smaleo
Antworten für Familien mit SMA

Spinal Muscular Atrophy (SMA)

Comprehensive information including newborn screening, confirmatory diagnostic tests and therapeutic options

NOVARTIS | Reimagining Medicine

Dear parents and family,

Newborn screening (NBS) of your baby has revealed a positive test for spinal muscular atrophy (SMA).

This brochure, together with our lioness SMALEO, will see you through the initial emotionally trying phase following the NBS and will provide answers to all your questions as a family with SMA. What kind of disease is SMA? What does this mean for my child? What are the available treatment options? You may visit www.smaleo.de for more information.

It is important to be aware that early initiation of treatment is important for your child.

SMALEO will explain the disease and its signs/symptoms, its cause, as well as the available treatment options, thereby enabling you to quickly arrive at important decisions for your child in cooperation with your neuromuscular centre (NMC).

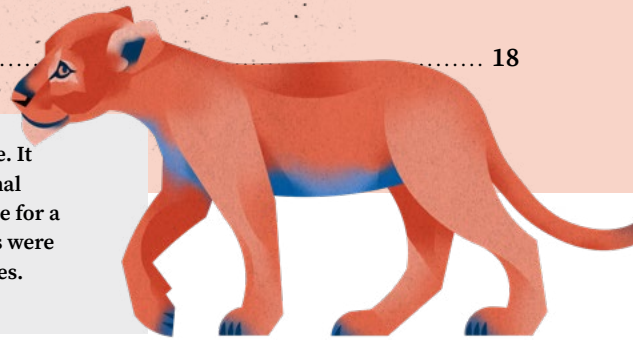
Even if you have a lot on your plate at the moment, try and remain calm and get to know your child further.

Whatever may happen: the “lion” in each of us helps us fight for what most important to us in difficult situations. We will find a way forward together.

Your SMALEO team

Contents

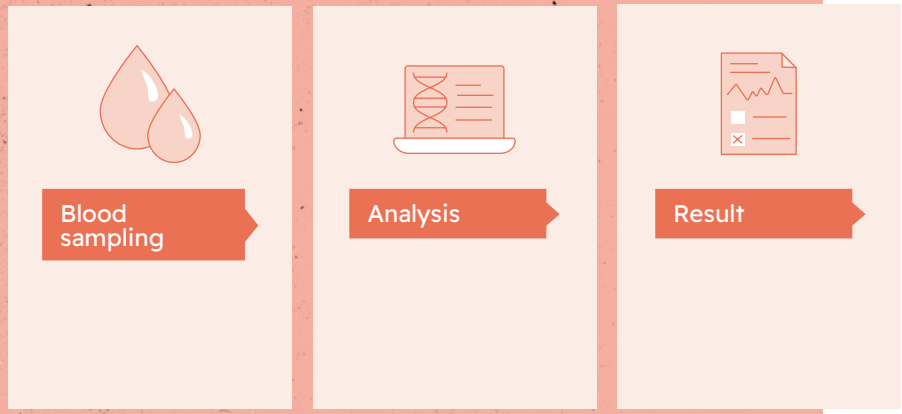
This brochure is by no means complete. It contains useful information about spinal muscular atrophy but is not a substitute for a discussion with your doctor. All photos were recreated and are fictitious patient cases.



What is the newborn screening (NBS) for?

NBS facilitates the early diagnosis of treatable diseases, thereby enabling the timely initiation of specific treatment if a suspected diagnosis is confirmed.

Newborn screening – step by step

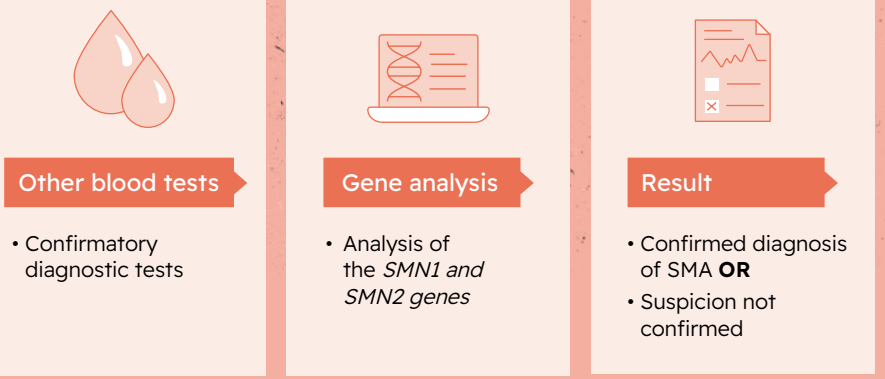


Any disease suspected during NBS must be confirmed or ruled out promptly by follow-up tests, also known as confirmatory diagnostic tests.

What are confirmatory diagnostic tests?

The diagnosis of suspected SMA is carefully validated by these confirmatory tests and treatment is initiated only once the diagnosis is confirmed. The diagnosis is only considered confirmed once a second blood sample confirms the first finding.

The next step: Confirmatory diagnostic tests



A short video on **smaleo.de** provides some insight into confirmatory diagnostic tests.

What can the diagnosis of SMA mean for a newborn?

Timely treatment can be initiated for your baby once the diagnosis suspected during screening is confirmed. Thus, most children with no signs of the disease (based on available information) may have a chance of normal or near-normal development.

The prognosis in children with early signs/symptoms during NBS is significantly improved by early diagnosis and thus early initiation of therapy.

Early diagnosis as an opportunity

Many things are currently probably different from how you imagined them before your child was born.

Try and view NBS as an opportunity, even if the suspicion of SMA is confirmed. Early initiation of treatment was not feasible until a few years ago.

Several treatment options are now available to you and your child with a confirmed SMA diagnosis, as explained on page 15.

What is SMA?

Spinal muscular atrophy (SMA) is a rare but treatable disease that presents as muscle weakness. The so-called motoneurons (specialized nerve cells) in the spinal cord – responsible for controlling movements – are particularly affected in patients with SMA.[1–5]

The diagnosis of SMA initially only implies that your child's body cannot produce adequate amounts of "survival motor neuron protein" (SMN protein) on its own, since the required *SMN1* gene is defective.[1–3,6]

The SMN protein is very important for the survival of the motor neurons which are responsible for the transmission of signals between the brain and the spinal cord. These nerves, which are necessary for the control of movement, perish if adequate amounts of SMN protein are lacking.[1–5]

The speed and extent to which this occurs depends on the extent to which the body can produce SMN protein despite the genetic defect. The quantity of a second gene closely related to the defective *SMN1* gene (the so-called *SMN2* gene) plays a significant role in this regard.

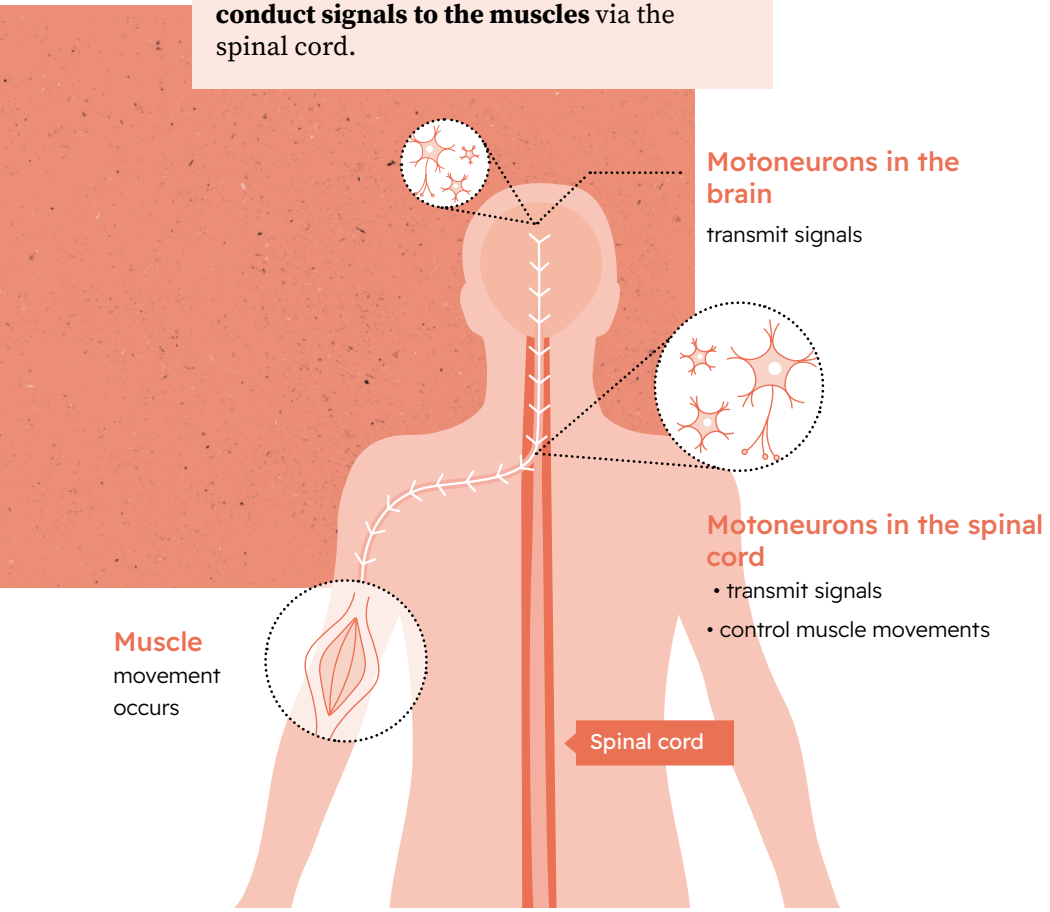
Admittedly, this is all rather complicated – which is why we will try and explain this complex disease a little more clearly in the following pages.

The video "Acting Quickly" on **smaleo.de** explains the approach after early diagnosis.

SMA simply explained

Signals are transmitted by specialized nerves in unaffected individuals. These nerves are called motoneurons and they are of great importance for mobility: Their task is to transmit signals from the brain via the spinal cord to the muscles. These signals in turn control the movements of the muscles.

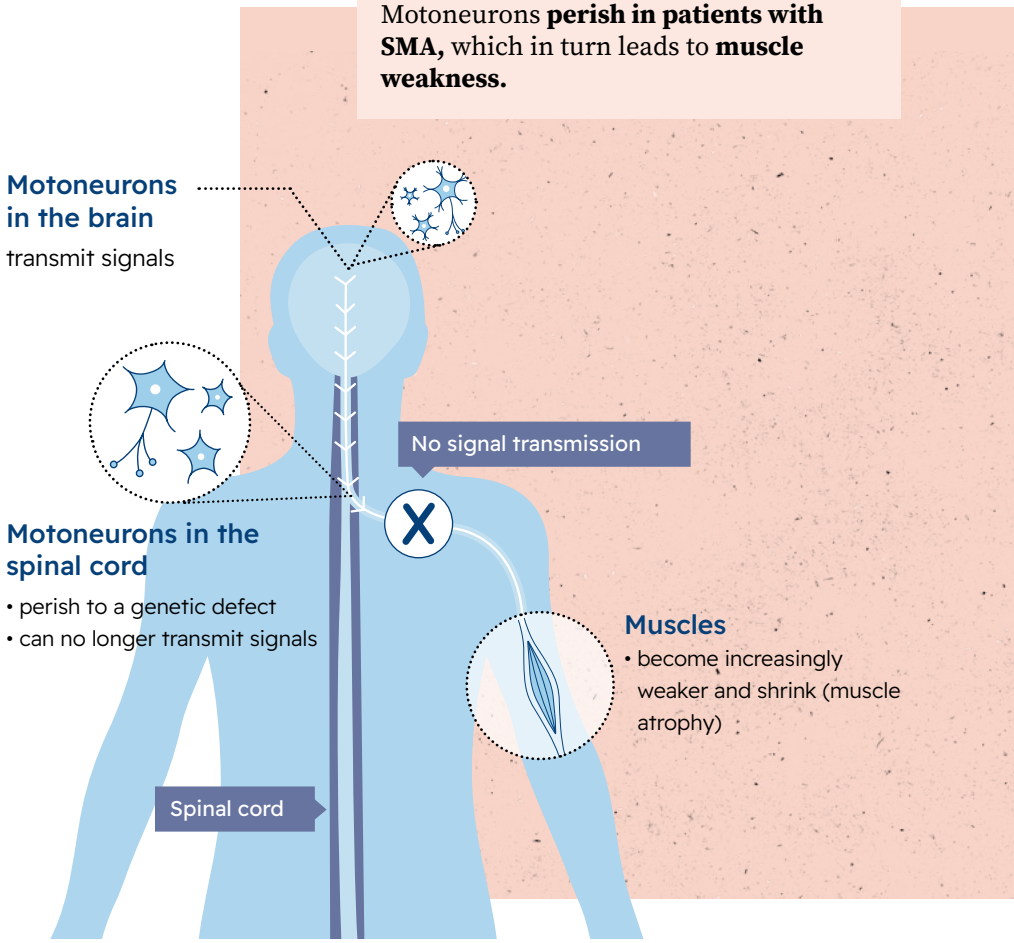
Specialised nerve cells (motoneurons) **conduct signals to the muscles** via the spinal cord.



Patients with SMA

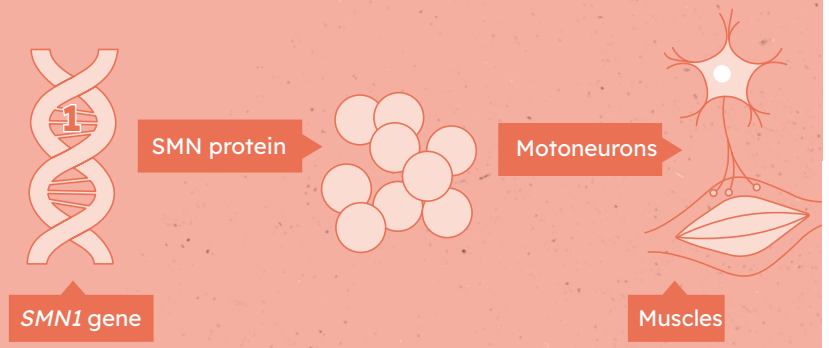
These motoneurons undergo atrophy in patients with SMA. Signals are no longer transmitted to the muscles, which subsequently shrink and become increasingly weaker. This phenomenon is called muscle atrophy in medical parlance.

Motoneurons **perish in patients with SMA,** which in turn leads to **muscle weakness.**

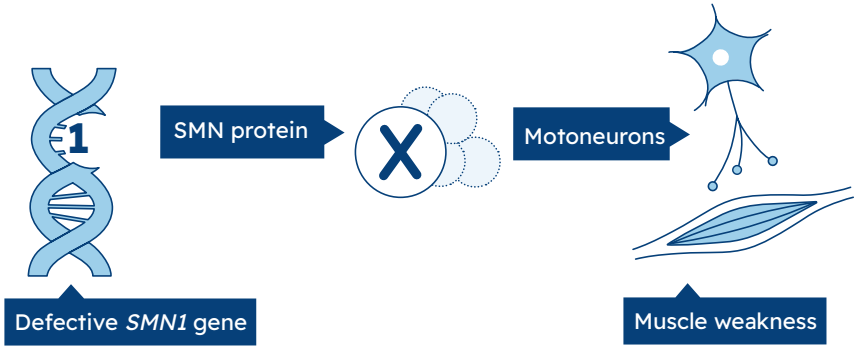


What causes SMA?

The body needs a protein called SMN protein for the optimal functioning of motoneurons and muscles. SMN stands for survival motor neuron. This SMN protein is produced using the *SMN1 gene in unaffected individuals.*



SMA is caused by a genetic defect in the main *SMN1* gene, which is either incomplete or completely absent. Consequently, there is too little SMN protein, causing motor neurons to atrophy and the muscles to weaken.



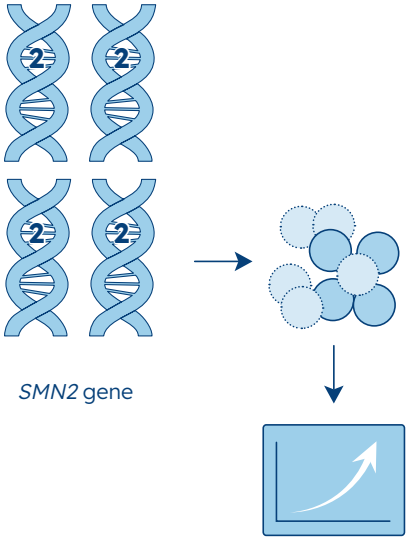
Do other influencing factors play a role in SMA?

The development of SMA also depends on the number of *SMN2* gene copies (helper genes), of which each person has a different number. The presence of several *SMN2* gene copies enables the formation of more SMN protein and the *SMN1* gene defect is partially compensated for. However, the *SMN2 gene only forms small amounts (approx. 10%) of functional SMN protein.* This implies that: The higher the number of available *SMN2* copies, the more favourable the course of SMA.

The number of *SMN2* gene copies is determined during confirmatory diagnostic tests.

SMN2 gene

Several available copies of the *SMN2* gene may imply a more favourable course of SMA.



SMN2 gene

What is the clinical course of SMA?

First off: The disease follows a variable course in different individuals. Early initiation of treatment – even before the first signs appear – may allow for age-appropriate development of your child. The decisive factor is early diagnosis. The NBS provides a great opportunity for a favourable course. Good treatment options are now available, which have been described on page 15 of this brochure.

Untreated SMA patients often find it difficult to raise their head and move their arms and legs. Eating food on one's own, swallowing, and breathing may also be impaired, since several muscle groups may be affected in SMA: hip, back, and shoulder muscles, as well as those involved in chewing, swallowing, and breathing. Muscle atrophy of the legs is usually greater than that of the arms in most cases.

However, SMA does not affect other nerve cells in the brain that determine one's intellectual capacity. The patient's senses, thoughts, perception, and intelligence remain unaffected.

Spinal muscular atrophy is also very clearly explained in the DGM [Deutsche Gesellschaft für Muskelkranke e.V. (German Association for Muscular Dystrophy)] video at **smaleo.de.**

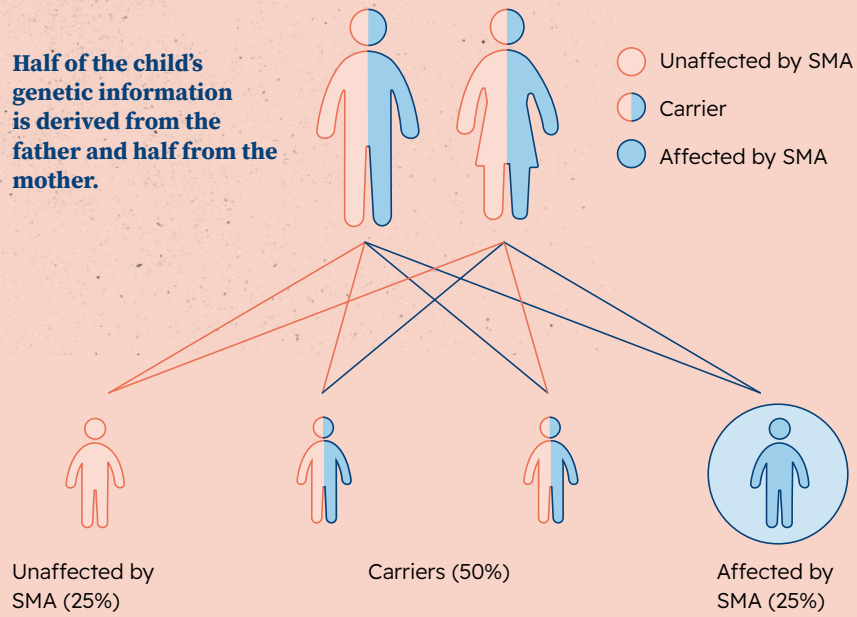
How is SMA inherited?

SMA is due to a genetic defect or a missing gene.

Half of the genetic information – the genes – is derived from the father and the other half from the mother. The child develops the disease only if both parents pass on the defective version of the *SMN1* gene to the child.

Why is that? Every human has two copies of every gene – except the genes for one's gender. If only one of the two copies is defective, the concerned person does not develop the disease since they still possess the other intact gene. The person himself is, therefore, unaffected by SMA, but can pass on the defective gene to his offspring. Such a person is called a "carrier of the disease". Incidentally, boys and girls can be equally affected by SMA.

Half of the child's genetic information is derived from the father and half from the mother.



What treatment options are available?

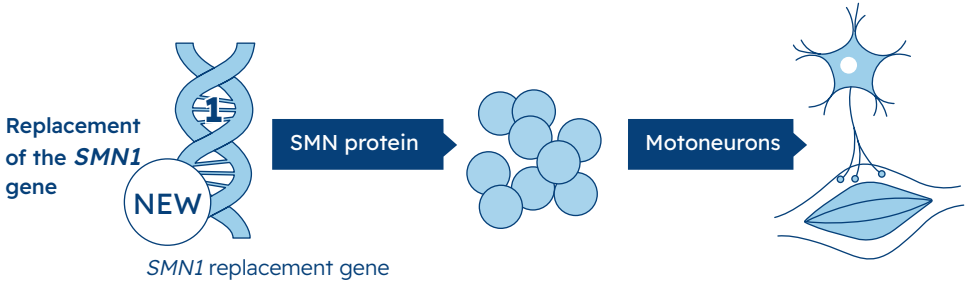
Early treatment of your child is crucial once the diagnosis of SMA has been confirmed. The first point of contact after diagnosis is always the specialist at your neuromuscular centre (NMC). This is followed by a comprehensive investigation and a detailed discussion with the treating team.

The good news is that SMA is treatable. Various treatment options are available with differing mechanisms of action, which have been explained below.

The video “Two types of treatment” on **smaleo.de** also clearly explains the two therapeutic approaches for SMA.

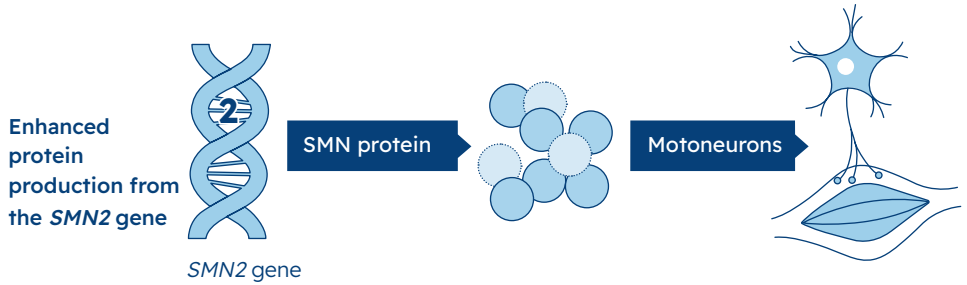
Drug treatment

1. Replacement of the main gene (*SMN1*)



SMA is due to an *SMN1* gene defect. This therapeutic approach involves replacement of the defective SMN1 gene by an intact *SMN1* **gene by a single infusion**. Therefore, this treatment is also known as **gene replacement therapy.** You will be required to remain in regular contact with your NMC for follow-up after treatment and for monitoring of your child’s development.

2. Enhanced protein production from the *SMN2* gene



The number of copies of the SMN2 gene varies from person to person. The greater the number of copies of the *SMN2* gene, the more favourable the course of SMA. The objective of this therapeutic approach is, therefore, to increase the **production of the *SMN2* gene.** This mechanism of action required a chronic therapy. You will likewise be required to remain in contact with the NMC besides your regular treatment appointments for monitoring of your child’s development.

The most important points at a glance:

- Newborn screening allows **early identification** of **treatable diseases.**
- SMA is diagnosed only when a second blood sample confirms the first finding.
- It is important to jointly initiate specific measures rapidly if the diagnosis is confirmed. This is a great opportunity for a favourable outcome.
- SMA follows a variable clinical course in different individuals. **Early diagnosis and prompt treatment are crucial.**
- Several good **treatment options are available.**

Useful addresses:

Initiative „Forschung und Therapie für SMA“

- www.initiative-sma.de

Deutsche Gesellschaft für Muskelkranke e. V.

- www.dgm.org

Deutsche Muskelstiftung
Philipp & Freunde [Philipp and Friends] – SMA Deutschland e.V.

- www.deutsche-muskelstiftung.de

Patient organizations will gladly put you in touch with families with prior experience with their child’s SMA, if you wish.

Further information in various languages is available here:

Cure SMA

- www.curesma.org

SMA Foundation

- www.smafoundation.org

SMA Europe e.V.

- www.sma-europe.eu

Glossary

The most important terms related to spinal muscular atrophy (SMA) have been listed below:

Atrophy describes the decrease in or loss of tissue. Muscle atrophy results in the wasting of muscle tissue.

Genes are akin to blueprints for a certain protein. Each gene performs a specific task in the body. Genes are anchored in the genetic information in every human being.

A genetic defect is defined as a defective or completely missing gene. A defective gene is due to a change in the genetic material, which is also called a mutation. The complete absence of a gene is called deletion.

Confirmatory diagnostic tests verify the diagnosis suspected during newborn screening. Confirmation is a synonym for verification. A detailed examination of a second blood sample in a human genetic laboratory can confirm the suspicion of SMA and thus confirm the diagnosis.

Motoneurons are nerves that are important for movement. They transmit signals from the brain via the spinal cord to the muscles, which then convert this information into movement.

A Newborn screening (NBS) involves the examination of the newborn's blood sample obtained from the heel or vein on the second or third day of life, and can help identify several severe but treatable diseases. You had agreed to this screening.

Neuromuscular implies: affecting the nerves and muscles.

Neuromuscular centre is a specialised treatment centre for the diagnosis and treatment of neuromuscular disorders such as SMA. These nationwide centres were founded on an initiative of the Deutschen Gesellschaft für Muskelkranke e. V. (DGM) [German Association for Muscular Dystrophy]. These are distributed throughout Germany. List of treatment centres: **dgm-behandlungszentren.org**

SMA genetic test is a blood test that determines the presence of a genetic defect of the *SMN1 gene and the number of available copies of the SMN2 gene.* SMA suspected during newborn screening may be confirmed by these tests, for instance.

SMN protein The survival motor neuron is essential for the survival of motoneurons. The quantity of available SMN protein determines the health and function of the motoneurons.

***SMN1* gene** is the blueprint for the SMN protein, and produces most of the SMN protein in the body. This gene is completely absent or is defective in patients with SMA.

***The SMN2* gene** can support the production of the SMN protein. A human can have up to four gene copies (rarely more) of the *SMN2* gene. The number is decisive for the occurrence and severity of the disease in a given child.

Spinal muscular atrophy (SMA) is a rare inherited neuromuscular disease leading to the atrophy of motoneurons due to inadequate SMN protein levels. Therefore, fewer signals are transmitted from the brain to the muscles.

Please log on to **smaleo.de for more detailed information, helpful links and downloads.**

Sources:

1. Coovert DD et al. Hum Mol Genet 1997;6(8):1205–1214. **2.** Lefebvre S et al. Cell 1995;80:155–165. **3.** Farrar MA and Kiernan MC. Neurotherapeutics 2015;12:290–302. **4.** Ogino S et al. Eur J Hum Genet 2004;12:1015–1023. **5.** D'Amico A et al. Orphanet J Rare Dis 2011;6:71. **6.** Mendell JR et al. N Engl J Med 2017;377:1713–1722. **7.** Govoni A et al. Mol Neurobiol 2018;55(8):6307–6318. **8.** Mercuri E et al. Neuromuscular Disord 2018;28:103–15. **9.** Finanger E, Leach ME, Prior TW, Russman BS. 2020. https://www.ncbi.nlm.nih.gov/books/NBK1352/ (retrieved on 01/03/2023).

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