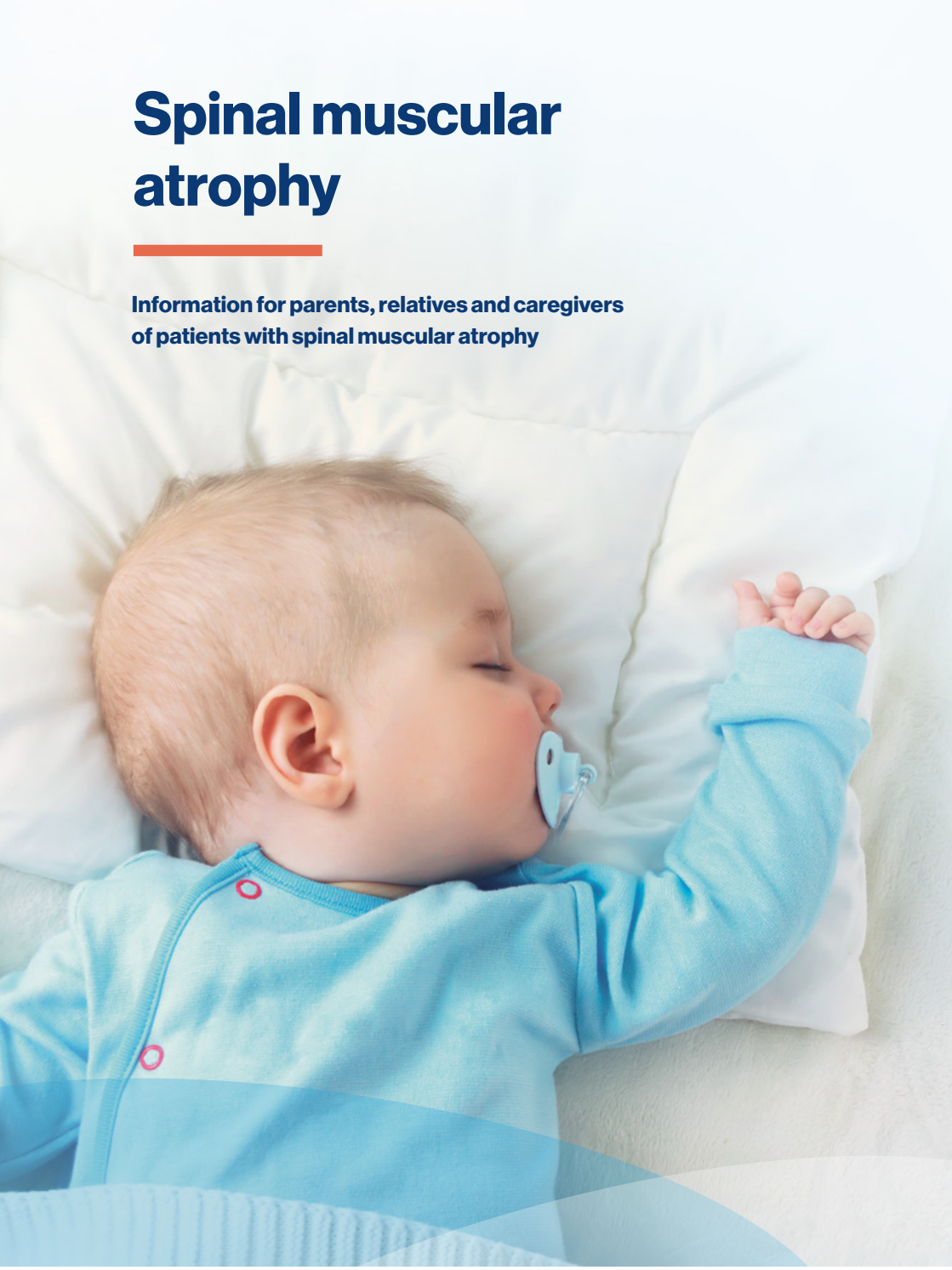
Spinal muscular atrophy

Information for parents, relatives and caregivers of patients with spinal muscular atrophy



NOVARTIS | Reimagining Medicine

PREFACE

Dear parents and family,

Your child has been diagnosed with rare hereditary muscle weakness called spinal muscular atrophy (SMA).

Naturally, the diagnosis presents you with a considerable challenge, and you are facing many uncertainties. Your child's health will require a lot of attention in the near future.

Early treatment is very important in spinal muscular atrophy. To be able to make important decisions for your child promptly together with your doctor, you need information.

Therefore, this brochure is intended to give you an overview of the disease and its symptoms, the cause as well as the treatment options and should therefore support you in discussions with your doctor.

If you have any further questions, your doctor will be happy to help you.

We wish you all the best.

This brochure does not claim to be complete. It may contain useful information on spinal muscular atrophy, but it cannot replace a discussion with the doctor.

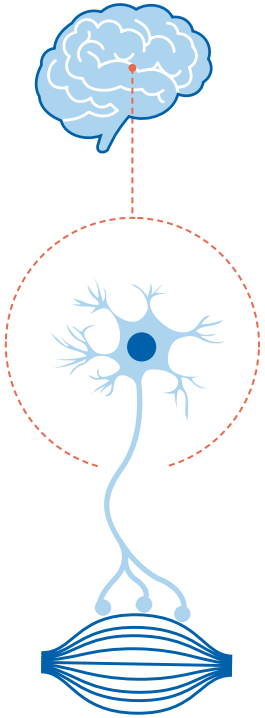
TABLE OF CONTENTS

WHAT IS SMA?

Spinal muscular atrophy (SMA) is a rare neuromuscular disease that manifests as muscle weakness. This weakness is caused by the wasting away of specialised (motor) nerves that are important for movement, called motor neurons.

The task of motor neurons is to carry signals from the brain through the spinal cord to the muscles. These signals control muscular movements. In healthy people, these motor neurons are fully functional.

→ Healthy people



Brain

This is where the signals and information about every individual muscle movement originate.

Motor neurons

Specialized motor nerve cells that conduct signals from the brain through the spinal cord to the muscles.

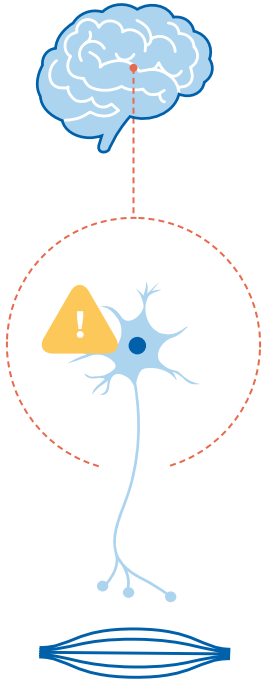
Muscle

Tension and relaxation produces all movements of the human body. This also includes respiratory muscles.

In people with SMA, the genetic defect causes atrophy of the motor neurons.

When the motor neurons atrophy, the signals from the brain are no longer conducted to the muscles. Muscles that no longer receive signals waste away and become increasingly weaker. The technical term for this regression is atrophy.

→ People affected by SMA



Brain

This is where, also in patients with SMA, signals and information about every individual muscle movement originate.

Motor neurons

In SMA, motor neurons atrophy due to a genetic defect. Movement signals from the brain are not conducted.

Muscle

Muscles that no longer receive signals waste away and become increasingly weaker (atrophy).

WHAT CAUSES SMA?

The SMN protein is vital for survival of motor neurons.

For motor neurons and hence muscles to function properly, the body requires a protein called SMN (SMN protein). SMN stands for “Survival Motor Neuron”, meaning it is responsible for survival of the motor neurons. In healthy people, the body is able to produce this protein by itself.

The information for the production of this important protein is located in the SMN gene.

SMN protein

A protein required by motor neurons,
produced by the body itself.
SMN stands for “Survival Motor Neuron”,
i.e. survival of the motor neurons.

In SMA, the SMN-1 gene is defective.

The SMN protein, which is important for motor neurons, is produced with the aid of the SMN gene. This gene is usually present in two versions:

1

SMN1

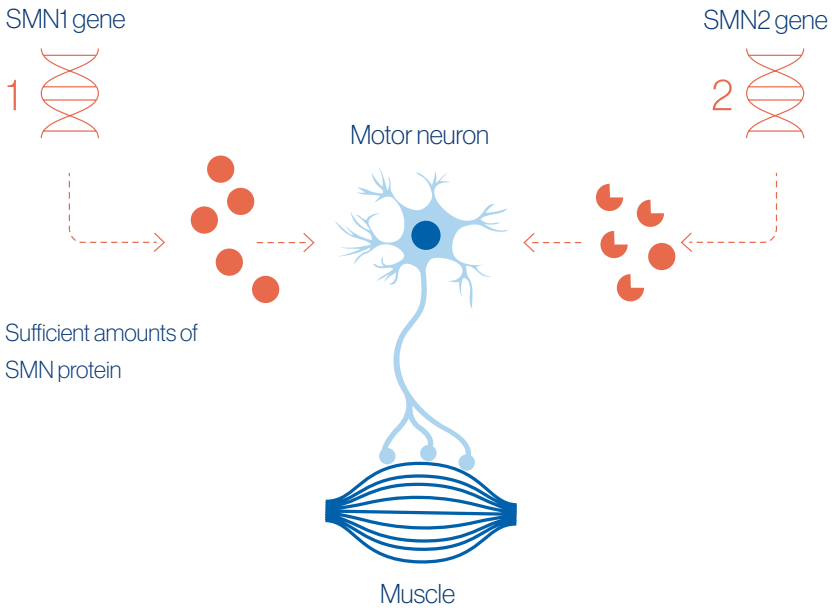
The SMN1 gene is very efficient, causing
the production of large amounts of the protein.
SMN1 is the main supplier of the protein.

2

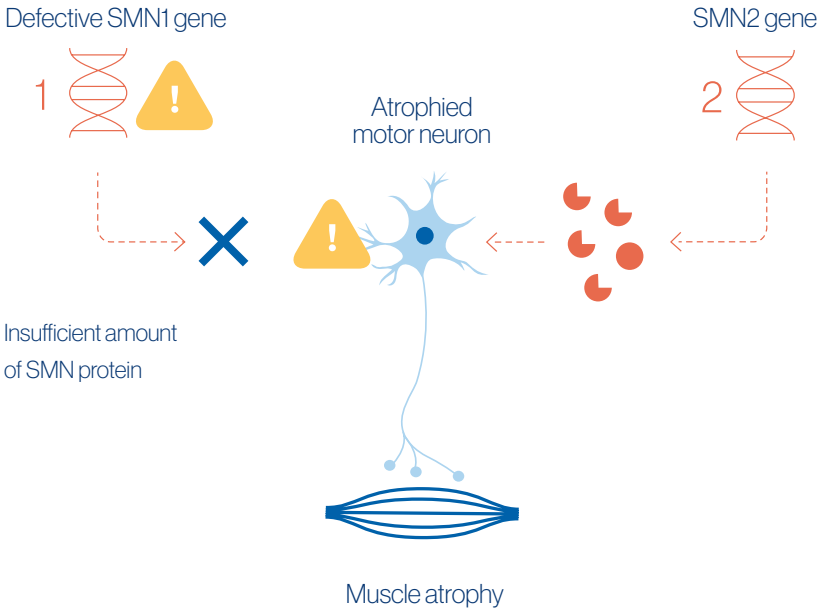
SMN2

The SMN2 gene plays a rather supportive role (auxiliary gene) and produces only small amounts of the protein. Each person can have a different number of copies of the SMN2 gene. Having a lot of SMN2 gene copies is usually associated with a milder progression of SMA.

→ Healthy people



→ People affected by SMA



- functional SMN protein
- dysfunctional SMN protein

The disease SMA is caused by a genetic defect in the SMN1 gene, which is the efficient gene. This means that in SMA the SMN1 gene is faulty or missing altogether. This results in insufficient amounts of the functional SMN protein.

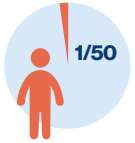
The result:
Motor neurons, which absolutely depend on SMN, atrophy.

HOW IS SMA INHERITED?

Since SMA is caused by the genetic defect or a missing gene, SMA is called a genetic disease. Genetic diseases usually occur through heredity.

Every human being has two copies of every gene (except the sex-specific genes). If one of the two copies is defective, the person concerned does not fall ill because they still have the other non-defective gene.

However, they can pass on the defective gene to their children if they have children of their own. They are therefore a carrier of the disease without being ill themselves.



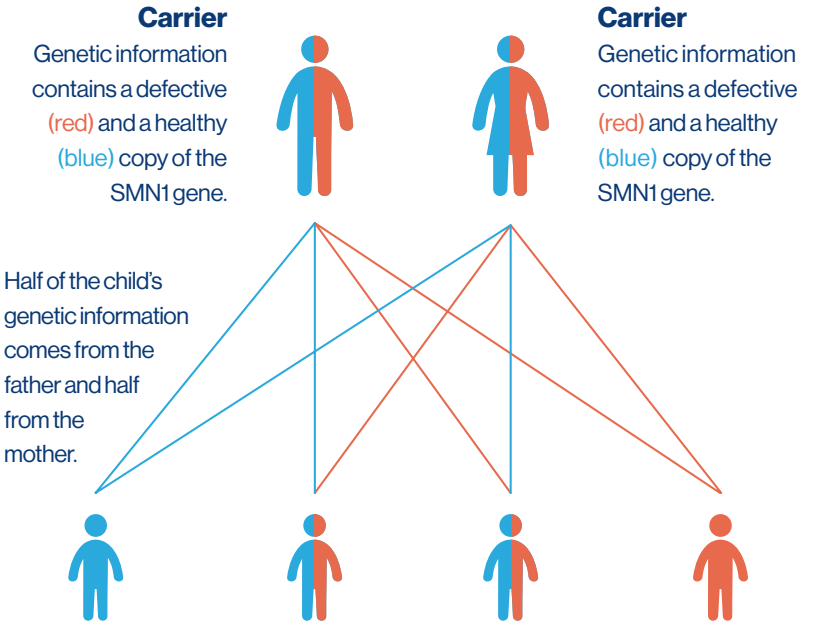
1 in 50 people is a carrier of the disease.

25% is the probability of having a child with SMA if both parents are carriers of the disease.

Approx. 1 in 10,000 newborns in Germany is affected by SMA.

→ How SMA is inherited

Half of the genetic information – the genes – come from the father, the other half from the mother. Only if the defective version of the SMN1 gene is passed on to the child from both parents does the disease occur.



Healthy (25%)
The child has inherited the healthy copy from each parent.

Carrier (50%)
The child has inherited one healthy and one defective copy and therefore also becomes a carrier of the disease, but is healthy themselves.

Diseased (25%)
The child has inherited the defective copy from each parent and therefore has the disease.

Boys and girls are equally affected by SMA.

Not affected by SMA | Affected by SMA | Carrier

HOW DOES THE DISEASE PROGRESS?

SMA is a progressive neuromuscular disease with symptoms that differ depending on the age of the person when symptoms begin and the severity of the disease

Muscle weakness mainly affects muscles close to the trunk, including muscles of the upper body such as those of the abdomen, back and chest. If left untreated, people with SMA suffer from muscle atrophy, which results in increasing difficulty to perform seemingly simple activities. This includes lifting the head, moving the arms and legs, eating/swallowing independently, and in particular breathing.

SMA particularly affects the motor neurons that control muscle movement

SMA does not affect other nerve cells in the brain that are responsible for thinking. The senses, thoughts, perception and intelligence remain unaffected by SMA.

The disease does not affect the development of their thinking and perception in children with SMA.

THE DIFFERENT TYPES OF SMA

How the SMA develops depends, among other things, on the number of copies of the SMN2 gene. This is because with a lot of SMN2 gene copies, more SMN protein can be produced and the defect of the SMN1 gene can be partially compensated. Therefore, more SMN2 gene copies are associated with a weaker course of SMA.

In general, the course of SMA is different for each person affected and can therefore only be roughly divided into different types.

This classification is based on the age at which the first symptoms of the disease appear. A prognosis for the different types is difficult, especially because the transitions between the types are fluid.

Early diagnosis and treatment in particular can have a positive influence on the course of the disease.

TYPE 1 SMA

Onset of the first symptoms:	0-6 months
Symptoms:	Among other things, hardly any movement of the arms and legs, weak crying and coughing, atrophied and weak muscles
Limited motor skills	Unable to sit

TYPE 2 SMA

Age at onset of disease:	7-18 months
Time of diagnosis:	Before reaching the age of 2
Limited motor skills	Able to sit but never stand or walk independently

TYPE 3 SMA

Age at onset of disease:	> 18 months
Time of diagnosis:	Before reaching the age of 3 (type 3a) until late adolescence (type 3b)
Limited motor skills	Can walk without support, but may also lose this ability again

TYPE 4 SMA

Age at onset and time of diagnosis:	In adulthood, first symptoms after the age of 35, rarely between ages 18 and 30.
Limited motor skills	Walking without support, but this ability may slowly diminish

Source: https://www.initiative-sma.de/hintergrundwissen/spinale-muskelatrophie-typ-i-typ-ii-typ-iii-typ-iv/

TYPE 1 SMA: THE EARLY FORM

Type 1 SMA has the most severe course and is also the most common form. Approx. 60% of those affected by SMA have type 1.

The course of the disease is different for each child with type 1 SMA. Type 1 SMA can be deceptive as babies may initially appear healthy after birth.

→ Early signs and symptoms of type 1 SMA

- Inability to raise the head
- Swallowing difficulties, also of their own saliva
- Tongue quivering

- Hardly any movement of the arms and legs (near the torso)
- Reduced, weak muscles
- Absence of reflexes

- Difficulty breathing
- Weak crying and coughing

- Bell-shaped chest

SUSPECTED SMA AND DIAGNOSIS

Diagnosis with a genetic test

As soon as the doctor suspects SMA may be behind the symptoms, a blood sample is taken from the child. A genetic test can be used to determine whether the disease is in fact SMA. The blood can be used to determine whether the SMN1 gene is defective or even completely missing. It is also possible to see how many SMN2 gene copies are present.

→ How the genetic test works

Blood test
If SMA is suspected, a blood test will be done.

Analysis
The SMN1 and SMN2 genes are analysed.

Result
The suspicion is confirmed (diagnosis) or SMA is ruled out (no findings).

Early treatment is very important in SMA

As already mentioned, SMA progresses differently in each child. However, the disease causes motor neurons to die before the symptoms are visible. That is why early diagnosis is very important.

Muscles can be built up through certain therapies, but unfortunately this is not the case with motor neurons. This means that any existing damage to the nerve cells cannot be reversed.

For a long time, therapies were mainly supportive, but today there are drugs available for SMA. Medicine has made great progress in this area in recent years.

You can support your child's doctor by making treatment decisions together quickly. If you have any questions, your doctor is of course always there to help you.

TREATMENT OPTIONS

Drug therapies

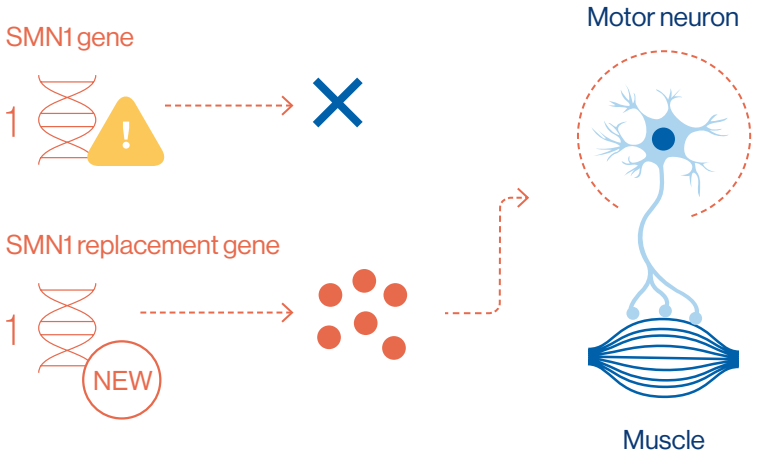
Nowadays, there are already treatment options available for the rare disease SMA, and others are still in clinical development. These therapies have different mechanisms of action, which are explained below.

→ Improving protein production from the SMN2 auxiliary gene

As described above, each person has different numbers of copies of the SMN2 gene. The more copies of SMN2 there are, the milder the course of SMA will be. There are medications that increase the productivity of the SMN2 gene.

→ Replacing the SMN1 gene

The defective SMN1 gene is the cause of SMA. One therapeutic approach is to replace the defective SMN1 gene with a functional SMN1 gene using a single infusion (gene replacement therapy).



Further treatment options

The following additional measures are used supportively during SMA therapy:

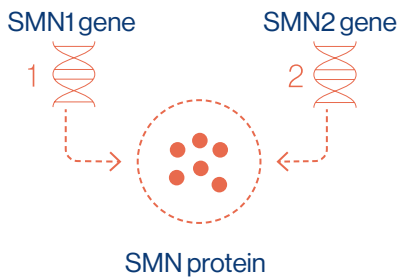
- Ventilation, for example using a sleeping mask
- Support for clearing the airways
- Physiotherapy treatments
- Nutritional support
- Orthopaedic treatments
- Prevention of respiratory infections, for example by antibiotics or vaccination

NOT AFFECTED BY SMA

Muscle movements depend on many factors

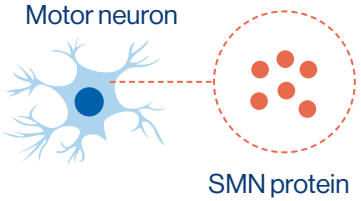
SMN genes produce the SMN protein

Each motor neuron can produce sufficient SMN protein itself with the SMN1 gene. The SMN2 gene copies produce a small amount of SMN protein that is not actually needed in a healthy person.



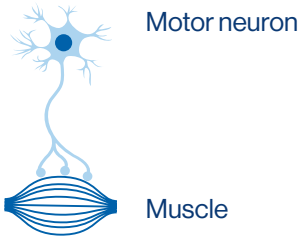
Motor neurons need SMN protein

In order to function properly, each motor neuron needs the protein SMN in sufficient quantities.



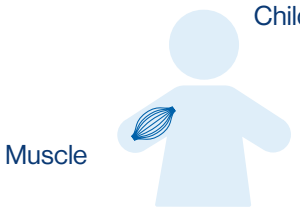
Motor neurons transmit the signals

Muscles can move because specialised nerves called motor neurons transmit signals from the brain to the muscle.



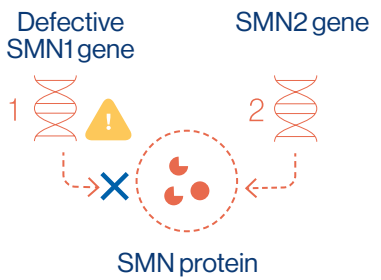
Muscle moves

The signals from the brain can control the movement of the muscle. The muscle is healthy and strong.



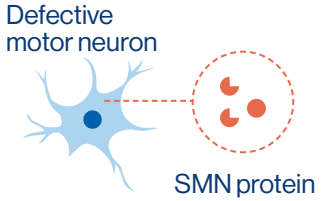
AFFECTED BY SMA

Spinal muscular atrophy is a genetic disorder



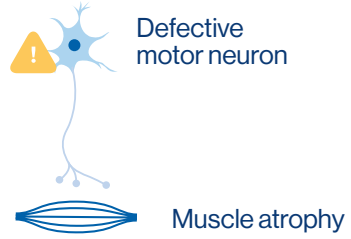
SMN1 gene defective or missing

Due to a gene defect in the SMN1 gene, the SMN protein cannot be produced in sufficient quantities. The existing SMN2 gene copies cannot produce the SMN protein in sufficient quantities.



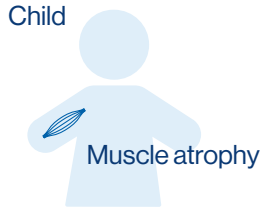
SMN protein not available in sufficient quantities

There is too little SMN protein, which the motor neurons absolutely need.



Motor neurons atrophy

The motor neurons atrophy and therefore cannot transmit the signals from the brain.



Muscle becomes weaker

The signals from the brain no longer reach the muscles. If muscles no longer receive signals, they become weaker and waste away (atrophy).

GLOSSARY

Atrophy

Degeneration of an organ or tissue.

Gene

A blueprint encoded in the genetic information for a specific protein that fulfils a special task in the body.

Genetic defect

A gene is either defective (through mutation) or completely missing (deletion).

Genetic test

A blood test shows whether there is a genetic defect in the SMN1 gene and how many copies of the SMN2 gene are present. SMA can be diagnosed in this way.

Motor neuron

A nerve that is important for controlling movement, which conducts signals from the brain via the spinal cord to the muscles.

Neuromuscular Concerning the nerves and muscles.

SMN protein

The protein “Survival Motor Neuron” is essential for the survival of motor nerves, i.e. motor neurons. The health and functioning of motor neurons depend on the amount of the SMN protein.

SMN1 gene

The blueprint for the SMN protein. This facilitates the production of the largest share of the total SMN protein in the body. In SMA patients, this gene is either missing or defective.

SMN2 gene

The gene supporting the production of the SMN protein. Only a small part of the required amount of SMN protein is produced per SMN2 gene copy. The number of SMN2 gene copies influences therefore the severity of the disease. A human can have up to six copies of the SMN2 gene.

Spinal muscular atrophy, (SMA)

rare neuromuscular disease in which motor neurons atrophy due to a deficiency of the SMN protein. This results in reduced signal transmission from the brain to the muscles, causing wasting and weakness of muscles.

NOTES

ADDRESSES

Diagnosegruppe SMA in der Deutschen Gesellschaft für Muskelkranke e. V. (SMA Diagnosis Group in the German Association for Muscular Dystrophy, registered association)

c/o Steffi Vogler
Seidlhofstrasse 14
80639 Munich , Germany
Tel.: +49 (0)176 22792965
steffi.vogler@dgm.org
www.dgm.org/diagnosegruppe/sma

DGM counselling services and contact person search
www.dgm.org

"Research and Therapy for SMA" initiative

c/o Dr. Inge Schwersenz MD
Seidlhofstrasse 14
80639 Munich , Germany
Tel.: +49 (0)89 12717447
info@initiativesma.de
www.initiativesma.de

Deutsche Muskelstiftung Phillip und Freunde – SMA Deutschland e. V. (German Muscle Foundation Phillip and Friends - SMA Germany, registered association)

Plättigweg 11
76189 Karlsruhe , Germany
info@muskelstiftung.de

or

Werner-von-Siemens-Ring 13
75015 Bretten , Germany
Tel.: +49 (0)7252 973663
info@sma-deutschland.de
www.muskelstiftung.de

OneGene website

Helpful information about SMA
can be found on our website:
www.onegeneprogram.de

Provided by Novartis Gene Therapies

DE-UNB-21-0137
Date created: February 2021
Medical information:
Email: medinfoemea.gtx@novartis.com
Tel: +49 (0)69 945189449