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SPINAL MUSCULAR ATROPHY: A RARE BUT TREATABLE DISEASE OF THE NERVOUS SYSTEM

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YOUNG REVIEWERS:

ADDIE
AGE: 14

ADRIANA
AGE: 14

AJAY
AGE: 8

AMELIA
AGE: 16

When something is rare it means that it happens very infrequently. Did you know that most diseases are rare? There are more than 6,000 known rare diseases, each affecting fewer than 1 in every 2,000 people. But if we put all the rare diseases together, they affect about 1 in 17 of us! Given that they are individually uncommon, rare diseases are often poorly understood. However, rare diseases have a large impact on families and society, thus they require increased attention. In this article, we will explore a rare disease of the nervous system called spinal muscular atrophy (SMA). We will tell you about the symptoms of SMA and explain how it is inherited. SMA has led the way in the discovery of treatments for rare diseases. Finding treatments for rare diseases requires intensive research and commitment from

BRUNA
AGE: 15

CAROLINE
AGE: 14

ELISHA
AGE: 14

MALCOLM
AGE: 15

MRITTIKA
AGE: 15

many people, but the success of SMA treatments highlights the importance of studying other rare conditions.

RARE DISEASES

Diseases occur when body parts malfunction. For example, Alzheimer's disease damages the brain, and cardiovascular disease affects the heart. These conditions are some of the leading causes of death and are therefore well-studied by scientific researchers around the world. However, there are many other lesser-known diseases that seriously impact patients and their families, and most of these diseases receive much less attention because they are rare.

There are over 6,000 known rare diseases, including cystic fibrosis, Duchenne muscular dystrophy, and sickle cell disease. Rare diseases affect fewer than 1 in every 2,000 people. Very few of these diseases have cures and most do not even have effective treatments to help patients who suffer from them. However, although each individual rare disease does not affect many people, it is estimated that 1 in every 17 people are affected by *some kind* of rare disease in their lifetimes. This means that, when taken together, rare diseases have a big impact—not only on a person's health and wellbeing, but also on their finances, their families, and society. This situation will only improve if rare diseases are carefully studied, both by doctors (to improve diagnosis and understanding of symptoms) and scientists (to identify which faulty molecules cause the disease and to develop treatments).

WHAT IS SPINAL MUSCULAR ATROPHY?

Spinal muscular atrophy (SMA) is a rare disease of the nervous system that affects ~1 in 10,000 people. People with SMA have muscle weakness and **atrophy** (wasting away/shrinking) that gets worse over time and affects their mobility [1]. Symptoms of SMA generally begin before 6 months of age. Without help for their breathing difficulties (or one of the new treatments discussed below), most children with SMA do not live beyond their second birthday.

To move our bodies, to swallow, and to breathe, our muscles must contract and relax. Muscle contraction is triggered by electrical signals from the brain, which are sent along nerve cells called **motor neurons** (Figure 1A). The command centers of these cells, called **cell bodies**, are found within the spinal cord and have long, thin extensions called **axons**. Axons connect the cell body to individual muscles, where they form specialized connections that help with nerve-to-muscle communication and muscle contraction (Figure 1B).

In SMA, motor neurons do not work properly and begin to break down and eventually die (Figure 1C). Motor neurons cannot be replaced so,

ATROPHY

The wasting away of a tissue or organ due to lack of use. Muscles atrophy in people with SMA.

MOTOR NEURONS

Nerve cells that carry electrical signals to muscles to cause them to contract.

CELL BODY

The part of the cell where the nucleus and genetic material are located, considered the command center of the cell.

AXON

A long, thin, tube-like extension of a nerve cell (neuron) that is vital for quickly sending electrical signals, for example to muscles.

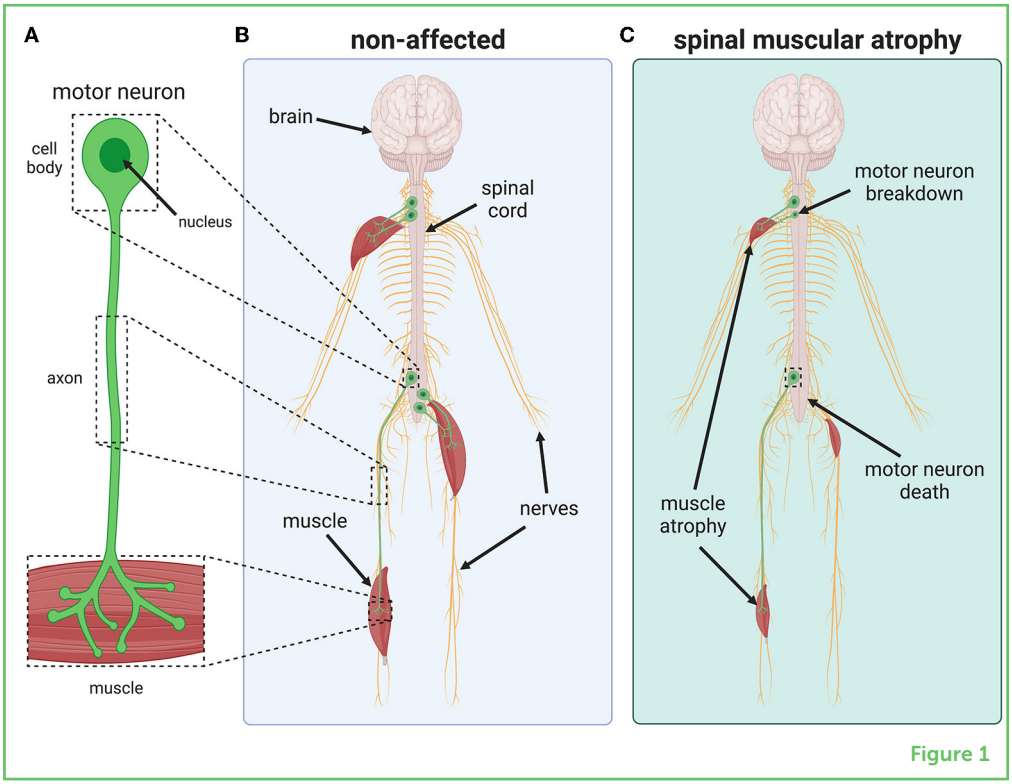


Figure 1

SMA is a rare disease that causes motor neurons to die. **(A, B)** Found within the spinal cord, motor neurons are nerve cells that have long, thin extensions called axons that connect to muscles. Healthy motor neurons transmit electrical signals from the spinal cord to the muscle, causing the muscle to contract and the body to move. **(C)** In people who have SMA, motor neurons break down and die, destroying the contact between the nervous system and the muscles. This results in muscle weakness and atrophy due to reduced use.

when they die, electrical signals no longer reach the muscles. This prevents the muscles from contracting and, over time, muscles that are not used weaken and atrophy.

WHAT CAUSES SMA?

GENETIC CONDITION

A disease that is inherited through DNA.

SMA, like most rare diseases, is a **genetic condition**. This means that it is inherited through the DNA, which is passed on from parents to children. Genes, which are short sections of DNA that code for proteins, sometimes become damaged or lost by a process called mutation (for details about mutations, see this Frontiers for Young Minds article). As humans have more than 20,000 genes, we can inherit many rare diseases through mutations.

SMA is caused by mutations in a gene called *Survival Motor Neuron 1* (*SMN1*) [1]. *SMN1* normally produces a protein called SMN (Figure 2A). All cells need SMN to stay healthy, but it is particularly important for motor neurons. When the *SMN1* gene is mutated, it no longer produces enough SMN protein for motor neurons to survive, so these cells break down and die in SMA patients (Figure 2B).

Unlike most proteins, SMN can also be made by a second gene, named *SMN2*. However, *SMN2* makes 10 times less SMN protein than *SMN1*. In people who do not have SMA, *SMN2* is not needed—*SMN1* makes plenty of SMN to keep cells healthy. However, people with SMA must

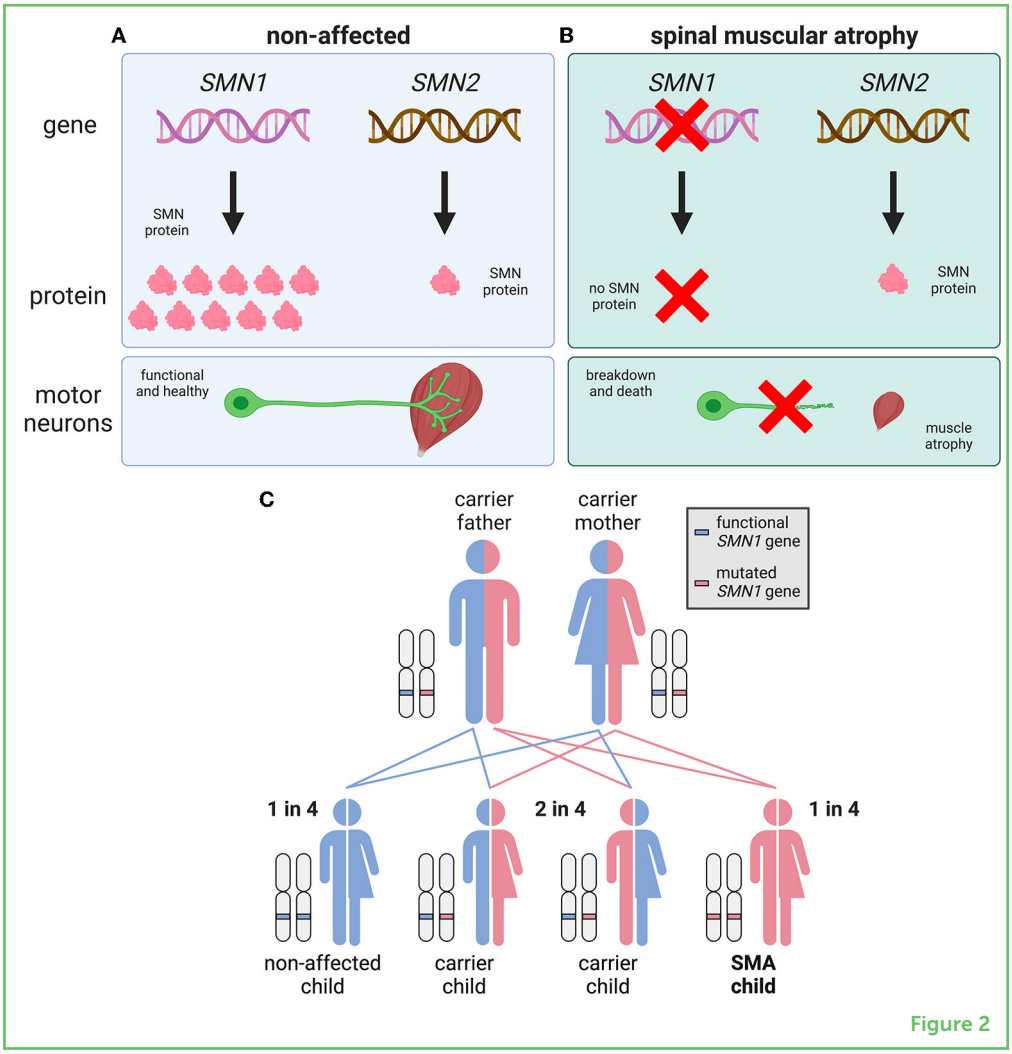


Figure 2

Figure 2

SMA is caused by mutations in the *SMN1* gene. **(A)** In healthy people, the *SMN1* and *SMN2* genes produce SMN protein, which is needed by motor neurons to survive. *SMN1* produces all the required SMN, while *SMN2* makes a much smaller amount. **(B)** *SMN1* is mutated or deleted in people who have SMA, and it no longer makes SMN. A small amount of SMN is made by *SMN2*, but this is not enough for motor neurons to survive. **(C)** SMA is an autosomal recessive disease, which means that two faulty/mutated copies of *SMN1* must be inherited for SMA to develop.

rely only upon *SMN2* for their SMN protein, because their *SMN1* genes do not work.

You may have heard that people have only two copies of each gene—one inherited from mom and one from dad. However, this is not true for every gene and, luckily, *SMN2* is one of those exceptions. Caused by an error, genes can sometimes be accidentally duplicated, which leads to there being more than the usual two copies. For people with SMA, the more copies of *SMN2* they have, the more SMN they make—and the less intense their symptoms. This is why some cases of SMA are severe and others are milder. This also means that small increases in SMN could improve the quality of life for a person with SMA. This is important for the treatment options discussed below.

AUTOSOMAL RECESSIVE

A way some genetic diseases are passed on to children that requires two faulty gene copies to be inherited (one from each parent) for the disease to occur.

HOW IS SMA INHERITED?

SMA is an **autosomal recessive** condition, which means that two faulty copies of the *SMN1* gene must be inherited (one from each

parent) for the disease to occur (Figure 2C). The word "autosomal" refers to the disease gene being found on one of the 22 non-sex chromosomes, known as autosomes. When a condition is "recessive," it means that one faulty gene copy is not enough to cause disease. Therefore, people can "carry" one faulty *SMN1* gene without showing any SMA symptoms; these SMA **carriers** occur at a rate of about in 1 in 40 people.

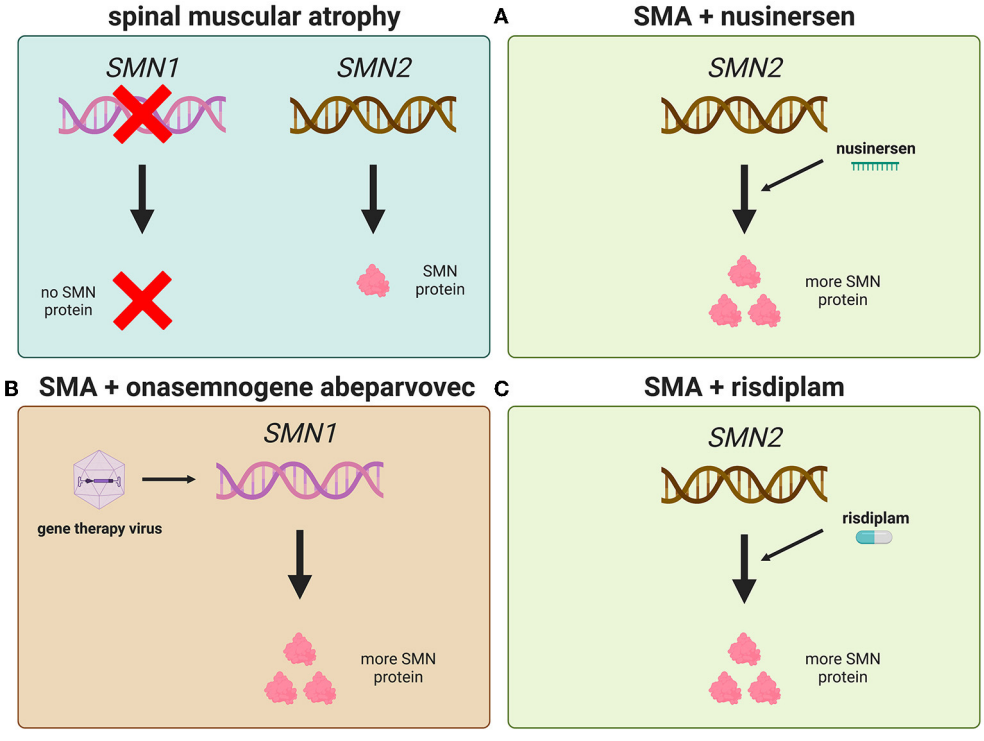
CARRIER

Someone who can pass on a faulty, disease gene to their children, but does not themself have the disease.

When two SMA carriers have a baby, there is a 1-in-4 chance that their child will develop SMA, a 2-in-4 chance that their child will be a carrier, and a 1-in-4 chance that the child will neither have SMA nor be a carrier (Figure 2C).

CAN SMA BE TREATED?

Like most rare diseases, SMA cannot currently be cured. But three new therapies can improve the symptoms of SMA (Figure 3) [2], and there are several more potential therapies being developed.



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Treatment for SMA	Brand Name	Medicine Type	Target	Treatment Route
A. nusinersen	Spinraza	Synthetic genetic material	*SMN2*	Injection into the fluid that bathes the brain and spinal cord
B. onasemnogene abeparvovec	Zolgensma	Gene therapy	*SMN1*	Injection into the bloodstream
C. risdiplam	Evrysdi	Small molecule	*SMN2*	By mouth in liquid form

Figure 3

Figure 3

Three medicines have been approved to treat the low levels of SMN protein seen in SMA. **(A)** Nusinersen increases the amount of SMN protein made from the *SMN2* gene. **(B)** Onasemnogene abeparvovec is a type of gene therapy that uses a virus to deliver the *SMN1* gene to the nervous system. **(C)** Risdiplam is a small molecule that also increases SMN production from *SMN2*. **(D)** A summary of the key features of each approved treatment for SMA.

While we do not know exactly why low SMN levels affect motor neurons, we *do* know that helping these nerve cells produce more

SMN can improve symptoms. This was originally shown in laboratory mice lacking SMN, and it matches what is seen when people with SMA have more copies of the *SMN2* gene. The three approved treatments all work by increasing SMN levels in motor neurons (and other cells).

Nusinersen (brand name Spinraza) was the first medicine approved for SMA. This drug specifically recognizes an intermediate molecule made from *SMN2* that is used to produce SMN protein, increasing the efficiency with which *SMN2* can produce SMN (Figure 3A). Getting medicines into the spinal cord and brain is complicated, as blood vessels and certain cells shield these important organs from potentially harmful substances. So nusinersen must be injected directly into the fluid bathing the spinal cord and brain. Four doses of the medicine are given in the first 2 months of treatment, and then it is administered once every 4 months.

GENE THERAPY

A treatment that aims to change a person's genes or gene activity to treat a disease.

Onasemnogene abeparvovec is a **gene therapy** known by its brand name Zolgensma. This treatment uses laboratory-modified viruses to carry a copy of *SMN1* into cells (Figure 3B). These viruses can enter the spinal cord from the blood and they are also very stable in cells that do not divide, like motor neurons. This means that a single injection of Zolgensma into the blood results in the therapy traveling around the body and entering many kinds of cells, including motor neurons, and then staying active for many years (we do not yet know exactly how long).

The most recently approved SMA treatment, risdiplam (brand name Evrysdi), is a small molecule that works similarly to nusinersen—by increasing SMN production from *SMN2* (Figure 3C). Risdiplam is taken daily by mouth in liquid form, and it can also move through the body into many cell types, including motor neurons. This medicine is convenient because it can be taken at home without medical help.

In people with SMA, these three approved treatments all result in more SMN protein in the nervous system, better muscle function, and reduced symptoms. However, none of these therapies can completely cure the disease. Testing indicates that starting therapy even before symptoms begin is the best way to treat SMA. This means babies must be tested for faulty *SMN1* genes at birth—something that is being slowly introduced around the world [3]. These three SMA treatments have brought hope to the rare-disease community, showing how improved understanding of a disease can lead to successful therapies that save lives and reduce suffering.

CONCLUSION: SMA IS A TREATABLE DISEASE

A diagnosis of SMA has a profound impact on patients and their families. Fortunately, several treatments have been developed that

can reduce the severity of SMA and increase the person's chance of a healthier life. These treatments have required much time, energy, and money, so we should appreciate the many people involved, including scientific researchers, doctors, patient organizations, drug companies, and, most importantly, SMA patients and their dedicated families. The success of SMA treatments clearly shows the importance of researching rare diseases and demonstrates how a motivated, supportive, and collaborative community is instrumental to developing successful medicines. Hopefully, future work will help us to develop even better treatment strategies for SMA and other rare diseases [4].

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CONFLICT OF INTEREST: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

YOUNG REVIEWERS

ADDIE, AGE: 14
I am a 9th grader who enjoys fashion design and math. I am passionate about the performing arts. I love to act! When I am not rehearsing for a play or musical, you can usually find me crocheting. My favorite color is purple and my favorite food is chicken wings. Someday I hope to be on Broadway. If that does not work out, I would like to be a costume designer.

ADRIANA, AGE: 14
I am a freshman in high school who enjoys song writing and playing the piano, as well as writing short stories. I enjoy biology and literature. I maintain high grades in school and pride myself in my ability to learn things quickly. I love riddles and puzzles, as well as video games—the more challenging, the better!

AJAY, AGE: 8
Eight-year old Ajay studies in the third grade and likes to write screenplays, put together storyboard for comics, make paper crafts, and lego models. He likes playing with friends and watches Arthur episodes. Ajay's favorite time during vacation trips is in the pool. Ajay is a voracious reader.

AMELIA, AGE: 16
I am a high school student who enjoys drawing fun comics, learning about cosmology, and the science of quantum physics. I like sleeping in on the weekends and sometimes procrastinated.

BRUNA, AGE: 15
My name is Bruna. I am a student of On A Beam of Light class. I love science because it is so vast and complex. Science provides solutions to many problems so I think that when science is studied, we are able to gain much more knowledge about the world we live in. A few other facts about me is that aside from liking science, I love reading, studying history and traveling. Also, I was born in Brazil; my first language is Portuguese.

CAROLINE, AGE: 14

I enjoy writing, specifically poetry. I have been writing since I was 6 years old, writing lyrics for songs. No matter what my age is, I would always tell stories through my writing. Having the ability to tell stories has helped me learn more about science! All science has a story behind it and the more attention you pay to the details of the story, the more secrets you uncover.

ELISHA, AGE: 14

I enjoy reading, creative writing, and making art. I have been playing the violin and learning taekwondo for over 7 years now, and continue to advance to more challenging skills! I like musical theater as well as acting; my favorite musical so far is *Hadestown*. My favorite color is olive green and I love understanding how the world functions, including science!

MALCOLM, AGE: 15

Yo! My name is Malcolm and I am 15 years old. My favorite subjects in school are Japanese and Physics. I enjoy learning about various STEM topics (especially aerospace), participating in robotics competitions and playing Volleyball. In my free time, I like to play video games and bike around my town. I am super excited to be a Young Reviewer and learn more about STEM along the way!

MRITTIKA, AGE: 15

15-year old Mrittika loves hanging out with friends and family. Her interests include: playing the viola, dancing, singing, reading, calligraphy, and she is a voracious reader. Math, Social Studies, and Music are her favorite subjects. Mrittika's favorite accomplishments are becoming a senior editor on her yearbook editing team and being a publicist for her school's Drama Department. She received an award for being the best foreign language student of the year in middle school and is a finalist in a nationwide computer science competition. Mrittika aspires to be a more open-minded and knowledgeable person.

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I am a researcher at the UCL Queen Square Institute of Neurology, University College London in the UK, and I run a laboratory that studies neuromuscular diseases like SMA. Our main aim is to improve understanding of what goes wrong in these diseases, so that we can develop treatments. I am also the scientific research correspondent for Spinal Muscular Atrophy UK, a charity dedicated to supporting patients and families affected by SMA. *j.sleigh@ucl.ac.uk

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I wear two hats! I am both the research programme manager for SMA Europe and research coordinator for SMA UK, both of which are charities/patient groups that represent the interests of people living with SMA. I initially worked as a research scientist, in the field of immunology, and subsequently left the lab to coordinate SMA UK's research activities and manage SMA Europe's research programme.

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I am an information coordinator for Spinal Muscular Atrophy UK, a patient group/charity that has provided information, support, and funding for SMA since 1985. I have a long professional background in social work and disability rights/services in both the United Kingdom and New Zealand.

RAFAEL J. YÁÑEZ-MUÑOZ

I am a professor at Royal Holloway, University of London in the UK, where I teach genetic medicine. My laboratory investigates possible genetic therapies for SMA and other diseases. I am also the current president of the *British Society for Gene and Cell Therapy*, which brings together UK scientists working in this field. On international *Rare Disease Day*, celebrated around the world on the last day of February (a rare day when a leap year), I organize an event to highlight the importance of rare diseases.