. In general, dominant *RYR1* mutations are associated with milder forms of RYR-1-RD. Recessive *RYR1* mutations generally cause more weakness, eye movement problems, and problems with chewing and swallowing.

In the past, RYR-1-RD has been classified based on the histopathologic appearance of the muscle cells taken from a biopsy and then viewed under a microscope. However, as genetic testing becomes more common, the classification system of RYR-1-RD based on the histopathologic classification is becoming less important. In fact, some patients who are diagnosed by genetic testing may never undergo a muscle biopsy. To make things even more complicated, there are forms of RYR-1-RD that are based not on the muscle biopsy, but rather on their clinical features (e.g., "Malignant Hyperthermia Susceptibility (MHS)"). Lastly, muscles can appear differently at different ages, and one type of histopathologic classification may be seen at one age, and a different one at another. This is not to suggest that RYR-1-RD patients should undergo multiple biopsies, but rather to reinforce that the specific type of pathology under the microscope is less important than clinical features and genetic mutations.

The different forms (based on the muscle biopsy appearance) are described in the table below; remember, these are generalizations, and every individual case is unique. Once again, it is important to remember that regardless of the classification, all forms of RYR-1-RD are due to a mutation(s) in the *RYR1* gene. For more detail, **please see Chapter 1, "The Genetics of RYR-1-RD."**

Types of RYR-1-RD



Central core disease (CCD)

Multi-minicore disease (MmD)

Centronuclear myopathy (CNM)

Congenital fiber type disproportion (CFTD)

Malignant hyperthermia (MH)

RYR-1-Related Diseases (RYR-1-RD) is an “umbrella” term that encompasses muscle conditions that occur as a result of mutations in the *RYR1* gene. These include conditions that historically received their names based on histopathologic classification, i.e., how the muscle biopsy appeared under a microscope (e.g., central core disease, multi-minicore disease, centronuclear myopathy, and congenital fiber type disproportion). In addition, many cases of malignant hyperthermia (MH) are due to a mutation in the *RYR1* gene.

Different Histopathologic Types of RYR-1-RD

<p>Central core disease (CCD)</p>	<p>Typically, people with CCD show muscle weakness especially around the pelvis and thighs. Babies with CCD appear “floppy” because of poor muscle tone. They tend to be delayed in sitting, crawling, and walking, but usually, once they begin walking, they remain able to walk. People with CCD also show mild facial weakness and mildly fixed or stiff joints. In severe cases, people with CCD can show severe physical disability. They might even be unable to walk. CCD can arise from dominant or recessive <i>RYR1</i> mutations.</p>
<p>Multi-minicore disease (MmD)</p>	<p>The clinical features of MmD range from mild to life-threatening. With the classic form of MmD, muscle weakness begins in infancy or early childhood. The weakness is most noticeable in the trunk and head/neck muscles. People with MmD show stiffness in the chest muscles and the muscles around the spine. They also have a hard time moving their eyes. Babies with MmD appear “floppy” because of poor muscle tone. They take longer to sit, stand, and walk. In severe cases, MmD begins before birth. With these forms, the fetus may move less before birth. Some individuals with MmD may require wheelchairs for ambulation, and may need support for breathing. MmD typically arises from recessive <i>RYR1</i> mutations.</p>
<p>Centronuclear myopathy (CNM)</p>	<p>CNM may progress slowly. Muscle weakness with CNM can begin at any time from birth to early childhood. Children with CNM take longer to crawl or walk. People with CNM also show weakness in the facial muscles. The eye muscles do not work as well (ophthalmoparesis), and the upper eyelids can droop (ptosis). Some people with CNM may need wheelchairs and may require support for breathing. CNM may arise from recessive <i>RYR1</i> mutations.</p>

Different Histopathologic Types of RYR-1-RD (continued)

Congenital fiber type disproportion (CFTD)

People with CFTD show muscle weakness in the face and eyes. They usually have a long narrow face and drooping eyelids (ptosis). They show poor muscle tone and fixed or stiff joints. People with CFTD might feel muscle pain, lose muscle strength, and tire easily. In rare cases, people with CFTD have weaker and larger heart muscles.

Other Forms of RYR-1-RD (not based on muscle biopsy)

Malignant hyperthermia susceptibility (MHS)

People with MHS generally appear healthy, with no muscle weakness. However, when they receive certain types of general anesthesia, their temperature can rise quickly, and they can experience muscle spasms and increased heart rate. This type of episode, called malignant hyperthermia (MH), can be fatal if not treated promptly. Of note, many individuals with RYR-1-RD, who have static weakness and/or who have the pathology patterns listed above, are still MH susceptible. This is particularly true with CCD, where approximately 30% of patients also have MHS.

Individuals with MHS, along with individuals with other subtypes of RYR-1-RD, can present symptoms of high temperature, muscle pain/cramping, and stiffness at times not associated with MH. Such episodes are sometimes referred to as "Awake MH." Though more accurately should be called "heat stroke" or "exertional heat illness (EHI)." Individuals with RYR-1-RD, particularly those with MHS, are also at risk for exertional rhabdomyolysis (ERM), where muscles suddenly break down while a person exercises.

Chapter 4, "Malignant Hyperthermia (MH)," will discuss MH in more detail.

Managing Neuromuscular Disease

This handbook should: 1) Help you better understand RYR-1-RD and 2) serve as a guide to you and your family on how to approach the management of RYR-1-RD. Not all standards will apply to all people with RYR-1-RD. The care plan you and/or your child will need depends on your specific disease and the symptoms you have.

In general, managing RYR-1-RD involves a team of specialists. Your doctors will pay close attention to the following:

- Spine
- Strength and movement
- Breathing
- Chewing, swallowing, and speech
- Nutrition

Individuals with *RYR1* mutations are at risk for malignant hyperthermia (MH). To learn more about this, **please see Chapter 4, "Malignant Hyperthermia (MH),"** which will discuss MH in more detail.

Multidisciplinary Care

Multidisciplinary care means that your care is managed by a team of specialists with expertise in different areas. Here are the types of doctors or specialists you might see on your team:

Neurologist	A doctor who specializes in disorders of the nervous system. You will likely want to see a neurologist who specializes in neuromuscular diseases. For more information on RYR-1-related providers, please visit: www.ryr1.org/provider .
Physiatrist (Physical Medicine and Rehabilitation Physician)	A doctor who specializes in rehabilitation medicine, and who is responsible for helping diagnose and manage problems related to bones, joints, and muscles as they impact mobility and function.
Orthopedic Specialist	A doctor who specializes in the bones, joints, and muscles. Please see Chapter 6, "The Bones and Joints/Orthopedics."

Multidisciplinary Care (continued)	
Occupational Therapist (OT)	A specialist who helps manage daily tasks and activities, particularly related to fine motor skills (buttons, zippers, writing, etc.). Please see Chapter 7, "Eating, Swallowing, and Speaking."
Physical Therapist (PT)	A specialist who helps you manage problems with movement and daily activities. Please see Chapter 9, "Physical Activity and Physical Therapy (PT)."
Pulmonologist	A doctor who specializes in the lungs. Please see Chapter 5, "The Lungs/Pulmonology."
Gastroenterologist (GI)	A doctor who specializes in the stomach and intestines, including problems with feeding. Please see Chapter 7, "Eating, Swallowing, and Speaking."
Speech-Language Pathologist (SLP)	A specialist who helps with speech, language, oral communication, and swallowing. Please see Chapter 7, "Eating, Swallowing, and Speaking."
Psychologist	A doctor who specializes in the mind and behavior.
Social Worker	A specialist who helps you manage social functions and overall well being.
Genetic Counselor (CGC)	A specialist who helps individuals and families understand their inherited disease and genetic risk. A genetic counselor can help you understand and interpret the results from your genetic testing. Please see Chapter 1, "The Genetics of RYR-1-RD."

The first person you see will likely be your neurologist (in some cases, you may see a genetic counselor prior to seeing a neurologist). Soon after you receive your diagnosis, your neurologist will talk with you about:

- Your diagnosis
- The likely course of the disease
- The genetic risk that children and future children might have RYR-1-RD
- The risk for malignant hyperthermia (**please see Chapter 4, "Malignant Hyperthermia (MH)"**)
- A specific plan for managing the disease
- Available support and resources

FOLLOW-UP

The frequency of follow-up visits varies from person to person. Babies younger than 12 months typically see their doctor every 3 or 4 months. Older children usually see their doctor every 6 to 12 months. The frequency of follow-up visits also depends on disease severity. At each follow-up visit, you may receive information about:

- Maintaining a healthy weight
- Exercise
- Good nutrition, including vitamin D
- Immunizations

MUSCLE PAIN

If you or your child have muscle pain, your doctor might recommend massage therapy or over-the-counter pain relievers. Some doctors who specialize in RYR-1-RD and anesthesia have prescribed oral **dantrolene** to treat muscle pain. This is likely only effective for patients with specific mutations and clinical symptoms, and may worsen symptoms in other contexts, so it should only be used after the recommendation of a clinician experienced with RYR-1-RD.

EXERCISE INTOLERANCE

If you or your child cannot exercise for long, the doctor might recommend that you change activities. Additional strategies to help combat exercise intolerance is frequent hydration, taking many “mini breaks,” and avoiding exercise during periods of high outside temperatures. The doctor might also recommend a walker, scooter, or wheelchair to help you ambulate.

EYE PROBLEMS

For eye problems, you may have to see an eye doctor (ophthalmologist) for evaluation of eye movements and/or drooping eyelids. Individuals who experience incomplete eyelid closure, which may occur particularly while sleeping, are at risk for corneal injury, and should consider liquid tears or other forms of eye protection (please consult your ophthalmologist (“eye doctor”) for best recommendation).

HOSPITALIZATION

If you or your child need to be hospitalized, the neurologist should provide information about your diagnosis and needs.

Brentney's Story

When Brentney was born in 1993, her parents noticed something was wrong right from birth. Doctors told her family that they did not think she would ever be able to walk or talk. Nevertheless, each and every day, Brentney has continued to exceed everyone's expectations.

Like many other individuals with RYR-1-related diseases, Brentney was initially misdiagnosed. Due to her rapid health decline in 2015, she and her family became skeptical about her initial diagnosis, which led to genetic testing. It was not until January 2016, at the age of 22, that Brentney received her true diagnosis – an RYR-1-related disease.

Despite unanswered questions and countless doctor appointments, Brentney and her family continue to remain optimistic, hopeful, and inspirational.

On May 6, 2016, Brentney graduated with her associate's degree from Trident Technical College. Although there were some serious health roadblocks along the way, Brentney never felt defeated. She accomplished a milestone in her life that no one can ever take away from her.

As an attendee of the first RYR-1 International Family Conference in 2016, Brentney personally experienced the value of the RYR-1 Foundation. "After discovering the RYR-1 Foundation, I was finally able to interact with and meet people who could identify with the same things I was going through," Brentney explains.

To watch a video on "Brentney's Story," please go to: www.ryr1.org/brentney

"Up until meeting other individuals of the RYR-1 community, no one else could fully understand what I have been going through...for that, I am forever grateful."

BRENTNEY, AFFECTED WITH AN RYR-1-RELATED DISEASE



Chapter 3

The Role of Calcium and the Ryanodine Receptor in RYR-1-RD

RYR-1 and Skeletal Muscles

The ryanodine receptor type 1 (RyR1) plays a central role in determining when and how much force is produced by skeletal muscles, which is needed for everyday activities including walking, moving, and lifting objects. Muscle contraction depends on calcium ions; more calcium results in greater force production. Inside a resting muscle cell, calcium is stored in a compartment called the sarcoplasmic reticulum (SR). RyR1 is the gatekeeper responsible for releasing calcium ions from the SR storage compartment when a muscle contraction is needed. The RyR1 calcium gatekeeper function is mechanically controlled by another protein called the dihydropyridine receptor (DHPR). When skeletal muscle is relaxed, the DHPR keeps the RyR1 protein closed so that calcium remains in the SR storage compartment. Please see Figure 3.1.

When we decide to move part of our body, the brain sends an electrical impulse transmitted through the nerves to skeletal muscles ("nerve signal"). The nerve signal causes the DHPR to pull on the RyR1 gatekeeper to open the RyR1 channel to allow calcium ions to flow from the SR storage compartment through the RyR1 channel into the cell interior (cytoplasm). Calcium ions that move into the cytoplasm of the cell (from the SR via the RyR1 channel) are now able to bind to components of the muscle which cause the muscle to shorten, or contract, which generates force. The more calcium that is released, the stronger the contraction and the greater the force production. Please see Figure 3.2.

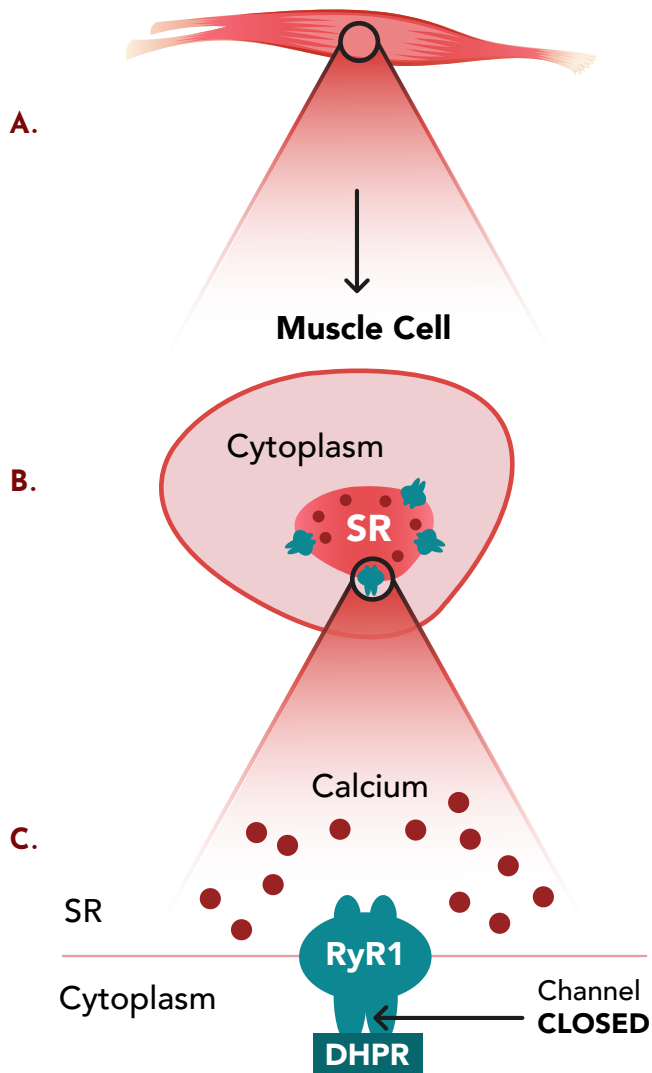
RELAXED MUSCLE

Figure 3.1 - A. Muscle in its relaxed, non-contracted state. **B.** In a magnified view of a muscle cell in its relaxed state, there are calcium ions within the sarcoplasmic reticulum (SR), but not the cytoplasm. **C.** In a magnified view of the wall of the SR, the DHPR has not been activated, and the RyR1 receptor is closed, preventing calcium from exiting the SR and entering the cytoplasm.

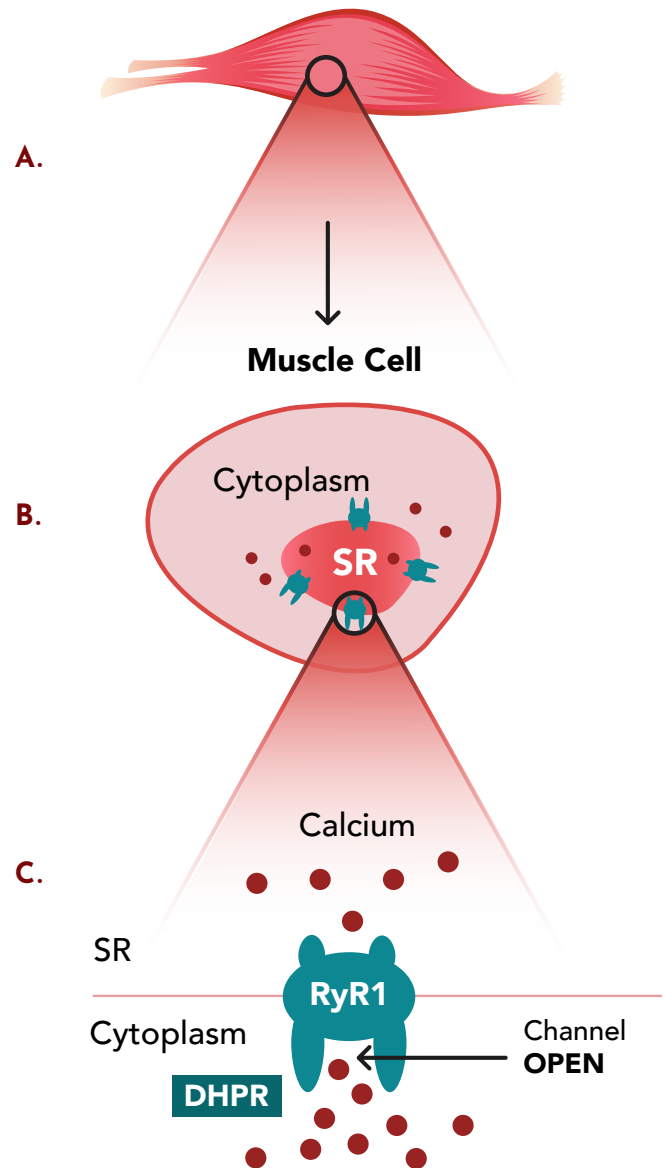
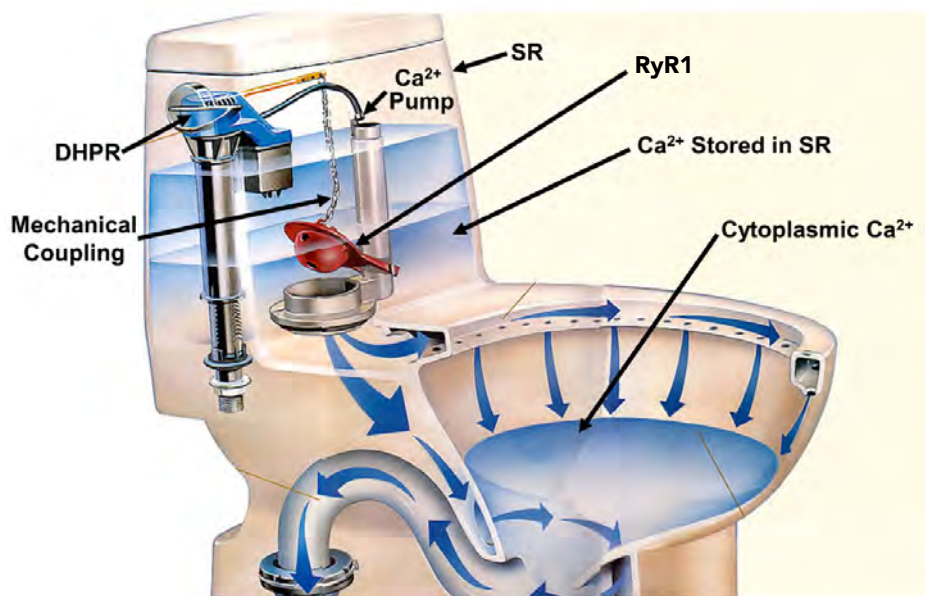
MUSCLE CONTRACTION

Figure 3.2 - A. Muscle in its contracted state. **B.** In a magnified view of a muscle cell in its contracted state, calcium ions have exited the SR and are now in the cytoplasm. **C.** In a magnified view of the wall of the SR, the DHPR has been activated, and the RyR1 receptor goes from closed to open. This allows calcium ions to exit the SR and enter the cytoplasm. By entering the cytoplasm, the calcium can then continue on to the next stage of muscle contraction.

This process is analogous to the flushing of a toilet. In this analogy, the toilet bowl is the inside of the cell (cytoplasm), the tank is the SR calcium storage compartment, and the water represents the calcium (Ca^{2+}) ions. The act of flushing the toilet releases water (calcium ions) from the storage tank (SR) into the bowl (cell interior or cytoplasm). The entire process is controlled by the toilet handle (DHPR) pulling on the toilet flapper (RyR1) to open a channel for water to flow from the storage tank to the toilet bowl. Please see Figure 3.3. The individual who pulls on the handle is analogous to the “nerve signal,” causing the DHPR to open the RyR1 gatekeeper channel. When the handle (DHPR) is pulled, this opens the flapper (RyR1) to release water (calcium) from the storage tank (SR) into the water bowl (cytoplasm). Thus, the flush represents the flow of calcium ions from the SR storage compartment into the cytoplasm needed for muscle contraction and force production.

The more water that is released at one time, the stronger the flush (muscle contraction). When the muscle needs to relax, the nerve signal ends, the DHPRs close the RyR1 calcium gatekeeper channels, and another protein pumps calcium from the cytoplasm back into the SR for storage (this is analogous to the water refill).

EC Coupling is Analogous to a Toilet Flush



To watch videos with Dr. Robert T. Dirksen explaining the RyR1 receptor, please click on the image to the left or visit: www.ryr1.org/ccg-calcium

Figure 3.3 - Source: Robert T. Dirksen, PhD. “Role of Calcium in RYR-1 Myopathy, Made Ridiculously Simple.” Presented at the RYR-1 International Family Conference, Baltimore, MD, 2016: www.ryr1.org/conference2016

What Changes Occur in RYR-1-RD?

Mutations in the *RYR1* gene cause problems with the RyR1 receptor, which affects the ability of skeletal muscle to function normally. The mutations in the *RYR1* gene can lead to a wide range of muscle problems, including muscle weakness, muscle pain, muscle breakdown, and a potentially fatal reaction to certain forms of anesthesia ("malignant hyperthermia (MH)").

With some mutations, the RyR1 gatekeeper is leaky. Calcium escapes from the storage compartment into the cytoplasm, which is the same as what happens when water leaks into the toilet bowl from the storage tank due to a leaky flapper. This results in less water being available to be released during a flush (resulting in a "weak" flush). By analogy, RyR1 leaks result in less calcium being stored in the SR to support muscle contraction (resulting in a "weaker" contraction). Other mutations can result in the cell not making enough RyR1 channels, which results in less calcium ions being able to flow into the cytoplasm, and thus, weaker contraction. With still other mutations, the RyR1 gatekeeper channels do not allow calcium ions to flow as easily from the SR storage compartment to the cytoplasm, again leading to less calcium being available to cause contraction, and thus, lower force production (resulting in muscle weakness).



For additional resources and to view a lecture on the "Role of Calcium in RYR-1 Myopathy," please click on the above image or visit: www.ryr1.org/ccg-calcium

Chapter 4

Malignant Hyperthermia (MH)

Words Your Doctor May Use

General Anesthesia: Medication(s) you receive during a surgical or medical procedure. General anesthesia puts you to sleep.

Hypermetabolic: The body's metabolism is abnormally high.

Local Anesthesia: Medication you receive during a surgical or medical procedure. Local anesthesia numbs a part of the body without putting you to sleep.

Myalgia: Muscle pain.

Pharmacogenetic condition: A genetic trait that is activated by a drug trigger.

Rhabdomyolysis: The death of muscle fibers, which releases their contents into the bloodstream.

Variable penetrance: The mutation or variant has a wide range of signs and symptoms, and the symptoms do not always appear.

Malignant hyperthermia (MH) is a reaction where your body overheats to the point that your muscles breakdown in response to certain anesthetic (drug) triggers; it is a medical emergency. If someone with MH does not get treated in time, MH can result in kidney failure, brain damage, cardiac arrest, failure of additional organs, and even death. MH is classically known as a **pharmacogenetic condition**. That means that someone has a genetic susceptibility to it (due to a mutation in a gene), but they do not have an MH episode/crisis unless they are exposed to anesthetic (drug) triggers. This is often called "Malignant Hyperthermia Susceptibility (MHS)." There are other symptoms that MHS individuals can experience in response to other external triggers (e.g., physical exertion), such as **rhabdomyolysis** (muscle breakdown), severe muscle cramping and stiffness, and heat intolerance.

In some cases, MHS can occur in the absence of muscle weakness; in other words, MHS individuals have normal (or even increased) strength, and their only “symptom” is susceptibility to MH reactions. Conversely, MHS can also occur in patients with RYR-1-RD with typical signs and symptoms of myopathy (muscle weakness) (**please see Chapter 2, “Clinical Features of RYR-1-RD”**).

Triggers for MH include certain drugs that are used for **general anesthesia**, when someone is “put to sleep,” usually before surgery. General anesthesia is used in a wide variety of settings, including operating rooms, emergency rooms, and intensive care units (ICU). Specific drugs that are known to trigger MH include: succinylcholine (given intravenously and inhaled gas anesthetics (e.g., isoflurane, sevoflurane, and desflurane), which are administered via a breathing tube.

The Genetics of Malignant Hyperthermia Susceptibility (MHS)

The genetics of MHS are complicated. In most cases, it is an **autosomal dominant** trait. That means if you have MHS, one of your parents probably has MHS as well. It also means that each of your children has a 50% chance of inheriting MHS. However, in some rare cases, a person’s MHS is **de novo**, meaning that the person is the first one in the family to have it. Doctors have also seen MH in people with **autosomal recessive** *RYR1* mutations.

There are many known *RYR1* mutations that have been shown to cause MHS. Most of them are autosomal dominant mutations. Most people with MHS do not have noticeable muscle weakness. They appear to be healthy and even strong, although they might not tolerate heat and/or exercise, or they might have stiff muscles in extremely cold temperatures. Regardless, all MHS patients should be tested for *RYR1* mutations. In addition, all patients with mutations/variants in the *RYR1* gene should be assumed to be at risk for MH.

MH-associated *RYR1* mutations show a **variable penetrance**. This means that a person might go through several exposures to triggers without difficulty before an MH reaction occurs for the first time. To make things even more confusing, people with the *same* mutation (including members of the same family) might look different clinically, meaning some may be sensitive to heat, some may have MH reactions to anesthesia, some may get rhabdomyolysis with exercise, and some may have no problem with these conditions.



Anesthesia-Related MH

The classic definition of MH includes a **hypermetabolic** response (e.g., high temperature, high exhaled carbon dioxide, rapid heart rate, and rhabdomyolysis) to certain kinds of general anesthesia and/or a specific drug. “Local” anesthesia, from an injection under the skin, is typically not a trigger for MH. There are two types of anesthesia-related medication used in general anesthesia that you should avoid:

- **Inhaled gases:** This includes isoflurane, sevoflurane, enflurane, ether, halothane, methoxyflurane, and desflurane.
- **Succinylcholine:** This is an IV medicine used to temporarily paralyze the muscles and is commonly used for general anesthesia before and during surgery or in cases of medical emergencies. It paralyzes your muscles immediately, and normally its effect wears off quickly.

When someone with an MH-associated *RYR1* mutation receives these types of drugs and has an MH reaction, the RyR1 receptor stays open and lets too much calcium into the muscle cell. This causes the muscle to keep contracting, and that causes rhabdomyolysis, where muscle cells burn through all their energy and die. Rhabdomyolysis releases heat. It also releases a high level of potassium and a muscle protein called myoglobin into the bloodstream. This results in the urine turning a dark color. Too much potassium and myoglobin in the bloodstream can cause serious and life-threatening injuries to other organs.

Typically, a person experiencing an MH reaction shows the following symptoms:

- Dangerously high body temperature
- Fast heart rate
- Rapid breathing
- Stiff skeletal muscles throughout the body
- Rhabdomyolysis (muscle breakdown)
- High levels of acid in the blood
- Dark urine

When an MH reaction occurs, doctors should immediately stop the gas anesthetics and maintain the anesthesia with trigger free agents. They should cool the patient and increase the amount of oxygen the person breathes in. They also should treat the patient through an IV with an emergency medicine called **dantrolene**. After the crisis ends, the patient is usually admitted to the Intensive Care Unit (ICU). There, they may receive additional dantrolene, and doctors will monitor the patient for complications, such as organ damage and blood clots.

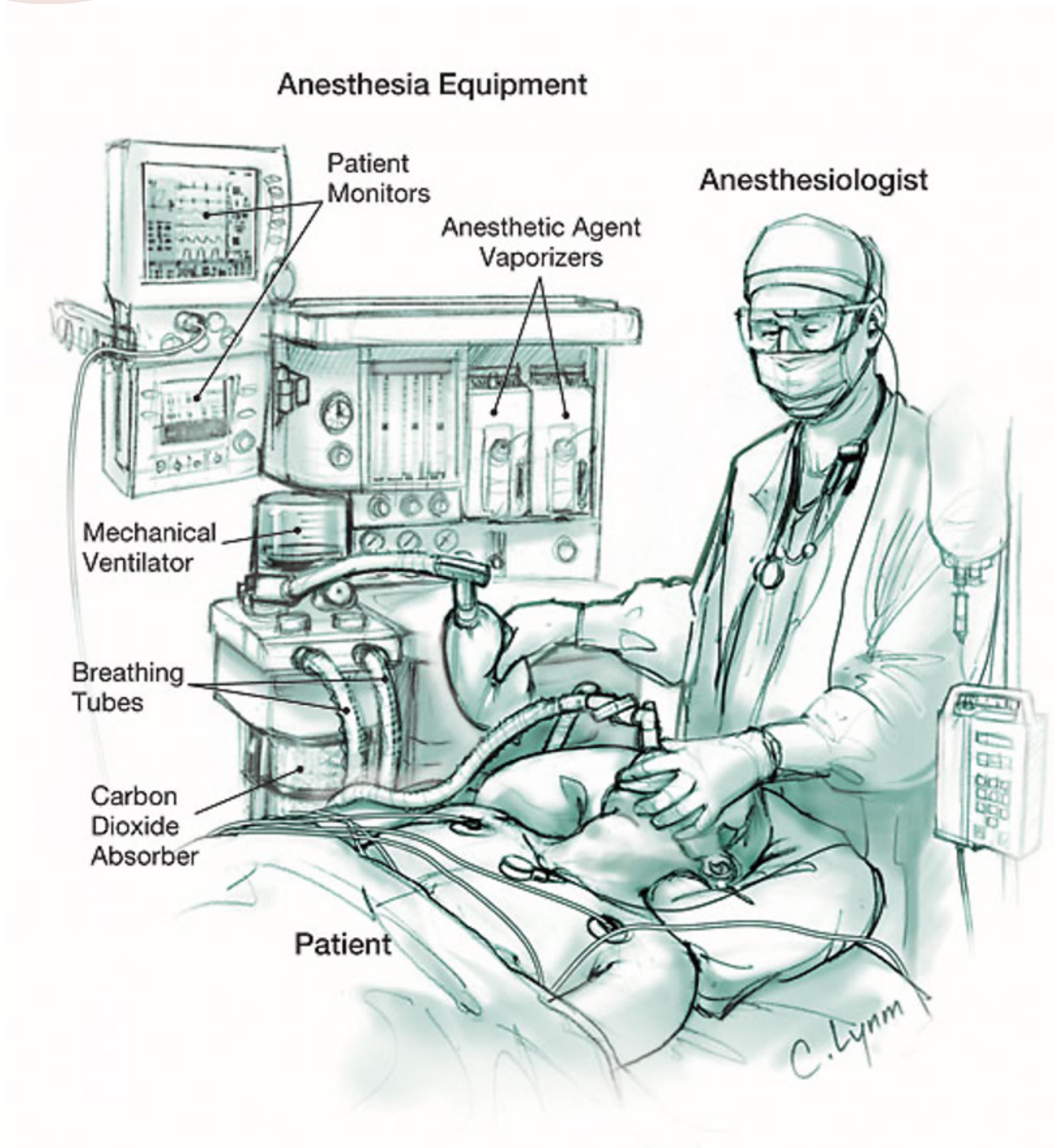


Illustration showing a patient in the operating room receiving general anesthesia from an anesthesiologist. Patients with *RYR1* mutations are at risk for malignant hyperthermia (MH), a potentially fatal reaction to general anesthesia.

Source: JAMA. 2005;293(23):2958. doi:10.1001/jama.293.23.2958

How is MHS Diagnosed?

Diagnosing MHS depends on:

- **Your family history:** Has a parent and/or sibling had signs or symptoms suggestive of MHS (e.g., episode of MH and/or rhabdomyolysis)?
- **Your own past medical history:** Have you had signs or symptoms suggestive of MHS (e.g., episode of MH and/or rhabdomyolysis)?
- **Genetic testing:** Have you or a family member had genetic testing for *RYR1* mutations (as well as other mutations that have been associated with MHS)?

Genetic testing is sometimes not enough. Sometimes, genetic testing is negative or inconclusive. In that situation, if there is still clinical suspicion that a person may have MHS, a special muscle biopsy may be needed. This special muscle biopsy is called the Caffeine Halothane Contracture Test (CHCT), and it is the gold standard for diagnosing MHS. There are only five centers in North America that do this type of testing:

- Toronto General Hospital, Toronto, Canada
- Uniformed Services University of the Health Sciences, Bethesda, Maryland, USA
- University of California, Davis, California, USA
- University of Minnesota, Minneapolis, Minnesota, USA
- Wake Forest Baptist Medical Center, Winston-Salem, North Carolina, USA

For European centers performing this test, please refer to the website of the European Malignant Hyperthermia Group: www.emhg.org/mh-units-map.

WHAT IF I NEED SURGERY?

All anesthesiologists should assume that all people with *RYR1* mutations are at risk for MH. If you let your surgeon and anesthesiologist know that you have an *RYR1* mutation and/or MHS, they can take precautions and give you a different kind of anesthetic, which is safe for you.

THINGS TO KEEP IN MIND:

- Purchase and wear a medical ID indicating your risk for MH, in case of an emergency
- Tell your surgeon AND your anesthesiologist about your *RYR1* mutation(s) and MHS as soon as possible, well before the day of the surgery (this gives them time to prepare their equipment and medications and take precautions)
- You do not need dantrolene treatment before surgery
- You do not need a muscle biopsy before surgery
- You do not need to stay in the hospital any longer than anyone else would after surgery
- You can be taken to the same recovery room as other patients (hospitals are well ventilated, so there is hardly any gas anesthetic in the air to trigger MH)

“Awake” MH

In rare cases, someone may have an MH-like reaction even though they do not receive anesthesia. No one knows what causes it, but some triggers include a combination of stress, physical exercise, heat, and illness. The term “awake” MH is controversial, because the classic definition says that MH is a reaction to anesthesia. Therefore, some doctors do not use the term “awake” MH and prefer an alternative name, such as “MH-like” reaction.

Exertional Rhabdomyolysis (ERM) or Exertional Heat Illness (EHI)

People who have had an MH episode or a family history of MH can also be sensitive to heat and strenuous exercise. Moreover, an otherwise healthy person might be diagnosed with MHS because they cannot tolerate heat or they had an ERM or EHI episode. *RYR1* mutations are associated with up to 30% of ERM episodes. There is a correlation between MH and ERM/EHI, but no one knows how strong that correlation is.

ERM/EHI looks like MH, except it happens in response to strenuous exercise, extreme heat, or both, rather than a gas anesthesia and/or receiving succinylcholine. Other triggers may include drugs and illness, such as viral infection. When these episodes occur, muscle cells die and release their contents into the bloodstream. The person feels severe muscle pain. Their urine contains products of rhabdomyolysis and therefore turns into a dark color. Their blood might show a spike in a protein called creatine phosphokinase (CK). If ERM/EHI is not treated, it can lead to kidney failure, blood clots, irregular heartbeat, and even death.

When ERM/EHI occurs, doctors examine the patient and determine whether to treat someone as an outpatient or admit them into the ICU. That decision depends on how severe the reaction is.

If you receive outpatient treatment, doctors might advise you to:

- Rest
- Hydrate - Drink lots of water
- Get adequate sleep
- Avoid heat
- Avoid sports for some time
- Avoid medications that might trigger another event (be sure to read about the potential side effects of any medication(s) you are taking)
- Do not use caffeine
- Take an ice bath (e.g., football players, etc.)

If the ERM/EHI is severe enough for you to be admitted to the ICU, you might receive:

- Treatment with dantrolene
- IV fluids
- Dialysis if you have kidney damage and cannot produce urine
- Advice to avoid drugs that might trigger another event
- Cooling of the body (cold IV fluids and cooling blanket)

After an ERM/EHI event passes, your doctor will advise you about returning to sports or activities. You do not have to avoid all exercise unless you have a history of heat strokes or rhabdomyolysis. Here are some precautions to keep in mind:

- Talk with your doctor before starting an exercise or sport program.
- Avoid extreme heat or cold.
- Avoid extremely strenuous exercise and listen to your body.
- Avoid training where you push your muscles past the point of failure/exhaustion.
- Do not do strenuous activity in extreme heat or cold, if you are sick, or if you have recently ingested drugs or alcohol.
- Stay hydrated while you exercise.
- Wear emergency medical identification, such as a MedicAlert, SOS necklace, or bracelet.
- Be sure there is cooling treatment available.
- Do not use NSAIDs (e.g., aspirin, ibuprofen) to treat headache, pain, or fever before sports. If you are ill, wait until you recover.

Cody's Story

As the 10th overall pick in the 2008 NHL Draft, Cody Hodgson had a bright career ahead of him in the NHL. Cody played for the Vancouver Canucks, Buffalo Sabres, and Nashville Predators over the course of a six-year career. Although Cody had experienced muscle cramps his entire life, he dismissed them as a regular part of being a competitive athlete. As his symptoms became more severe during his professional playing days, he recalled, "I knew I had to get medical help." He experienced many distressing signs and symptoms, including: trouble breathing, heart arrhythmias, severely low blood pressure resulting in "blacking out," and tea-colored urine. The severity of these symptoms culminated in a hospitalization in 2015, when doctors diagnosed him with rhabdomyolysis, a severe and potentially fatal condition related to abnormal muscle breakdown.



Cody (right) at the 2018 RYR-1 International Family Conference with Lindsay Goldberg (left) and Cody's brother, Clayton (middle).

During the 2015-2016 season with the Predators, Cody was referred to Dr. Sheila Riazzi, an anesthesiologist and one of the world's leading experts on malignant hyperthermia, a muscle condition most commonly due to a mutation in the *RYR1* gene. Dr. Riazzi, a member of the RYR-1 Foundation's Scientific Advisory Board, quickly realized that Cody's numerous injuries, severe symptoms, and episodes of rhabdomyolysis were all likely due to RYR-1-related malignant hyperthermia. She ordered genetic testing and a muscle biopsy, which confirmed the diagnosis.

Receiving this diagnosis from Dr. Riazzi was a source of tremendous relief for Cody. "You put up with a lot of injuries, and it takes a physical toll when you play hockey," Cody said "but it really scares you when you are not sure what is going on with you."

Dr. Riazzi informed Cody of the RYR-1 Foundation and put him in touch with its President, Dr. Michael Goldberg. After meeting with Dr. Goldberg in early 2018 and learning more about the work of the RYR-1 Foundation, Cody said, **"Hopefully, the RYR-1 Foundation and I can help to not only push for a cure, but also help the parents, patients, and families affected by it now so that they can better understand their condition, take the appropriate precautions, and have a treatment available to them."**

To watch a video on "Cody's Story," please go to: www.ryr1.org/cody

Can I Go Back to Sports?

Talk with your doctor about returning to sports and follow the doctor's directions on follow-up visits. People who have an ERM/EHI episode can usually return to sports gradually. Typically, you will start by doing light activity for a certain amount of time. If you do not have any ERM/EHI symptoms, you can usually go back to your sports. Following up with the doctor is very important. You should also see your doctor if you have symptoms such as muscle weakness, cramping, swelling, or pain.

Statins

People take statins if they have high cholesterol. About 10% to 29% of people who take statins can have a side effect called **statin myopathy**. Symptoms of statin myopathy may include:

- Muscle weakness
- Cramping
- Muscle pain
- Swelling of muscles

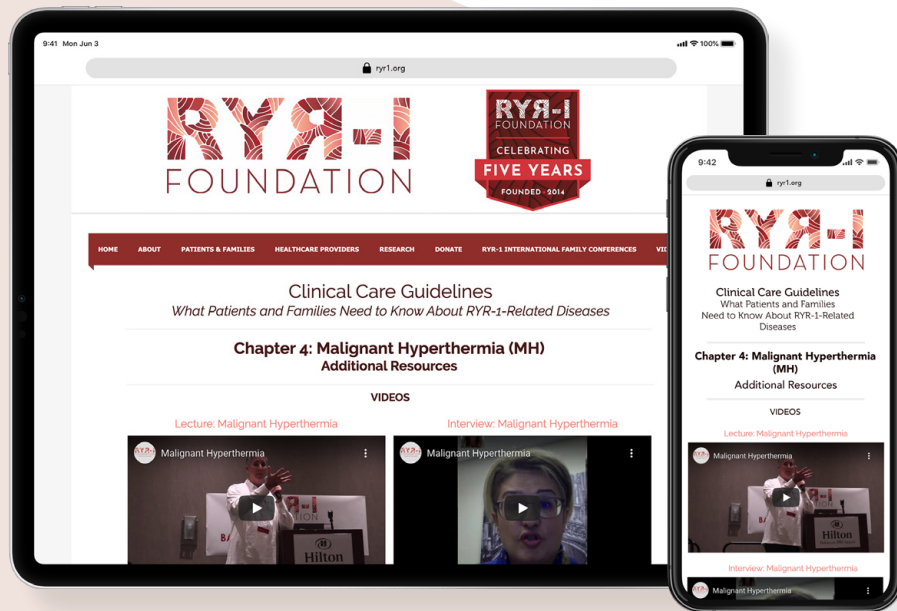
Studies have shown that statins can cause the RyR1 receptor to stay open. This leads to more calcium in the muscle cell cytoplasm. In most cases, that does not change how the muscle works. However, some people who have statin myopathy also have *RYR1* mutations. In one animal study, the drug Simvastatin triggered an MH-like event in mice with an *RYR1* mutation. We need more research to fully understand the connection between statins, *RYR1* mutations, myopathy, and MHS. Therefore, if you have high cholesterol, you should let your doctor know about your *RYR1* mutation in order to determine the most appropriate medication(s) for you.

Resources on MH

The Malignant Hyperthermia Association of the United States (MHAUS) provides information for patients and their families: www.mhaus.org.

The North American Malignant Hyperthermia Registry keeps track of people who have had MH episodes. It also provides data and information to researchers so they can learn more about MH. If you have had MH and you are not registered, visit their website at www.mhreg.org.

The European Malignant Hyperthermia Group supports research on MH. The group also helps to increase awareness among patients and families: www.emhg.org.



For additional resources, please click on the above image or visit:
www.ryr1.org/ccg-mh

Chapter 5

The Lungs/Pulmonology

Words Your Doctor May Use

Airway clearance: Clearing mucus and other things out of the lungs.

Diaphragm: The primary muscle for breathing in.

Kyphosis: Abnormal backward curve of the spine (“hunchback”).

PFT: Pulmonary Function Test.

Respiration: Breathing.

Respiratory failure: The respiratory muscles cannot bring in sufficient oxygen and get rid of enough carbon dioxide.

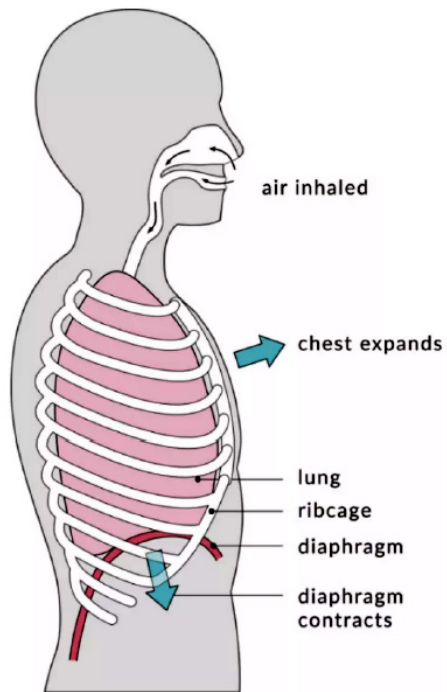
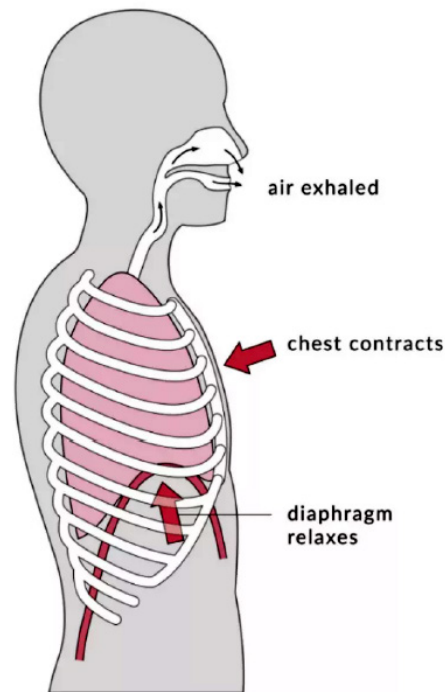
Scoliosis: Abnormal sideways curvature of the spine.

Sleep apnea: A disorder where you “stop and start” breathing while you sleep.

Thoracic cage: The chest wall and upper abdomen together. The bony part of the thoracic cage is the rib cage.

All of our cells need oxygen to make energy. When they make energy, the cells produce carbon dioxide. Breathing brings oxygen into our body and gets rid of carbon dioxide.

The **diaphragm** is the primary breathing muscle. When we breathe in, the diaphragm contracts and moves downward, and the chest wall expands. This draws air in through the mouth and nose. The air goes down the windpipe (trachea), into the lungs, and into tiny air sacs called alveoli. The walls in the alveoli are so thin that oxygen can move from the alveoli into the blood. The blood carries the oxygen to all our organs and cells.

INHALATION**EXHALATION**

Schematic diagram illustrating the role of the diaphragm and chest wall during inhalation ("breathing in") and exhalation ("breathing out").¹

Carbon dioxide can also move from the blood into the alveoli. When we breathe out, the diaphragm relaxes upward, and the chest wall moves inward. As air is exhaled from the lungs, the carbon dioxide leaves the body. The diaphragm helps us inhale, and the abdominal muscles help us exhale.

Weakness in the diaphragm and abdominal muscles can make it harder to clear the airways, because it becomes hard to inhale deeply and exhale forcefully and fully. If someone gets a cold, having weak breathing muscles can lead to a pneumonia. That can lead to more muscle weakness, and that can lead to more problems clearing the airways.

The chest wall and abdomen form the **thoracic cage**. If the chest wall is weak, the chest may move inward instead of outward during inhalation. That makes it harder to take a deep breath. As the chest wall becomes weaker and moves less, it can become stiff. Stiffness in the chest wall makes it even harder to take a deep breath.

¹**Source:** wetcake/DigitalVisionVectors/Getty Images; found in Respiration: Definition and Types. Accessed 2/17/20 at www.thoughtco.com/respiration-definition-and-types-4132422

Weakness in the thoracic cage can also lead to spinal instability. This can cause your spine to curve, which causes **kyphosis**, or “hunching” of the back. Or, it can cause your spine to curve sideways, which causes **scoliosis**. This can limit chest wall movement during breathing, which makes it harder to take a deep breath and produces lower lung volumes.

Together, these problems can lead to a situation where the breathing muscles do not work well enough to bring in oxygen and get rid of carbon dioxide. This is called **respiratory failure**.

TYPES OF RYR-1-RD: RESPIRATORY FEATURES

Type	Typical Respiratory Features
Central core disease (CCD)	Typically mild In severe cases, the person needs help to breathe
Multi-minicore disease (MmD)	Severe, can be life-threatening in some cases
Centronuclear myopathy (CNM)	Breathing problems range from mild to severe
Congenital fiber type disproportion (CFTD)	Some cases are severe from birth, with respiratory failure Other cases may need breathing support at night

RYR-1-RD and Breathing

As is the case with other symptoms, the effects of RYR-1-RD on breathing vary in severity. Some people with RYR-1-RD might have no problems. Some might have mild problems, but need help breathing while they sleep or when they are sick. In severe cases, someone with RYR-1-RD may need a ventilator to help them breathe.

If you or your child have RYR-1-RD, doctors typically check breathing regularly. For low-risk *RYR1* mutation(s) or mild disease, this may happen once per year. For people with high-risk *RYR1* mutation(s) or more severe disease, it may happen every six months. For patients five years and older, **pulmonary function testing (PFT)** is a way for the pulmonologist to assess the presence, type, and severity of breathing problems someone has. You may also be asked to do a “sleep study,” in which your doctors evaluate your breathing while you sleep. A sleep study measures how well you inhale oxygen and exhale carbon dioxide, and whether you have obstructive sleep apnea (temporary or complete obstruction of breathing during sleep) or respiratory failure (inability to inhale enough oxygen and exhale enough carbon dioxide).

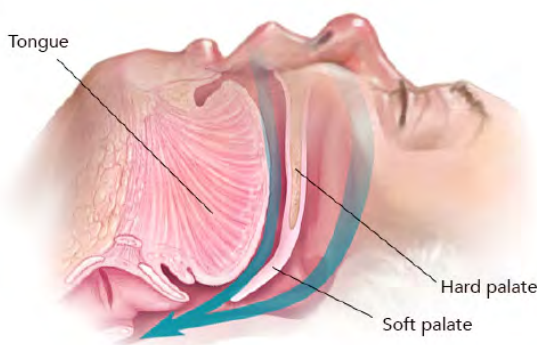
What is Obstructive Sleep Apnea?

Obstructive sleep apnea is a disorder where your breathing “stops and starts” because the upper airway is obstructed. With obstructive sleep apnea, the throat muscles can relax too much and cause the upper airway to narrow or close. When that happens, it is hard or not possible to inhale. When this happens, your blood oxygen can decline and become low. You might snore, choke, or gasp. That can happen anywhere from 5 to 30 times in an hour. The brain senses this and wakes you up briefly so you can reopen your airway. That means that you cannot reach the deep, restful phases of sleep.

Symptoms of Sleep Apnea Include:

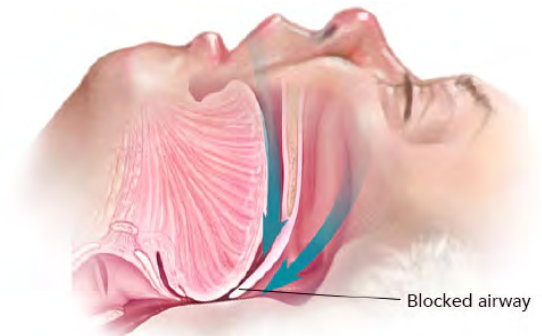
- Loud snoring
- Episodes where you stop breathing while you are asleep
- Dry mouth when you wake up
- Morning headache
- Problems staying asleep
- Daytime sleepiness
- Problems paying attention
- Irritability

A. NORMAL BREATHING DURING SLEEP



A. Under normal circumstances, the air passages (curved, blue arrows) in the back of the mouth and throat remain open during sleep. This allows sufficient flow of oxygen into the lungs and bloodstream.

B. OBSTRUCTIVE SLEEP APNEA



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B. In obstructive sleep apnea, the muscles in the back of the mouth and throat relax to the point that the air passages (curved, blue arrows) become obstructed. This prevents sufficient flow of oxygen into the lungs. This ultimately leads to lower levels of oxygen in the bloodstream.

Source: Mayo Foundation for Medical Education and Research. Accessed 2/17/20 at:
www.mayoclinic.org/diseases-conditions/sleep-apnea/symptoms-causes/syc-20377631

What Happens During a Sleep Study?

A sleep study is an overnight exam. You will spend the night at a hospital or sleep center. You can bring personal items you need for sleeping. You can wear your own pajamas.

Your doctor will ask you to arrive about two hours before bedtime. You will go to a room that is dark and comfortable for sleeping. Before you go to sleep, a technician will place sensors on your head and body. You can still move around. Technicians can help you if you need to go to the bathroom during the night.

While you sleep, technicians monitor your sleep. They also measure:

- Eye movement
- Blood oxygen levels
- Carbon dioxide levels
- Heart rate
- Breathing rate
- Snoring
- Body movements

After the study, your doctor analyzes the data that the technicians collected. Your doctor will discuss this with you either by phone or at a follow-up visit.

Managing Respiratory Complications

There is no standard treatment plan for breathing problems associated with RYR-1-RD. The plan will depend on the severity of the symptoms. In most cases, however, you will receive advice on:

- Flu and pneumonia vaccines
- Techniques to help with coughing
- Techniques to make the mucus easier to clear
- Treatment for sleep apnea

AIRWAY CLEARANCE—COUGH ASSISTANCE

There are three phases to a cough:

- You take a deep breath to fill your lungs
- You exhale, but your vocal cords close (this creates pressure in your chest)
- The vocal cords open, and you push out a big flow of air carrying mucus and other particles

There are cough assistance strategies that can help you take a deep breath, breathe out, or both.

Breath-stacking helps you breathe in. With breath-stacking, you wear a mask over your mouth and nose that allows you to inhale but not exhale. The doctor asks you to breathe in to fill your lungs as much as possible by breathing in a number of times until you cannot breathe in any further. Then the mask is removed, and you breathe out as much as you can. If you cannot breathe in effectively on your own, then you can use a device to help you breathe in deeply.

Mechanical assistance helps you breathe out. With mechanical assistance, you lie down. Someone places their hands on your chest or abdomen and pushes down while you breathe out. *The person helping you breathe out has to be trained to do it properly.*

You can combine breath-stacking with mechanical assistance by forcefully pushing on the chest and abdomen to help breathe out forcefully.

Many people with RYR-1-RD use a **Cough Assist® machine**. This machine simulates a cough. It can be set to help you breathe in, breathe out, or both. You can use the Cough Assist® machine as often as you need to. Typically, people with RYR-1-RD use the Cough Assist® machine twice a day when they are well. If you get sick, you might use it every hour or more frequently.

AIRWAY CLEARANCE—MUCUS MOBILIZATION

Mucus mobilization makes mucus easier to cough up. Mucus mobilization by itself will not clear your airways. You have to do it with coughing or the Cough Assist® machine. To mobilize mucus, you can:

- Use a device that vibrates your chest - this shakes the mucus loose and makes it easier to clear
- Take medications (under a doctor's supervision):
 - For mucus that is too thick, you can take concentrated saline or a medication called Pulmozyme® (dornase)
 - If you have too much saliva, you can take medications to decrease it
 - For allergies, you can take antihistamines
 - For gastroesophageal reflux ("heartburn"), you can take antacids

VENTILATION

People with RYR-1-RD often get breathing assistance with a BiPAP (“Bilevel Positive Airway Pressure”) or CPAP (“Continuous Positive Airway Pressure”) machine while they sleep. The BiPAP machine provides high pressure while you breathe in and low pressure while you breathe out and helps you breathe in more deeply to treat respiratory failure. This is different from a CPAP machine, which continuously provides pressure to keep your upper airway open when you have obstructive sleep apnea; this does not help you breathe deeper if you have respiratory failure.

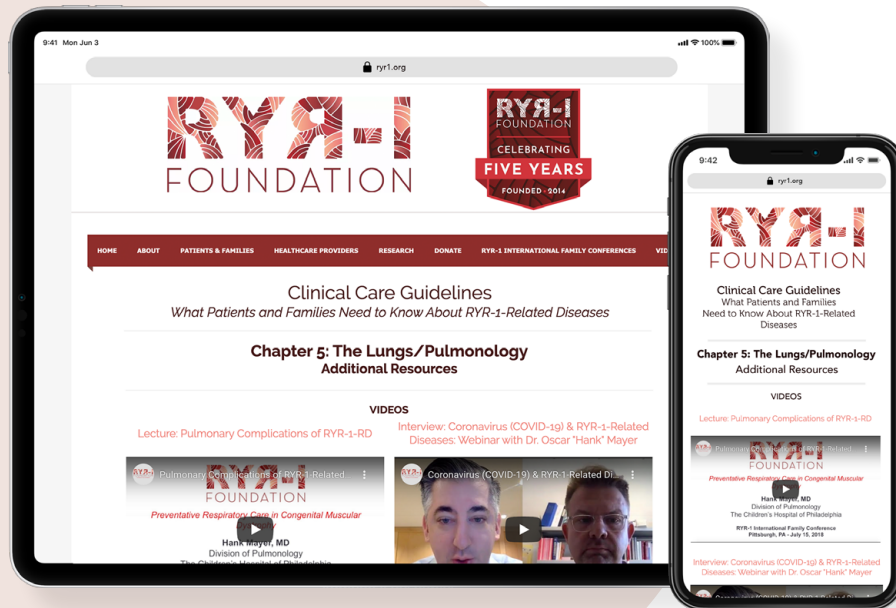
For more severe problems, such as respiratory failure, you would need a ventilator. The ventilator can come with a nose mask, face mask, or nasal plugs. You might use a nose mask or face mask at night while you sleep, then a mouthpiece during the day. While you sleep, you might need a chin strap to keep your mouth from opening. Otherwise, air will leak, and the ventilator will not give you the support you need.

In very severe cases, if BiPAP ventilation does not work, you might need a breathing tube for invasive ventilation. When this happens during an infection or other illness, the expectation is that the breathing tube is eventually removed and that you return to the level of breathing support that you were using before you got sick. If you need a ventilator through a breathing tube for a long time, a tracheotomy, where an opening is made in the trachea (“windpipe”), may be recommended. But that should only be done with a clear understanding of why it is needed and after all other options have been contemplated.

A Word About Illness

Remember that RYR-1-RD can make the respiratory muscles weaker. That means that even a mild respiratory infection, like a cold, can lead to severe breathing problems. Viral infections can also lead to bacterial infections that can be life threatening. When you get sick, your doctor will check for pneumonia, low blood oxygen, or high levels of carbon dioxide. Your doctor might also give you an antibiotic to prevent or treat bacterial infections.

If you need to be hospitalized, it is important to have a plan to get help with breathing before you need it. If you are having surgery, doctors can take precautions to help you with breathing before and after surgery.



For additional resources, please click on the above image or visit:
www.ryr1.org/ccg-pulmonology

Chapter 6

The Bones and Joints/Orthopedics

Words Your Doctor May Use

Contracture: Fixed or stiff joints without a full range of motion

Flexion contracture: A joint is stuck in a flexed or bent position

Functional goal: An activity you want to do

Functional limitation: An activity you cannot do

Hip dislocation: The hip bone is out of its joint

Impairment: A problem with body function and structure

Kyphosis: Abnormal backward curve of the spine ("hunchback")

Lordosis: Abnormal forward curve of the spine ("arched back")

Restriction: The inability to do an activity

Scoliosis: Abnormal sideways curve of the spine

Shared decision making: A process where clinicians and patients work together to make decisions about care

Thoracic insufficiency syndrome: A condition where the chest wall does not support lung function

Managing Orthopedic Complications: The Big Picture

Your multidisciplinary care team will likely include an orthopedic specialist. Orthopedic specialists are experts in the bones, joints, and muscles. Like everyone else on your care team, the orthopedic specialist looks at the whole patient. Every person with RYR-1-RD is unique, so each person's care will be unique.

In the orthopedics world, specialists want to know:

- Who you are - what is your diagnosis and what is your mutation?
- How has your disease progressed?
- What kinds of activities do you want to do?
- What kinds of activities can you not do?

Patients, families, and orthopedic specialists work together to make decisions. Orthopedic specialists talk about the clinical problems and ways to address them. Patients and families talk about how the disease affects them and what they want to achieve. Together, patients, families, and orthopedic specialists set a reasonable **functional goal**. That is, they make a realistic decision about an activity the patient wants to achieve. Once the patient, family, and orthopedic specialist set a functional goal, the orthopedic specialist might recommend treatments. Patients and families, along with their orthopedic specialist, then decide on a plan together. With **shared decision-making**, the patient's preferences and values are just as important as the specialist's expertise. Remember, each person with RYR-1-RD is unique. Therefore, what fits one person might not fit another.

Setting Functional Goals

When you and your orthopedic specialist set a functional goal, you set a goal for an activity you would like to achieve. The goal depends on:

- The impairment, or problems in body structure and the way it works
- The restriction, or things you cannot do
- What you want to do
- How much the impairment and restriction get in the way
- What is realistic

Setting Functional Goals (continued)

For some people with RYR-1-RD, the goal could be something like, “I want to play sports.” For others, the goal might be, “I want to be able to sit or stand.” For yet others, the goal might be, “I want to get dressed without help.”

General Steps in Orthopedic Health

In general, orthopedic health will focus on the following things:

- Bone health: Your care team may recommend daily vitamin D supplements. They may check your vitamin D levels each year. The team may also recommend that you take the daily recommended level of calcium, either through supplements or your diet.
- Bone density: Your team may recommend yearly DEXA scans to quantify bone density. In some cases, drugs can be given either orally or intravenously to improve bone density.
- Physical activity: Your team may recommend standing. They may also recommend regular strength and endurance exercises. You might also get stretching exercises to help with your range of motion. Finding fun activities can help keep you active.
- Technology: You might need devices such as orthotics, standing frames, wheelchairs, or body braces to help you stand and move.
- Pain management.
- Preventing bone deformities, or correcting them if necessary.

Common Orthopedic Features of RYR-1-RD

The most common orthopedic problems among people with RYR-1-RD are:

- Weakness
- Contractures
- Hip dislocations
- Scoliosis and/or other spinal deformities

Managing contractures and hip dislocations can be complex. Decisions to treat them depend on your restrictions, your goals, and other medical problems you may have.

Managing scoliosis and other spinal deformities depend on a wide range of factors, as discussed below.

TYPES OF RYR-1-RD: ORTHOPEDIC FEATURES

Type	Common Orthopedic Features
Central core disease (CCD)	Scoliosis , hip dislocation at birth, mild contractures
Multi-minicore disease (MmD)	Progressive scoliosis
Centronuclear myopathy (CNM)	Scoliosis
Congenital fiber type disproportion (CFTD)	Hip dislocation, contractures, foot deformities, scoliosis , lordosis

CONTRACTURE

Contracture means that a joint does not have its full range of motion, so it is fixed or stiff. In most cases, it is a **flexion contracture**. That means the joint is stuck in a flexed or bent position, and it cannot straighten out.

A contracture can have several causes:

- The muscle is too weak or too short
- Muscle is replaced with stiff connective tissue
- There are problems with a joint capsule

Orthopedic specialists need to determine the precise cause of the contracture before they can determine how best to treat or manage it.

Proactive or **preventive** methods aim to keep the contracture from happening in the first place. These methods include:

- Positioning: Adjusting how the joint is customarily positioned
- Physical therapy: Activities that will help you maintain the normal range of motion
- Orthotics: Splints or devices to hold the joint in place

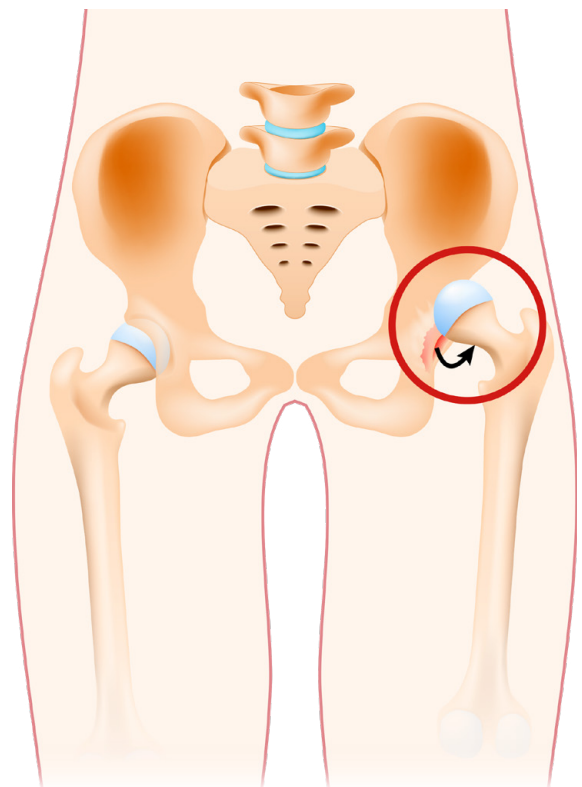
If these methods do not work, the orthopedic specialist might recommend surgery to restore the joint's range of motion. With some types of surgery, where the orthopedic specialist lengthens the muscle, there is a risk that the patient will lose function in that muscle. With all surgeries, there is a risk that the contracture could return. In most cases, it is important for the person to get moving as soon as possible after the surgery. Orthopedic specialists also might recommend splints or other devices to maintain what you have gained from surgery. For more on surgery and the risk of malignant hyperthermia (MH) for patients with RYR-1-RD, **please see Chapter 4, "Malignant Hyperthermia (MH)."**

HIP DISLOCATIONS

Hip dislocation means that the hip bone (femur) is out of its joint or out of its socket. There are no standard rules on treating hip dislocations in people with neuromuscular diseases. Treatment depends on:

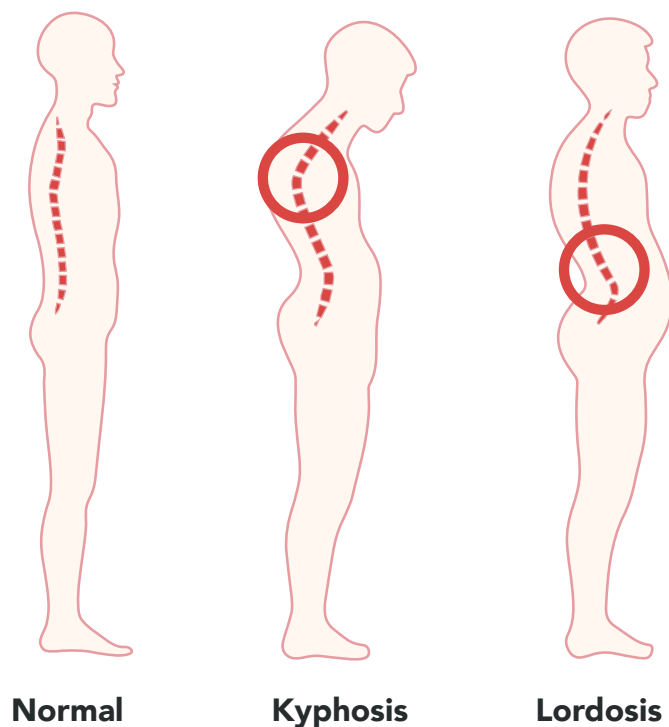
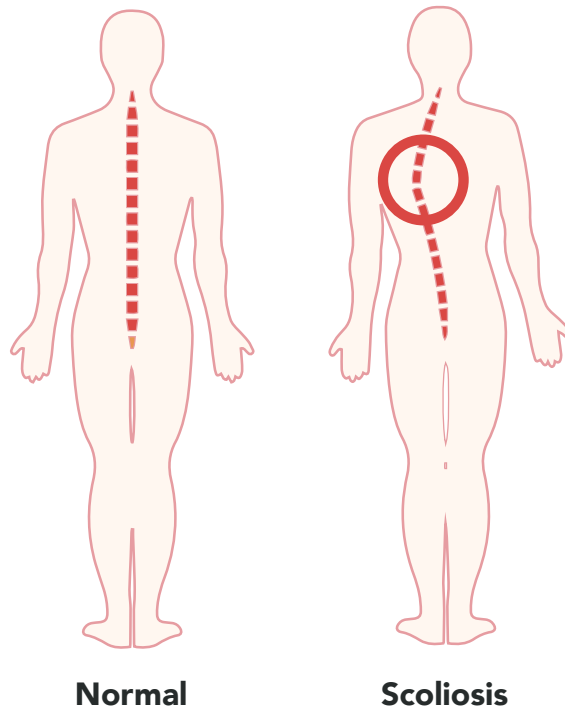
- The age of the patient
- If there is enough muscle control and power to support the hip
- If the dislocation affects one or both sides
- If the dislocation affects the person's function
- If the person has symptoms, such as pain

For babies with hip dislocations, treatment may begin with a Pavlik Harness (or similar splinting device). If that does not manage the dislocation, specialists will consider surgery. There is no standard for older children who have hip dislocations in the absence of pain. In these cases, orthopedic specialists typically choose not to operate unless the dislocation is severe and there is pain. In most cases, the hip dislocation does not interfere with the person's ability to walk.



SCOLIOSIS/SPINAL DEFORMITIES

Scoliosis is a sideways curve in the spine. **Kyphosis** means that the spine curves too much backward ("hunchback"). **Lordosis** means that the spine curves too much forward ("arched back").



These deformities can cause the chest wall to become too narrow. They can also interfere with the lungs and diaphragm. Spine deformities also can interfere with:

- A person's balance
- A person's ability to use their arms
- How easy it is to take care of the person
- A person's quality of life
- Life expectancy

The chances of a spinal deformity getting worse depend on:

- The age of the person
- The type of curve
- Severity of curve

Orthopedic specialists use “watchful waiting” to manage small spinal curves that do not look like they will get worse. They examine the person's spine at each visit and take a radiograph (“X-ray”) about once a year. Specialists may also try a soft brace or wheelchair to keep the spine in position.

Surgery is often the best way to manage a curve that is getting worse. However, surgery can do more harm than good in younger patients, because it could interfere with lung function. **Thoracic insufficiency syndrome** is a condition where the chest cannot support breathing or lung growth. This is also a concern because neuromuscular diseases, such as RYR-1-RD, can also interfere with breathing due to weakness of the breathing muscles (**please see Chapter 5, The Lungs/Pulmonology**). If surgery is needed, orthopedic surgeons will make sure that the lungs and chest wall have developed enough. The lungs will grow in size and add new air spaces called alveoli, where oxygen enters the blood and carbon dioxide leaves, through 18 years of age.

For younger patients, surgeons may use growing rods, which act like an internal brace. These rods do not interfere with the child's growth. If the spinal deformity starts later, or if the person is older, surgeons may do a spinal fusion, which makes the small bones in the spine grow together. As always, every patient is unique, and decisions regarding surgical repair of scoliosis should be made after close consultation between the orthopedic specialist and patient.



For additional resources, please click on the above image or visit:
www.ryr1.org/ccg-orthopedics

Chapter 7

Eating, Swallowing, and Speaking

Words your Doctor May Use

Aspirate: Breathe in foreign objects/substances (e.g., food and liquids) into the airway through the vocal cords (“vocal folds”)

Augmentative and Alternative Communication (AAC): Encompasses a wide range of nonverbal communication methods, from sign language and picture boards to mobile device apps and high-tech dedicated speech-generating devices (SGDs)

Bulbar involvement: Problems chewing, swallowing, and speaking because of weakness in the bulbar muscles

Bulbar muscles: Muscles in the face, mouth, and throat

Dysarthria: Slurred or slow speech that can make it difficult to be understood

Gastroenterologist: A doctor who specializes in the stomach and intestines

Nutritionist: An expert in food and nutrition

Occupational Therapist (OT): An expert who helps you improve and maintain skills for daily living

Penetration: When food or liquid enters the airway but does not pass through the vocal cords

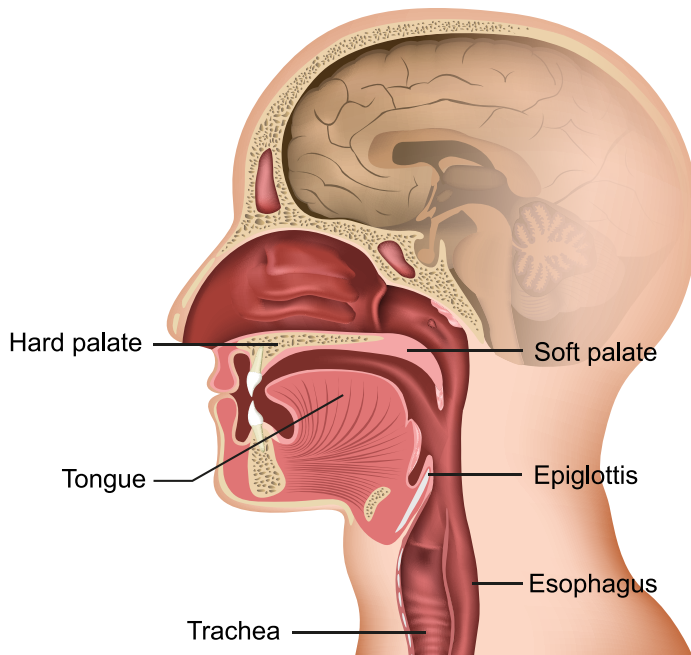
Pulmonologist: A doctor who specializes in the lungs

Respiratory: Related to breathing or the lungs

Speech-Language Pathologist (SLP): An expert who assesses, diagnoses, and treats communication and swallowing problems

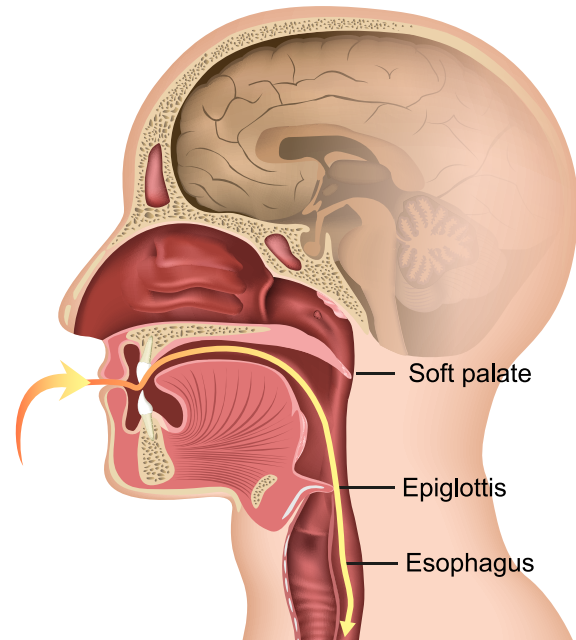
The **bulbar muscles** are muscles in the face, mouth, and throat. Muscles in your mouth and jaw help you chew your food. When you swallow, muscles in your mouth and throat push the food to a long tube called the esophagus. From there, the food goes to the stomach to be digested. Muscles in the throat also keep the food from going down the windpipe (trachea) and into the lungs. Up to 26 muscles work together for you to chew and swallow properly.

A. MOUTH AND CHEEK ANATOMY



A. Schematic diagram demonstrating the anatomy of the mouth and throat.

B. INGESTION



B. During ingestion, the muscles of the face, mouth, and throat direct food (yellow arrow) towards the esophagus and away from the trachea. If there is muscle weakness of the face, mouth, and/or throat, this swallowing process can be impaired--this can result in food and/or liquid going into the nose or trachea.

You also need your facial and bulbar muscles to speak. When you speak, muscles in your face (jaw, tongue, and lips) work together to form words. Your diaphragm, lungs, and voice box (the larynx) work together to make sound.

RYR-1-related weakness in the facial and bulbar muscles can lead to problems with eating, swallowing, and speaking. Doctors call this **bulbar involvement**. Like other symptoms of RYR-1-RD, bulbar involvement differs by disease subtype and severity. In general, **autosomal dominant** *RYR1* mutations tend to be associated with milder symptoms. **Autosomal recessive** *RYR1* mutations tend to be associated with more common and severe symptoms.

TYPES OF RYR-1-RD: BULBAR INVOLVEMENT AND OTHER FEATURES

Type	Bulbar Involvement and Other Features
Central core disease (CCD)	In severe cases
Multi-minicore disease (MmD)	Common
Centronuclear myopathy (CNM)	High arch in the roof of the mouth
Congenital fiber type disproportion (CFTD)	High arch in the roof of the mouth Crowded teeth Swallowing difficulties appear in about 30% of people with CFTD

Managing Problems with Feeding and Swallowing

People with problems chewing and swallowing tend to:

- Drool
- Take longer to eat
- Breathe food or other foreign objects into their airway (aspirate)

These problems can lead to poor growth, acid reflux, and frequent respiratory infections. At the same time, weight gain can also be a problem, because RYR-1-related weakness in other muscles can lead to problems with moving. Therefore, doctors should pay attention to nutrition and eating as much as they pay attention to movement, the spine, and breathing.

As with other aspects of your care, a multidisciplinary team will help with feeding and speech problems. The team can include the following kinds of specialists:

- **Nutritionist** or Dietician: This specialist will talk with you about the calories and nutrients you or your child are getting to ensure that health needs are being met. If possible, this should happen at every clinic visit.

- A specialist who will do a feeding evaluation (typically a speech-language pathologist specializing in feeding and swallowing). The evaluation can include an examination of:
 - The inside of the mouth
 - The strength, speed, and range of motion of the muscles in and around the mouth
 - How you or your child take food and liquids
- **Pulmonologist:** This specialist will monitor your respiratory system and breathing. The pulmonologist might do a chest radiograph (“X-ray”) to see whether problems with chewing and swallowing affect the lungs.
- **Speech-Language Pathologist (SLP)** and/or **Occupational Therapist (OT):** These specialists assess if you are having swallowing problems (dysphagia) with various foods and liquids and help determine the course of treatment. They might do a modified barium swallow study (MBSS) if there is a concern for food and liquid going into your airway (aspiration). An MBSS is a test in which X-ray videos (“fluoroscopy”) are taken while the patient eats and drinks foods of varying consistencies. This allows the SLP and/or OT to determine the risk of aspiration and what kinds of foods will be safe to consume.
- **Gastroenterologist (GI):** This specialist might do a swallow study and/or use a camera (“endoscope”) to evaluate the upper gastrointestinal (GI) tract (i.e., esophagus, stomach, and a portion of the small bowel).

HOW ARE THESE PROBLEMS MANAGED?

If a baby with RYR-1-RD has problems with feeding, the clinical team might suggest that you:

- Adjust the baby’s position
- Make the formula or breastmilk thicker
- Use a breast nipple shield to help the baby latch on
- Get special bottles and nipples

For older children, the care team should monitor their nutrition. They should check the child’s height and growth. A therapist might also help children sense the taste, temperature, and texture of food, so they do not shy away from eating. If the child cannot get the calories they need from their diet, a doctor may recommend a feeding tube.

For more information, please visit:

www.feedingtubeawareness.org/education-materials/

Doctors should also measure your or your child's calcium and vitamin D, approximately once a year.

- **Acid reflux:** Symptoms of acid reflux include chest and/or stomach pain (a burning feeling), vomiting/spit up, frequent respiratory infections, or aspiration. Oral medications and diet modifications may help you manage acid reflux.
- **Constipation or delayed stomach emptying:** Make sure the individual has plenty of fluids. Stool softeners or laxatives can also help. Your team might advise you on how to position yourself and/or your child while eating.
- **Drooling:** Muscle weakness around the face and mouth can make it hard to close the mouth or swallow saliva. Your team might suggest suction to help with drooling or therapy by a speech-language pathologist or occupational therapist to help children control, reduce, or eliminate their drooling.

Oral and Dental Care

Some people with RYR-1-RD might have facial deformities, or the alignment between their upper and lower teeth might be abnormal. This can result in poor oral hygiene.

Adolescents and adults should see a dentist regularly. Parents should brush their children's teeth twice a day once the first tooth appears. A dentist can help if the child is very sensitive to brushing. Children should see a pediatric dentist by the time they turn one year old. Children with RYR-1-RD may need to see an orthodontist to assess for dental alignment problems.

Speech and Communication

For some people with RYR-1-RD, it can be hard to speak because of:

- Weakness in the mouth muscles (lips, tongue, palate)
- A weak voice
- Problems controlling breathing
- Structural abnormalities in the mouth

For some people with RYR-1-RD, their muscle weakness results in too much air coming out of their nose during speech. The sound of the air leaking through the nose during speech has a characteristic effect on speech quality and is referred to as "hypernasality." Others with RYR-1-RD might have problems with slurred or slow speech (**dysarthria**).

A speech-language pathologist can help with these problems. Speech-language pathologists can help you learn how to control your breathing and speak clearly. If the problem is more severe, other communication tools might help, including **Augmentative and Alternative Communication (AAC)**. The speech-language pathologist might teach you sign language, gestures, writing, or you can use a device or communication board to help with communication and help preserve your voice.

Chapter 8

Considerations for School

Words Your Provider May Use

Accommodation: A change to how a student learns material

FAPE: Free and Appropriate Public Education

GEP: General Education Plan

IDEA: Individuals with Disabilities Education Act

IEP: Individualized Education Program

LRE: Least Restrictive Environment

Modification: A change to what a student is taught or expected to learn

SDI: Specially Designed Instruction

504 Plan: Blueprint for how the school will support a student with a disability and remove barriers to learning; this differs from an IEP in that it does not provide an SDI to meet a child's unique learning needs

THE INDIVIDUALS WITH DISABILITIES EDUCATION ACT (IDEA)

The **Individuals with Disabilities Education Act (IDEA)** requires public schools to provide special education and related services to eligible students. IDEA includes the “Child Find” requirement where all school districts are to identify, locate, and evaluate all children with a known disability or suspected disability to determine the need for services. The “Child Find” mandate covers every child no matter where they attend school, and includes:

- Children from birth through 21 years of age
- Children who attend public, private, parochial, or any school
- Children who are homeless or lack a permanent residence
- Migrant children
- Wards of the state

School districts must identify all children with disabilities. They typically use a general screening process to look for these children. For children not yet in school, they may be referred by a hospital, doctor, or other agency providing assistance. Parents can ask for assistance at any time. Schools often send a general call for families in the community to bring children in for vision, hearing, speech and language, and social-emotional skills screenings once or twice per year. Once the child is in school, universal screeners, teacher reports, and parent reports are how schools become aware of children with disabilities. If the school identifies a child who is at risk, further screening or a formal assessment will be completed.

Eligibility is determined after a comprehensive psycho-educational evaluation by the school's multidisciplinary team. Parents are part of the review. To be eligible for special education, the child's school performance must be "adversely affected" by the disability. Note, that just because a child is identified with a disorder, that does not automatically qualify him or her for an educational "disability." A child is eligible for "special education" only after the school team makes a determination that the child's disorder impairs their educational performance; "educational performance" is broadly defined to include not only academic performance (i.e., grades), but also social relationships and adjustment. Importantly, a child without a formally diagnosed disorder may still be eligible for "special education" if there is an impairment in "educational performance."

A parent may ask for an evaluation of their child. However, the school can refuse if no educational problem is apparent; the school must document its decision in writing to the parent. If the disagreement between the parent and school persists regarding the need for special education, there is a formal dispute resolution process that schools and parents can follow.

As required by IDEA, for a child to receive special education, his or her school performance must be "adversely affected" by a disability in one (or more) of the following 13 categories:

SPECIAL EDUCATION DISABILITY CATEGORIES UNDER IDEA

Category	Definition
<i>Specific Learning Disability (SLD)</i>	<p>Affects a child's ability to read, write, listen, speak, reason, or do math. Includes (but not limited to):</p> <ul style="list-style-type: none"> • Basic reading skills • Listening comprehension • Mathematics calculation • Mathematics problem solving • Oral expression • Reading comprehension • Reading fluency skills • Written expression <p>Other terms that may be used include: Dyslexia, Dyscalculia, Dysgraphia.</p>
<i>Other Health Impairment (OHI)</i>	<p>Limits a child's strength, energy, or alertness. Includes chronic or acute health problems (but not limited to):</p> <ul style="list-style-type: none"> • Asthma • Attention deficit disorder • Attention deficit hyperactivity disorder • Diabetes • Epilepsy • Heart condition • Hemophilia • Lead poisoning • Leukemia • Sickle cell anemia • Tourette syndrome
<i>Autism/Autism Spectrum Disorder</i>	<p>Developmental disability that affects social interaction, verbal communication, and nonverbal communication. The problems usually appear before age three.</p>

SPECIAL EDUCATION DISABILITY CATEGORIES UNDER IDEA (continued)

Category	Definition
<i>Emotional Disturbance</i>	<p>Condition that has one or more of the following characteristics over a long period of time and to a marked degree. Includes (but not limited to):</p> <ul style="list-style-type: none"> • Inability to learn cannot be explained by intellectual, sensory, or health factors • Inability to build or maintain satisfactory relationships with peers and teachers • Inappropriate behavior or feelings under normal circumstances • General mood of unhappiness or depression • Tendency to experience physical symptoms or fears associated with school or personal problems
<i>Speech or Language Impairment</i>	<p>Difficulties with speech or language. Includes (but not limited to):</p> <ul style="list-style-type: none"> • Language delay • Stuttering
<i>Visual Impairment, including blindness</i>	<p>Vision impairments that affect educational performance, even after they are corrected. Includes (but not limited to):</p> <ul style="list-style-type: none"> • Blindness • Partial sight
<i>Deafness</i>	<p>Impairments in processing linguistic information through hearing, with or without amplification. Includes (but not limited to):</p> <ul style="list-style-type: none"> • Inability to hear all or most sounds, even with a hearing aid
<i>Deaf-Blindness</i>	<p>Both severe hearing and vision loss at the same time; the child's needs are not met with programs exclusively for deaf OR blind persons.</p>

SPECIAL EDUCATION DISABILITY CATEGORIES UNDER IDEA (continued)

Category	Definition
Orthopedic Impairment* *most applicable to RYR-1-RD	Impairment of motor function or ability in the body. Includes (but not limited to): <ul style="list-style-type: none"> • Congenital myopathies (e.g., RYR-1-RD) and dystrophies (e.g., Duchenne's) • Acquired diseases, such as poliomyelitis • Other: Cerebral palsy, amputations, or post-traumatic
Intellectual Disability	This term is no longer referred to as "mental retardation." Significantly reduced general intellectual functioning, existing concurrently with deficits in adaptive behavior, which adversely affects a child's educational performance. Includes (but not limited to): <ul style="list-style-type: none"> • Down Syndrome
Traumatic Brain Injury (TBI)	Brain injury caused by external physical force (e.g., trauma) that results in functional disability, intellectual disability, and/or psychosocial impairment.
Multiple Disabilities	More than one of the above conditions concurrently (at the same time).

Especially in the above categories of "Other Health Impairment" and "Orthopedic Impairment," children with RYR-1-RD may qualify for special education.

INDIVIDUALIZED EDUCATION PROGRAM (IEP)

Once a child is found to be eligible for special education, the next step is creating an **Individualized Education Program (IEP)**. The IEP is a written legal document that makes sure your child receives a **Free and Appropriate Public Education (FAPE)** in the **Least Restrictive Environment (LRE)**. If a child is found eligible for special education (as defined by IDEA), he or she is entitled to an IEP within 30 days of the initial finding. Like other aspects of managing RYR-1-RD, the IEP team is multidisciplinary. Parents are always part of the team.

Who Is on the IEP Team?

The following people must be on your IEP team:

- Parent or legal guardian
- Representative for the school (e.g., principal, vice principal, etc.)
- One or more general education teachers
- One or more special education teachers
- Individual who can interpret evaluation results (e.g., school psychologist)
- Other individuals with knowledge or expertise needed to help your child (e.g., speech-language pathologist, occupational therapist, physical therapist, school nurse, etc.)
- Child (depending on the age)

You may invite others (advocates, your physician, or other experts) as you deem necessary.

It is critical that the IEP meets your child's individual needs. The IEP should be developed prior to the school providing services and used by all of your child's teachers. The law requires that the IEP team meets at least once per year. However, any team member, including parents, can request a meeting at any time.

What are the Components of the IEP?

The IEP should address all areas that are required to help the child succeed, including the use of related services (e.g., counseling, parenting support, and transportation, etc.) for the child to meet their educational goals. The IEP must discuss:

1. Statement of the child's current level of academic achievement and functional performance. Issues to consider are:
 - a. How does the child's disability affect his or her involvement in the general education curriculum?
 - b. A statement of the child's "present levels" must be included:
 - i. How is the child currently doing in school?
 - ii. How does the disability affect his or her performance in class?

What are the Components of the IEP? (continued)

2. Statement of measurable, annual goals:
 - a. Once a child's needs are identified, the IEP team works to develop appropriate academic and functional goals to address those needs. Annual goals describe what the child is expected to do or learn within a 12-month period.
 - i. Benchmarks or Short Term Objectives:
 1. Only needed for students who are taking alternate assessment aligned to alternate achievement standards.
 2. Used if student has specific academic goals due to performing below grade level.
3. Description of how the child's progress toward the annual goals will be measured and when it will be measured.
4. Statement of special education and related services that will be provided to the child:
 - a. Measuring and Reporting Progress
 - i. The IEP must contain a description of how progress will be measured and when it will be reported to parents:
 1. Who is collecting data?
 2. How is it being collected?
 3. How frequently?
 4. How will data be disseminated to the IEP team, including parents?
 - b. Related Services:
 - i. Areas where the student might need extra assistance:
 1. Speech-language pathology (SLP).
 2. Occupational therapy (OT).
 3. Physical therapy (PT).
 4. Counseling services.
 5. Vocational counseling.
5. Program modifications or supports for school personnel to use in order to enable the child to advance towards annual goals; including things such as participation in extra curricular and non-academic activities.
6. Explanation of the extent to which a child will not participate with nondisabled peers.

What are the Components of the IEP? (continued)

7. Statement of individual accommodations necessary to measure academic and functional performance on state and districtwide assessments.
8. Additional questions to consider: What is the projected date for services to begin? Where will these services occur? How long will a “session” last?

How Do You Write an Annual Goal?

IEP goals need to be:

1. Specific:
 - a. Target areas of academic and functional performance.
 - b. Include clear descriptions of knowledge and skills.
2. Measurable:
 - a. Means you can count or observe it.
 - b. Allow parents and teachers to know how much progress has been made since last measurement.
3. Utilize Action Words:
 - a. Using phrases like “The child will be able to...”
 - b. IEP goals contain 3 components:
 - i. Direction of the behavior (increase, decrease, or maintain).
 - ii. Area of need (reading, social studies, transition, communication, etc.).
 - iii. Level of attainment (to age level, without assistance).
4. Realistic:
 - a. Address the student’s unique needs that result from his or her disability NOT on the district/state curricula or other standards.
5. Time-Limited:
 - a. What does the child need to know and be able to do after one year of special education?
 - b. Time-Limited enables you to monitor at regular intervals:
 - i. By the month, by the quarter, by the semester, by the school year.

High school children will need plans to help them move successfully from high school to life after high school. This planning should begin when your child is 14 years-old. The IEP requires a “transition plan” by the time your child turns 16 years-old. The transition plan should discuss all areas of post high school needs, including how your child will take the Scholastic Assessment Test (SAT), American College Testing (ACT), or other standardized, college-entry exams.

When a child requires an IEP, the school team is acknowledging that the child needs **specialty designed instruction (SDI)** to benefit from their educational environment. SDIs are usually delivered by special education teachers (they can also be delivered by a related service provider). However, in order to meet the mandate to deliver services in the LRE, families are likely to encounter:

1. A range of educational plans from co-teaching (general and special education teaching together)
2. Push-in (special education teachers come to the general education room to help identified children)
3. The child being pulled out of the general classroom for the following amounts of time per day:
 - a. Itinerant: 20% or less of the time
 - b. Supplemental: between 20%-80% of the time
 - c. Full-time: 80% or more of the time

Accommodations and Modifications

In addition, the school will address the need for **accommodations** and **modifications**.

When a child receives an **accommodation**, how they learn is altered. Examples of accommodations include:

- Your child may take tests in a quiet room
- Teachers should check in with your child frequently when teaching key concepts
- Changes to how a lesson is presented
- Services to help a child build specific skills
- Support for emotional or social challenges

Accommodations and Modifications (continued)

In contrast, a **modification** changes what is taught or what the child is expected to learn. Examples of modifications include:

- Decreasing the total number of math questions or spelling words
- Changing the pace of delivery of the curriculum
- Teaching at the child's ability level, not the grade level

For more information, please go to:

www.understood.org/en/learning-thinking-differences/treatments-approaches/educational-strategies/the-difference-between-accommodations-and-modifications

All may be used in an IEP.

Special Education eligibility also gives families *Procedural Safeguards and Due Process Rights*. Procedural safeguards are designed to ensure that children and their families receive a FAPE and will be protected from discrimination. These safeguards also provide several options for settling disputes between schools and families. Due process rights guarantee that a person has the right to the fair application of the law. These are used to help to facilitate appropriate decision making and services for children with disabilities.

What is a 504 Plan?

Section 504 of the Rehabilitation Act of 1973 aims to help parents and schools work together to design an educational plan to help children with disabilities. **The 504 Plan** guides how teachers should support a student in the classroom. The 504 Plan and the IEP have the same goal: to make sure a child with a disability can participate in school. Both of them ensure a FAPE. However, 504 Plans differ from an IEP in that they do not provide SDIs to meet a child's unique learning needs.

There are no set rules for how 504 Plans should look. Typically, your child is educated in a general education classroom and receives services, accommodations, and educational aids. In rare cases, the 504 Plan might include **modifications**.

The process for getting a 504 Plan differs across school districts. In some cases, parents request a 504 Plan through a school district coordinator. In other cases, schools offer them. Schools might even offer one for children who do not qualify for special education, but need other types of general support. Formal assessments are not necessary for a 504 Plan.

Once a 504 Plan is requested or offered, the school holds a meeting to determine what kind of support your child needs. Most schools involve the parents in creating the plan, but they are not required to do so. Under the Rehabilitation Act of 1973, families have a right to be notified when their child is identified with a disability. Parents also have a right to see their child's records. Parents can also disagree if they have a problem with the 504 Plan process.

What is a General Education Plan?

Parents and school officials may develop a **General Education Plan (GEP)**. Relative to the IEP and 504 Plan, the GEP is the most informal. Often, it is an agreement between the teacher, principal, and family. The benefits of a GEP is that it can start immediately, based on your child's needs. You might develop this type of plan while you are still establishing an IEP or 504 Plan. A "concussion protocol" is an example of a GEP, and it allows teachers to know immediately what to do to support the child's learning.

Advocating for Your Child

As a parent or guardian, you are a natural advocate for your child. You are your child's first teacher. You are responsible for your child's welfare. You have your child's best interests at heart and you know your child better than anyone else. You have the power to influence decisions about your child's education.

As your child's advocate, you have several goals:

- Make sure that the school provides a FAPE
- Determine the types of support plans needed to meet your child's unique needs
- Build a healthy relationship with the school

Here are some things to think about:

- What kind of long-term goals do you have for your child?
- What are your child's strengths?
- What does your child need to learn to meet those goals?
- What kind of services and support does your child need?

What Can I Do As My Child's Advocate?

- Gather facts and information. Organize documents. These will help you if you have disagreements with the school.
- Keep written records. Documents are the key to success.
- Ask questions. Listen carefully to the answers.
- Identify problems. Look at them from all angles.
- Propose solutions.
- Learn about your local school district. What services are they good at? What is the reputation for service delivery?
- Know your rights.
- Understand that the law requires that your child receive an "appropriate" education. This does not mean "the best education" or an "education that maximizes your child's potential."
- Understand the procedures you need to protect your rights and your child's rights.

Source: Wright P. Advocating for your child—getting started. Accessed 2/19/20 at www.wrightslaw.com/advoc/articles/advocacy.intro.htm

Is Help Available?

You do not have to do this alone. There are people and resources that can help you.

- Lay advocates use their specialized knowledge and expertise to help parents resolve problems with schools.
- Educational advocates evaluate children with disabilities. They make recommendations about services, support, and special education programs.
- Many teachers and special education providers see themselves as advocates. However, they may be limited in what they can do, because they are school district employees.
- Talk to as many relevant people as possible. Every school has a school psychologist. You can ask them for help if you need it.

Your state or region may support hotlines and mediators to help you get the services your child needs. Other free resources include school special education advocates, online advocacy, and parent organizations. If necessary, local law offices and advocacy groups can also help, but these are often paid services.

Resources

Wrightslaw/Self Advocacy: www.wrightslaw.com/info/self.advocacy.htm

Wrightslaw/Five Mistakes Parents Make (And How to Learn From Them):
www.wrightslaw.com/info/advo.five.mistakes.htm

Understood.org: www.understood.org

Overseas Schools Offering Support to Children with Special Needs 2017-2018:
www.state.gov/wp-content/uploads/2019/08/2017-Special-Needs-List.pdf

Protecting Students with Disabilities: www2.ed.gov/about/offices/list/ocr/504faq.html

Tips for Talking with Your Doctor

- Write down a list of questions and concerns before your appointment. Ask the school if it has questions you can take with you.
- Ask questions to make sure you understand the diagnosis and treatment.
- Ask about the symptoms, what they might look like, and how they might change.
- Ask questions about your child's abilities and limitations.
- Ask how you can access medical records and keep track of treatment plans, medications, and documents that you can provide to the school.
- Ask for the doctor's contact information and the best way to communicate with him/her, in case the school needs more information.
- Ask if the doctor's office has a school liaison.

- Take notes or have a family member or friend take notes.
- Make sure to provide written orders from your doctor to the school staff. This is a great way to bring attention to needed medical support.

Education takes place in schools by a team that includes parents and students. When talking with your school, work towards consensus from your team to achieve desired outcomes.

Tips for Talking with Your School

- Remember, you are the expert on your child's strengths and needs
- If possible, before the school year starts, meet with teachers, aides, and paraprofessionals who will be working with your child
- Explain how RYR-1-RD affects your child - provide a detailed handout with information regarding how RYR-1-RD affects your child and the specific needs of your child
- Provide them with recommendations on how they can be supportive
- Allow the school staff to ask questions
- Schedule regular communications or contact during the school year
 - Agree on the preferred method of communication (email, text, phone call, in-person meetings, etc.)
 - Agree on how often to communicate
 - Track your child's progress
- Keep teachers informed
 - Be prepared to talk about your child's capabilities and limitations
 - Explain what challenges are expected, and discuss together how they might cause problems in the classroom or in specialized classes like gym, art, or music
 - Discuss any medication your child will need to take at school
 - Give the teacher a brief summary of your child's health records
 - Let the teacher know about expected absences to manage symptoms or doctor appointments
- Put in writing who they can share information with

Special Considerations for Children with RYR-1-RD

Schools need to know about your child's specific manifestations of RYR-1-RD. This may include building in extra time for rest due to persistent fatigue. Given that some children experience heat intolerance, there may be a need for arrangements that will monitor and ensure appropriate classroom temperature. Other children may require 1:1 paraprofessional support. Some activities to consider include:

CLASSROOM

- Planning for how your child can get down on the floor and get back up.
- Planning for alternate seating options and weight shift schedule if your child is in a wheelchair.
- Incorporating specialized equipment in the classroom (e.g., stander, gait trainer, other assistive devices).
- Reviewing potential obstacles in every classroom. Consider the placement of cubbies or lockers, coat and backpack hooks, classroom desks, tables and chairs, trash cans, etc. Consider all common areas and common supplies including headphones, pencil sharpeners, classroom books, mailbox, behavior charts, school supplies, etc.
- Having two sets of books, one for the classroom, and one for home; this will relieve your child from traveling with a heavy backpack.

BATHROOM

- Making sure the bathrooms are accessible for your child's needs. Consider the toilet, sink, soap, and paper towel dispenser, as well as the type of equipment your child may need to utilize the bathroom (such as a specific toilet seat, sliding board, larger bathroom space, etc.).

BUSES

- Considering how your child will get on and off of the bus - can they safely manage the stairs, or will they need to utilize the lift?
- Determining if they need an additional staff member on the bus with them.
- If your child is in a wheelchair, checking to ensure staff know how to properly tie down wheelchairs.
- Planning for class trips.

CAFETERIAS

- Ensuring that there is accessible seating for your child with their class.
- Ensuring that the lines, food, and cashier are accessible for your child.
- Ensuring that all doorways (i.e., classroom, cafeteria, and to recess) are accessible.

AUDITORIUMS

- Considering where your child's class will sit during pep rallies, assemblies.
- Determining if your child can navigate the stairs on the bleachers.
- Preparing for any occasion where there is a need to sit on the floor. Can your child get up off of the ground independently or do they need assistance? If so, who will provide that assistance?

SAFETY

School Safety Drills (fire, tornado, evacuation, shelter in place):

- Discussing the evacuation plan from every spot in the school. Ensuring that it is wheelchair accessible if needed.
- Planning for how drills are carried out, including who will assist your child.

HALLWAYS

- Planning for your child's access to ramps and railings.
- Planning for how close your child will be to his/her locker.
- Having your child use the elevator instead of the stairs.
- Determining if your child needs extra time to navigate the hallways.

POTENTIAL MODIFICATIONS

The school might also need to modify the number and timing of classes to reduce your child's workload. For example, your child might need modifications for participation in gym class or Physical Education (PE). Your child also might need flexible attendance, where they receive both public and homeschooling. This can ensure your child still receives instruction even when they cannot attend school.

Mental and Social Health

Children with RYR-1-RD may also have psychological and social needs as they manage the disease in school and in other social situations. Therefore, you need a plan to manage stress/anxiety. Talk with your child about what he/she thinks and how he/she feels about RYR-1-RD. You can also talk with your child about ways to answer questions from other students.

Encourage children to:

- Track their own symptoms
- Speak up for their needs when they are in the classroom
- Take care of themselves
- Manage chronic fatigue or exhaustion

The advocacy resources mentioned above can help you with mental and social needs as well.

Resources

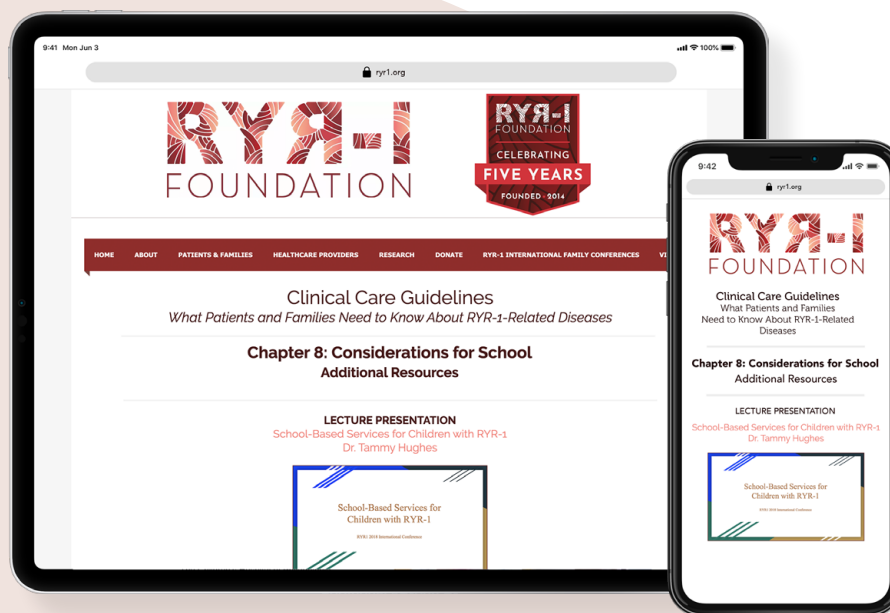
Wrightslaw/Self Advocacy: www.wrightslaw.com/info/self.advocacy.htm

Wrightslaw/Five Mistakes Parents Make (And How to Learn From Them):
www.wrightslaw.com/info/advo.five.mistakes.htm

Understood.org: www.understood.org

Overseas Schools Offering Support to Children with Special Needs 2017-2018:
www.state.gov/wp-content/uploads/2019/08/2017-Special-Needs-List.pdf

Protecting Students with Disabilities: www2.ed.gov/about/offices/list/ocr/504faq.html



For additional resources, please click on the above image or visit:
www.ryr1.org/ccg-school

Chapter 9

Physical Activity and Physical Therapy (PT)

Physical activity is important to keep you moving and maintaining your independence. A **consensus statement** on congenital myopathies recommends regular aerobic exercise, if possible, at least two or three times a week. Under certain circumstances, aerobic exercise can be helpful for people with congenital myopathies. It can improve your fitness. **This consensus statement can be accessed below:**



Published in final edited form as:

J Child Neurol. 2012 March ; 27(3): 363–382. doi:10.1177/0883073812436605.

Consensus Statement on Standard of Care for Congenital Myopathies

Ching H. Wang, MD, PhD¹, James J. Dowling, MD, PhD², Kathryn North, MD, FRACP³, Mary K. Schroth, MD⁴, Thomas Sejersen, MD, PhD⁵, Frederic Shapiro, MD⁶, Jonathan Bellini, BS¹, Hali Weiss, MD¹, Marc Guillet, PT⁷, Kimberly Amburgey, MS², Susan Apkon, MD⁸, Enrico Bertini, MD⁹, Carsten Bonnemann, MD¹⁰, Nigel Clarke, FRACP, PhD³, Anne M. Connolly, MD¹¹, Brigitte Estournet-Mathiaud, MD¹², Dominic Fitzgerald, MD³, Julaine M. Florence, DPT¹¹, Richard Gee, PT, MS¹, Juliana Gurgel-Giannetti, MD, PhD¹³, Allan M. Glanzman, PT, DPT, PCS¹⁴, Brittany Hofmeister, RD¹, Heinz Jungbluth, MD¹⁵, Anastassios C. Koumbourlis, MD, MPH¹⁶, Nigel G. Laing, PhD¹⁷, Marion Main, MA, MCSP¹⁸, Leslie A. Morrison, MD¹⁹, Craig Munns, MD³, Kristy Rose, PT³, Pamela M. Schuler, MD²⁰, Caroline Sewry, PhD¹⁸, Kari Storhaug, DDS, PhD²¹, Mariz Vainzof, PhD²², and Nanci Yuan, MD¹

www.ncbi.nlm.nih.gov/pmc/articles/PMC5234865/pdf/nihms831819.pdf

Here are some things to keep in mind:

- Avoid high-impact sports. Low-impact aerobic exercises include: walking, swimming, dancing, or cycling. For aerobic exercise, factors to monitor include: heart rate, degree of exertion, duration of workout, and frequency of workout.
- Make it fun! Try virtual reality games that involve moving around (e.g., Nintendo Wii, Xbox, PlayStation, etc.). Include recreational activities in your exercise plan.
- If you cannot exercise without getting tired quickly, consider changing the type of activity you do.
- Everyone is different. Exercises that work for someone else with RYR-1-RD may not be helpful to you or your child. You may find that certain exercises are more harmful than helpful. A physical therapist may support you in finding ways to exercise at an appropriate level. As always, you need to consult with your physician before initiating any exercise regimen.

Even in cases of severe myopathy, physical activity is important. There are several ways to stay active:

- Standing frames
- Assistance with walking
- Wheelchairs
- Arm supports
- Bath aids
- Reachers
- Service dogs

Avoid bed rest for long periods of time. If you do need bed rest, resistance exercise with vibration may help maintain muscles. Resistance exercises cause the muscles to contract against an external resistance. Here are some examples of external resistance:

- Elastic bands
- Weights
- Your own body weight

Safety and Falls

You may need modifications at home, school, or work to prevent falls. Modifications include:

- Ramps
- Rails
- Shower chairs
- Stair glides
- Lifts, elevators, or hoists
- Grab bars near the toilet and in the shower/bathtub
- Wheelchair accessible doorways, hallways, counter tops, light switches

Managing contractures and hip dislocations can be complex. Decisions to treat them depend on your restrictions, your goals, and other medical problems you may have.

Managing scoliosis and other spinal deformities depend on a wide range of factors (**please see Chapter 6, "The Bones and Joints/Orthopedics"**).

In addition to these modifications, individuals with RYR-1-RD should have a greater awareness of tripping hazards (e.g., throw rugs, doorway treads, furniture, pets, etc.). To reduce the risk of falling, these tripping hazards should be removed and/or avoided.

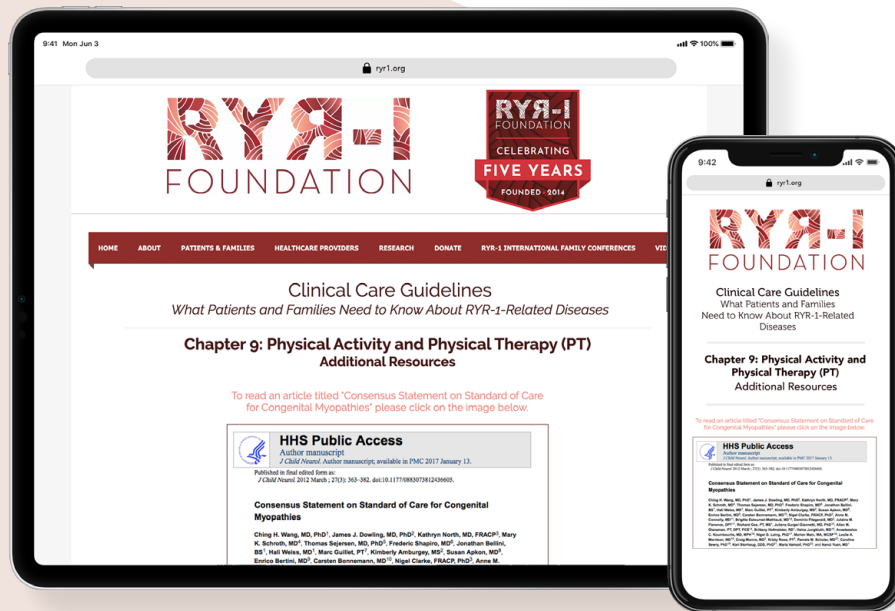
To reduce the risk of fractures in case of falls, it is important to have strong, healthy bones. If you think you could be at risk for fragile bones (i.e., osteopenia/osteoporosis), please discuss potential treatment options with your physician.

Physical Therapy (PT)

Physical therapy is an important part of managing RYR-1-RD. It can:

- Help prevent contractures
- Manage pain, fatigue, and problems with endurance
- Improve functional mobility (i.e., transferring, ambulation, stair negotiation)
- Increase cardiovascular and muscular endurance
- Slow progression of disease
- Get you moving after orthopedic surgery
- Help you to use mobility aids in the correct way

There are no standard guidelines for physical therapy for RYR-1-RD. Your physician and physical therapist will need to develop a plan that is best for you.



For additional resources, please click on the above image or visit:
www.ryr1.org/ccg-pt

Chapter 10

Is There a Treatment for RYR-1-RD?

Words Your Doctor May Use

Clinical trial: Clinical trials are research studies performed in people that are aimed at evaluating a medical, surgical, or behavioral intervention. They are the primary way that researchers find out if a new treatment, like a new drug, diet, or medical device (e.g., a pacemaker) demonstrates **safety** and **efficacy** in people.

Efficacy: The ability of the intervention (e.g., drug, medical device, etc.) to work as intended.

Ex vivo: The experiment is carried out in a laboratory on cells or other material that has not been significantly modified.

Gene therapy: An experimental technique that uses genes to treat or prevent disease. In the future, this technique may allow doctors to treat a disorder by inserting a gene into a patient's cells instead of using drugs or surgery.

In vitro: The experiment is carried out in a laboratory on cells or other material that has been modified.

In vivo: The experiment is carried out in a living organism (e.g., laboratory animal or human).

Nucleotides: The building blocks of DNA, including: adenine (A), cytosine (C), guanine (G), and thymine (T).

Safety: The risks associated with an experimental intervention (e.g., drug, medical device, etc.), including side effects and potential harm.

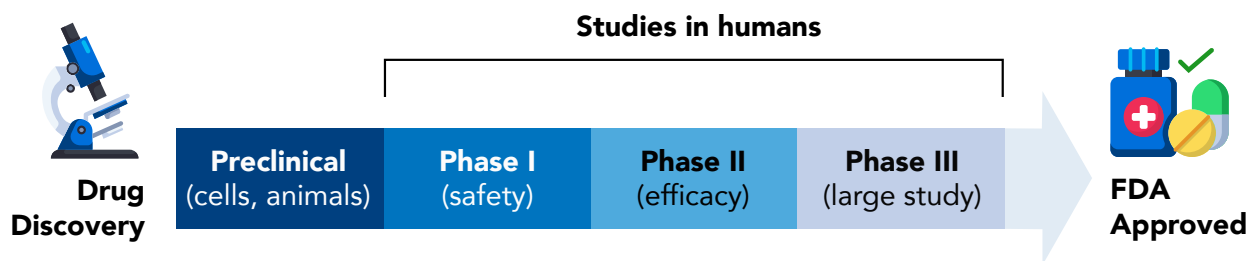
Tolerability: The degree to which patients may accept side effects from an intervention (e.g., drowsiness from a drug).

Vector: A carrier molecule used to introduce a gene for gene therapy (e.g., a virus).

Currently, there are no FDA-approved treatments specific for RYR-1-RD. However, scientists are actively studying several potential approaches to treat RYR-1-RD. Developing therapies for any disease, including RYR-1-RD, is a complex process that typically takes many years and costs millions of dollars. The table below describes the standard process for drug development.

CLINICAL DRUG DEVELOPMENT

Once potential drugs are discovered, they go through several steps before they can receive FDA approval for routine use in humans.



In the preclinical stage, researchers test the drugs ***in vitro*** (in a dish) and ***in vivo*** (in animal models) rather than in humans. With *in vitro* studies, researchers can test whether the drug works on muscle cells from patients with RYR-1-RD. They can also test the drugs on cells that have been engineered with *RYR1* disease mutations. With *in vivo* studies, researchers test whether the drug works in animals with RYR-1-RD or conditions similar to RYR-1-RD. In most cases, these models have been engineered to carry select/specific *RYR1* mutations. There are more than 15 mouse models for RYR-1-RD, many of which contain mutations that have been observed in humans (see www.ryr1.org/mice). There is also a zebrafish model, called the “relatively relaxed” model.

Once researchers have gained enough evidence on **efficacy** and **safety** from preclinical studies, they may receive approval from the FDA for clinical trials in humans. There are three phases of clinical trials:

- Phase I tests whether the drug is safe
- Phase II tests whether the drug works (efficacy)
- Phase III tests the drug’s efficacy and safety in hundreds to thousands of people

This process takes several years and costs millions of dollars. Only a small percentage of drugs that are discovered make it all the way through this process.

Potential Drugs

Several drugs are under development as potential therapies for RYR-1-RD. Some of these drugs are already approved for other conditions. Researchers are testing whether they can repurpose those drugs for RYR-1-RD. Some of the drugs target the RyR1 receptor itself. Others target specific characteristics and symptoms of RYR-1-RD. **Before taking any medication, you must consult with your physician.**

N-ACETYLCYSTEINE (NAC)

One feature of RYR-1-RD is oxidative stress, an imbalance between free radicals and antioxidants that occurs in all of us, but can be a particularly vicious cycle with leaky *RYR1* mutations. Too much calcium leak leads to oxidative stress, and that causes the receptor to become leakier. Studies in zebrafish have shown that NAC decreases oxidative stress and improves muscle function. A Phase I/II clinical trial was completed at the National Institutes of Health (NIH) to study NAC in people with RYR-1-RD. In January 2020, published results of the completed trial reported that NAC, unfortunately, did not decrease elevated oxidative stress. The trial also reported that NAC did not improve how far participants could walk in 6 minutes (endurance/fatigability). **This article can be accessed below:**



Randomized controlled trial of N-acetylcysteine therapy for *RYR1*-related myopathies

Joshua J. Todd, PhD, Tokunbor A. Lawal, PhD, Jessica W. Witherspoon, PhD, Irene C. Chrismer, RN, Muslima S. Razaghyar, BA, Monal Punjabi, PharmD, Jeffrey S. Elliott, MA, Fatoumata Tounkara, BS, Anna Kuo, BA, Monique O. Shelton, BS, Carolyn Allen, DNP, Mary M. Cosgrove, MS, Melody Linton, BS, Darren Michael, PhD, Minal S. Jain, DSc, Melissa Waite, MSPT, Bart Drinkard, MSPT, Paul G. Wakim, PhD, James J. Dowling, MD, PhD, Carsten G. Bönnemann, MD, Magalie Emile-Backer, PharmD, and Katherine G. Meilleur, PhD

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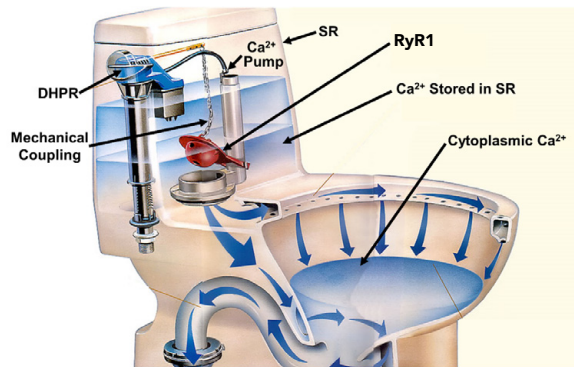
Neurology® 2019;00:1-11. doi:10.1212/WNL.0000000000008872

RYCALs

As was discussed in **Chapter 3, “The Role of Calcium and the Ryanodine Receptor in RYR-1-RD,”** muscle function is dependent on the normal flow of calcium through the RyR1 receptor. In the **toilet bowl analogy**, we think about calcium as the “water,” the sarcoplasmic reticulum (SR) as the “tank,” the cytoplasm as the “toilet bowl,” and the RyR1 receptor as the “flapper.” Remember, RyR1 does not open and let calcium through

until a signal activates DHPR, which acts like the “handle” on the toilet. Under normal conditions, RyR1 also interacts with a protein called calstabin, which stabilizes RyR1 in its closed state. In other words, calstabin helps the “flapper” keep a seal to prevent the leakage of calcium. Some *RYR1* mutations keep RyR1 from binding to calstabin. As a result, RyR1 becomes leaky. Just like a leaky flapper allows water to escape, leaky RyR1 allows calcium to leave the SR. This causes the muscle to not function properly.

EC Coupling is Analogous to a Toilet Flush



For more details on the role of calcium in RYR-1-RD, please see Chapter 3, “The Role of Calcium and the Ryanodine Receptor in RYR-1-RD.”

Rycals is a new class of drugs that stabilizes the RyR1 receptor by improving the binding of RyR1 and calstabin. This restores the seal to prevent calcium leak. Researchers have shown that treatment with Rycals restores muscle function in mice *in vivo* and in human muscle tissue **ex vivo**. Specifically, a recent study showed that Rycals improved the binding of calstabin to the RyR1 receptor in muscle cells taken from the biopsies of RYR-1-RD patients (**an article on this can be accessed below**).



Acta Neuropathologica
<https://doi.org/10.1007/s00401-020-02150-w>

ORIGINAL PAPER



Intracellular calcium leak as a therapeutic target for *RYR1*-related myopathies

Alexander Kushnir^{1,2} · Joshua J. Todd³ · Jessica W. Witherspoon³ · Qi Yuan¹ · Steven Reiken¹ · Harvey Lin¹ · Ross H. Munce¹ · Benjamin Wajsborg¹ · Zephany Melville¹ · Oliver B. Clarke⁴ · Kaylee Wedderburn-Pugh¹ · Anetta Wronska¹ · Muslima S. Razaqyar³ · Irene C. Chrismer³ · Monique O. Shelton³ · Ami Mankodi⁵ · Christopher Grunseich⁵ · Mark A. Tarnopolsky⁶ · Kurenai Tanji⁷ · Michio Hirano⁸ · Sheila Riazzi⁹ · Natalia Kraeva⁹ · Nicol C. Voermans¹⁰ · Angela Gruber¹¹ · Carolyn Allen³ · Katherine G. Meilleur³ · Andrew R. Marks^{1,2}

Researchers have also shown that treatment with Rycals improves muscle force and exercise capacity in mice with muscular dystrophies. At the time of the writing of this chapter in mid-2020, there is a human clinical trial of Rycals to evaluate its **safety** and **tolerability**. In addition, this clinical trial will assess Rycals' effects on muscle/motor function and fatigue. For more information on this trial, please go to: www.clinicaltrials.gov/ct2/show/NCT04141670.

DANTROLENE

Dantrolene is a muscle relaxant. In its *intravenous* (IV) form, it is the only treatment approved for acute episodes of malignant hyperthermia (MH) secondary to general anesthesia. There have been some reports that the *oral* (taken as a pill by mouth) form of dantrolene reduces muscle pain and cramping in people with certain types of RYR-1-RD. However, the drug has not been studied formally for RYR-1-RD. For more on dantrolene, **please see Chapter 4, "Malignant Hyperthermia (MH)."** Once again, please consult with your physician prior to taking any medication, including dantrolene.

SALBUTAMOL/ALBUTEROL

Salbutamol and albuterol are both members of a class of drugs called "beta agonists" and are typically used to help control asthma. They increase the expression of a protein (SERCA) that pumps calcium back into the **sarcoplasmic reticulum from the cytoplasm**; by reducing calcium levels in the cytoplasm, this may reduce oxidative stress in the muscle cells. They also appear to build muscle volume and build strength. In a pilot study in the United Kingdom that included people with RYR-1-RD, treatment with salbutamol improved breathing and muscle contractions.¹ A case study also reported that albuterol improved motor function and breathing in a 9-year-old boy.²

¹ Messina S, Hartley L, Main M, Kinali M, Jungbluth H, Muntoni F, Mercuri E. Pilot trial of salbutamol in central core and multi-minicore diseases. *Neuropediatrics*. 2004;35:262-266.

² Schreuder LTW, Nijhuis-van der Sanden MWG, de Hair A, Peters G, Wortmann S, Bok LA, Morava E. Successful use of albuterol in a patient with central core disease and mitochondrial dysfunction. *J Inherit Metab Dis*. 2010;33 Suppl 3:S205-S209.

Nolan's Story



Nolan's doctors noticed there was something wrong the moment he was born. His weakness at birth was so profound that it took Nolan several weeks to even open his eyes or move a finger. Nolan spent the first two months of his life in the hospital. Mandy, Nolan's mother, recalled grieving for the loss of the typical mother-newborn bonding experience, as she was unable to take Nolan home to simply "cuddle on the couch."

Nolan is a young boy who is affected with an RYR-1-related disease. Although Nolan's strength has improved somewhat since birth, he currently cannot sit independently, lift his head, eat, or clear his oral secretions. This puts him at risk for numerous medical complications, including life-threatening infections.

When Nolan's parents learned of the RYR-1 Foundation, they were shocked that an organization existed specifically to help individuals with Nolan's rare disease. When asked about the RYR-1 Foundation's mission to support research for RYR-1-related diseases, Mandy said, "It is everything--the most important thing. If we only get one thing in life, it would be to have a treatment or a cure for Nolan."

Eager to accelerate the pace of research, Lindsey, Nolan's Aunt, organized a fundraiser, "Hike for Team Nolan," which raised over \$11,000 for the RYR-1 Foundation. In reference to the RYR-1 Foundation and the "Hike for Team Nolan," Mandy says, "When we got Nolan's diagnosis, we never dreamed that a cure was even possible. Recent developments in gene therapy make us believe that it is more than possible, and we are hopeful that through the work of the RYR-1 Foundation, Nolan will someday be able to complete this hike alongside his Aunt Lindsey."

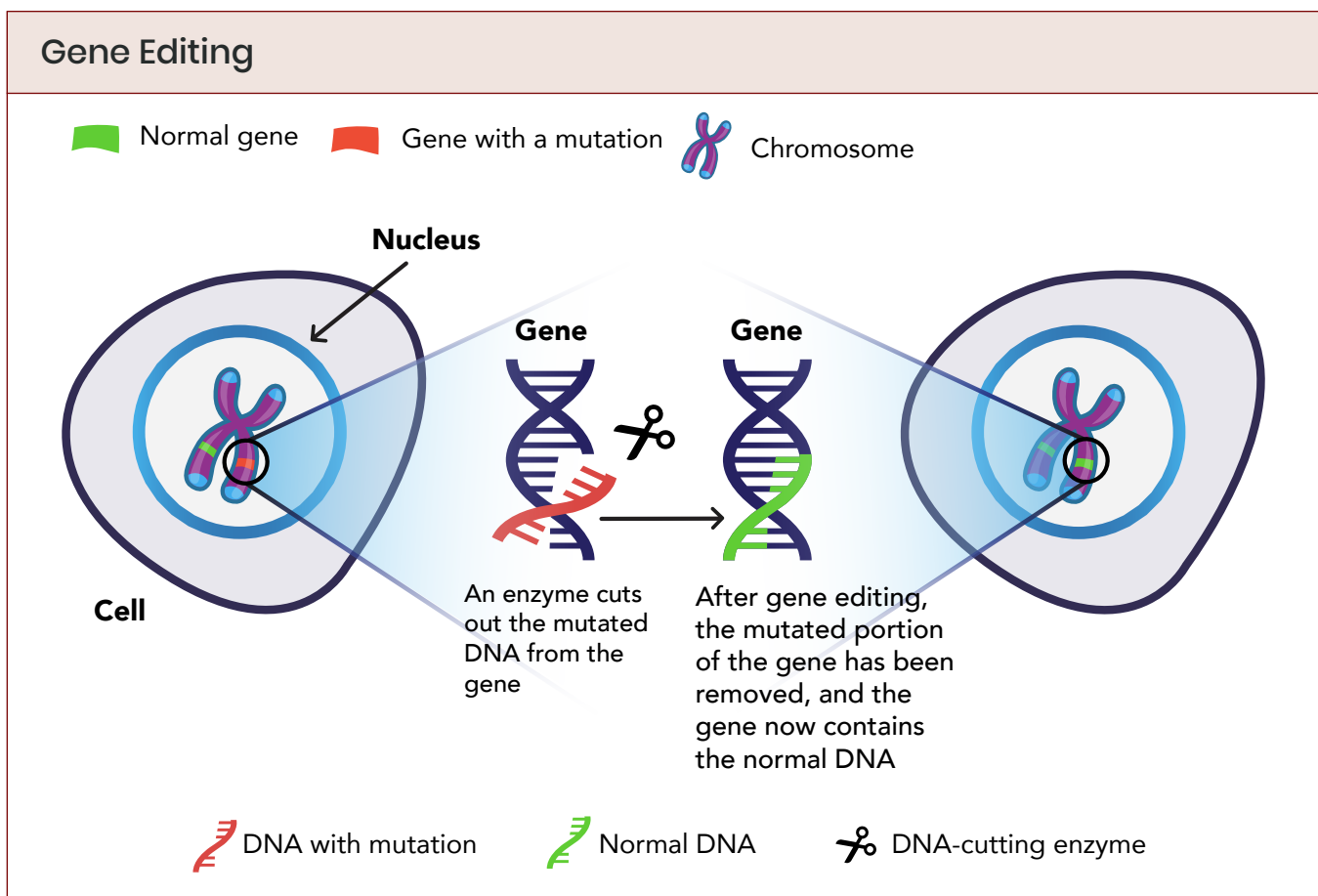
To watch a video on "Nolan's Story," please go to: www.ryr1.org/nolan

Other Potential Strategies for Treating Inherited Genetic Conditions

Gene therapy: Gene therapy treats a disease by targeting the gene itself. Gene therapy could introduce a gene to help fight disease, replace a mutant gene, edit a mutant gene, or delete a mutant gene. In theory, gene therapies offer the potential for a cure, not just a treatment.

GENE EDITING

As mentioned below, “gene replacement therapy” introduces a new and working copy of a gene. Gene editing is a different approach that is aimed at making more precise and permanent changes. With “gene editing,” the goal is to correct or “edit” only a small part of the gene.



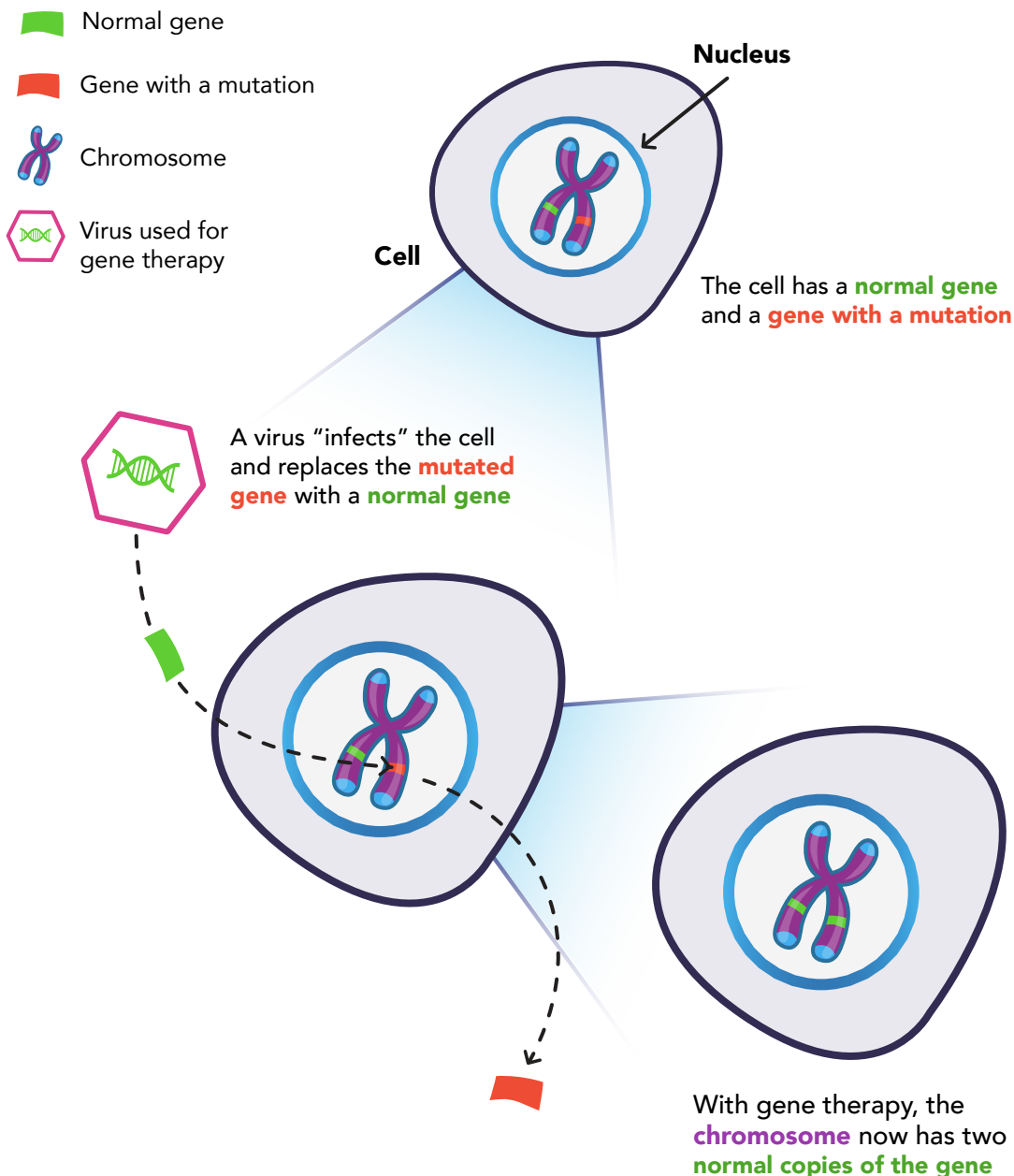
GENE REPLACEMENT THERAPY

With gene replacement therapy, the doctor introduces a molecule, called a vector, that carries a normal copy of a gene. Vectors are usually viruses, because they can enter a cell. However, the viruses are engineered so that they do not make people sick. Some commonly used vectors, called Adeno-Associated Viruses (AAV), take the normal gene to the nucleus of the cell. By replacing the defective/mutated gene with a new, normal copy of the gene, the cell now

produces a normal protein rather than the abnormal, disease-causing protein (for more information on genes and proteins, **please see Chapter 1, "The Genetics of RYR-1-RD"**).

Gene replacement therapy using a standard viral vector is currently not feasible for RYR-1-RD, because the *RYR1* gene is too big to be packaged into the commonly used viral vectors. Gene replacement therapy may become a therapeutic option in the future when other vectors for gene delivery are discovered, or when totally new techniques are invented.

Gene Replacement Therapy



Remember that a gene is a segment of DNA, a code of instructions for how to make important proteins. DNA is a very long double-stranded molecule that has a twisted helical shape, like a winding staircase. The building blocks of DNA are called **nucleotides**. There are four types of nucleotides: adenine (A), cytosine (C), guanine (G), and thymine (T). The important thing to remember is that the sequence of nucleotides (A,C,T, and G) is the instruction that your cells use to make proteins. In most cases, severe genetic diseases are caused by a single misspelling of this code- for example you have an "A" where there should be a "G." These errors in the DNA code might prevent your cells from making an important protein, or make a bad version of it instead. The goal of gene editing is to permanently correct these changes, by changing the sequence of your own DNA. Think of taking an eraser and pencil to fix a spelling mistake in a hand-written letter. In principle this sounds easy, but it is still a major challenge to do it correctly, efficiently, and safely in every cell.

Most of the current gene editing approaches involve using proteins called nucleases that cut DNA at specific locations. In general, you would want to cut the DNA only at or near the nucleotide that is incorrect. Think of putting your eraser down exactly on the word that you need to rewrite. You would not want to cut DNA at other places, because this could cause dangerous errors that would change the meaning of the code and cause your cells to function incorrectly.

The most commonly used nuclease for gene editing is the CRISPR/Cas9 system. This is composed of two parts: Cas9 which is a protein that was discovered in bacteria, and a guide RNA. Cas9 and the guide RNA come together to form the active nuclease, which you can think of as the eraser to the hand-written letter. These scissors will bind to DNA based on the sequence of the guide RNA. Scientists can change the sequence of the guide RNA as needed to cut almost any sequence of DNA, with a few limitations. Once the DNA is cut, it will be repaired by the cell. Controlling the DNA repair process determines what kinds of changes we can make to the DNA. Unlike precisely editing a hand-written letter, we do not yet have complete control over what the sequence will be changed to. Some types of changes are easy to make, while others are more difficult and less predictable.

In addition to CRISPR/Cas9 and other gene editing nucleases (e.g., zinc fingers), there are also promising new tools in development. "Base editors" are modified versions of the CRISPR/Cas9 system that do not completely cut the double stranded DNA molecule. Instead, they cut only one strand, and chemically change one nucleotide to another within a certain editing window. Think of this as changing an "l" to a "t" by adding a horizontal stroke to a hand-written document. No eraser was needed, since this version of Cas9 does not completely cut DNA. Therefore, the risk of missing words is minimized. However, it is still difficult to target exactly the letter you want to change, and if you want to change the misspelled word "buller" to "butler," you might instead make the word "butter" which is still incorrect. The efficacy of

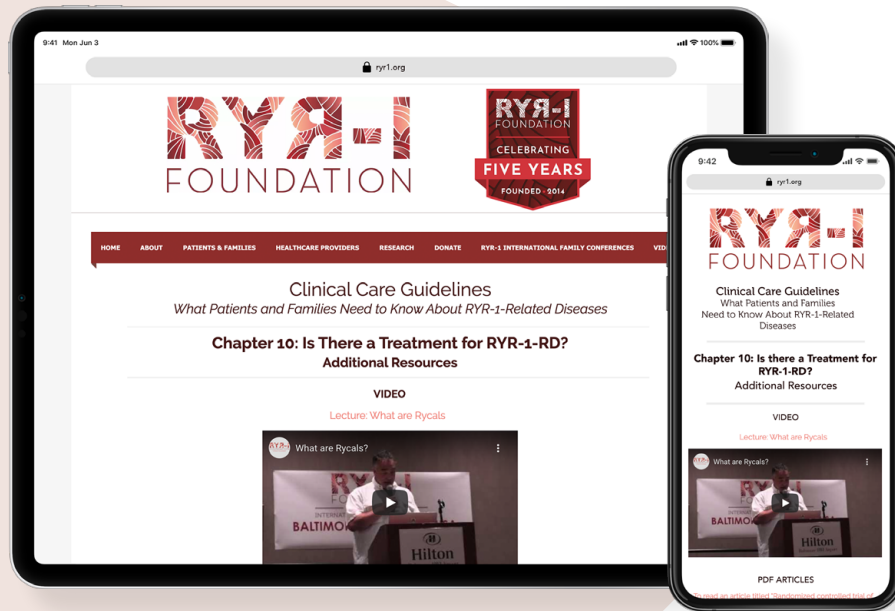
base editors is improving, and they have significant advantages for correcting single nucleotide changes. However, more work is needed to improve their precision.

The most recent addition to the gene editing toolbox is Prime Editing. The advantage of Prime Editors is that they would let us fix virtually any type of small error in the DNA, which is not currently possible with base editors. For example, you can modify any letter of the alphabet to any other, not just converting “l” to “t” (as in the previous example). However, far more work is needed to demonstrate that they are safe, effective, and reliable.

To summarize, gene editing is a very exciting technology that has only recently become possible, primarily in a research laboratory setting. In contrast to traditional gene therapy, the goal is to precisely change the patient’s own DNA in every cell of the affected tissue. This would ensure that the changes provide an accurate and permanent set of DNA instructions that will last for a lifetime. While this field has tremendous promise, the current tools still have major limitations. One of the greatest is delivering the genome editing mechanism to the target cells in the patient’s body. Other considerations include managing any immune response to prevent a patient’s body from attacking the gene editing tools. In addition, greater precision is needed in controlling the types of changes that are made to the intended site (on-target editing, as well as avoiding mistakes elsewhere in a patient’s DNA (off-target editing. Despite these challenges, the future of gene editing is very bright, and is something to look forward to in the coming years.

Gene Therapy/Editing and RYR-1-RD

A small amount of preliminary research has been done exploring a potential therapeutic role for gene editing in RYR-1-RD. This is a rapidly evolving field, and the RYR-1 Foundation will continue to promote research in this area.



For additional resources, please click on the above image or visit:
www.ryr1.org/ccg-treatments

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RYR-1 CCG Reference List

To access free, online medical literature about RYR-1-RD, please go to:
www.ryr1.org/medical-literature.

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