What is Spinal Muscular Atrophy?

Spinal Muscular Atrophy (SMA) is a rare, genetically inherited neuromuscular condition. It causes progressive muscle weakness and loss of movement due to muscle wasting (atrophy). This may affect crawling and walking ability, arm, hand, head and neck movement, breathing and swallowing. There are different forms of SMA and a wide spectrum of how severely children, young people and adults are affected.

The most common form of SMA is known as ‘5q SMA’ due to its genetic cause. 5q SMA includes the different ‘types’ or clinical classifications – Types 1, 2, 3 and 4.

There are also rarer forms of SMA that have different genetic (non-5q SMA) causes. Information about some of these can be found here:

www.smauk.org.uk/rarer-forms-of-SMA

Includes

SMA Types 1, 2, 3 & 4

What causes 5q SMA?

How is it inherited?

How many people are affected?

Is there a treatment or cure?
It’s important as you read this guide to remember that:

➢ Each child and adult is affected differently
➢ Although SMA is clinically classified into different ‘Types’ which reflect the severity of its impact, it is considered a spectrum
➢ For children and adults, the severity of the condition varies from person to person, both within and between ‘Types’

SMA Types 1, 2, 3 & 4

Symptoms of SMA Types 1, 2 and 3 begin at different ages in childhood. Symptoms of SMA Type 4 begin in adulthood. The Types are defined by the best developmental milestone achieved, for example, if a child is able to walk at some point then they have SMA Type 3.

Sometimes, as well as being diagnosed with a Type of SMA, a child may also be described as ‘strong’ or ‘weak’ or having ‘early onset’ or ‘later onset’. This can be confusing as sometimes this refers to breathing being affected, yet at other times, it may mean age of onset. The international Standards of Care for SMA\(^1\) talk about classifications a, b and sometimes c – these describe the age of onset of the SMA.

A child / young person’s ability to sit, stand or walk and how their breathing ability is affected by their SMA are also important when it comes to managing the condition. Bearing all of this in mind, broadly speaking, each type of SMA is currently understood to be as follows:

➢ **SMA Type 1: the most severe form of SMA** with symptoms usually beginning between 0 and 6 months. Generally speaking, the earlier the onset of symptoms, the more severe the condition. Babies are unable to sit without support and may be described as ‘non-sitters’. It’s not possible to predict life expectancy accurately but for most children, without intervention for breathing difficulties, this has previously been estimated as less than two years\(^3\). Evidence suggests that since the International Standards of Care for SMA introduced more proactive managements in 2007, children have been living longer\(^1\).
SMA Type 2: symptoms usually begin between the ages of 7 and 18 months. Children are unable to stand without support and may be described as ‘sitters’. Their weak respiratory muscles can make it difficult for them to cough effectively, which can make them more vulnerable to chest (respiratory) infections. Though this is a serious condition that may shorten life expectancy, improvements in care standards mean that the majority of people can live long, fulfilling lives.

SMA Type 3a: symptoms usually begin between 18 months and 3 years of age. Children can stand and walk, although this will become more difficult with age and they will need more support over time.

SMA Type 3b: symptoms usually begin after 3 years. Difficulties with standing and walking usually occur later than they do for children with SMA Type 3a. Depending upon the individual impact of their condition, children and adults with SMA Type 3 may be described as ‘sitters’ or ‘walkers’. Very few people with SMA Type 3 have breathing problems and their life expectancy isn’t usually affected. Most can live long, fulfilling lives.

SMA Type 4: symptoms begin in adulthood and include mild to moderate muscle weakness in the arms and legs and some difficulty walking. SMA Type 4 isn’t life-threatening.

You can read more about SMA Type 2 in ‘Symptoms, diagnosis and effects of 5q SMA’. If you are a parent or carer you may find it helpful to read our guide, ‘Looking after your child who has had a recent diagnosis of SMA Type 2’.

You can read more about SMA Type 3 in ‘Symptoms, diagnosis and effects of 5q SMA’. If you are a parent or carer you may find it helpful to read our guide: ‘Looking after your child who has had a recent diagnosis of SMA Type 3’.

You can read more about SMA Type 4 in ‘Symptoms, diagnosis and effects of 5q SMA’. Our guide, ‘Looking after yourself if you are an adult who has had a recent diagnosis of SMA’ answers many questions asked by adults newly diagnosed with SMA Type 4.
What causes 5q SMA?

➢ The SMN1 gene

All types of 5q SMA affect the nerve cells called lower motor neurons. These are found within the spinal cord and transmit signals to muscles. These nerve cells carry electrical signals from the brain to activate the muscles used for movement such as crawling and walking. These signals control movement of arms, hands, head and neck as well as breathing and swallowing. For these nerve cells to be healthy, our Survival Motor Neuron 1 genes (SMN1 genes) must produce enough Survival Motor Neuron (SMN) protein.

Most people have two copies of the SMN1 gene. People with 5q SMA have two faulty copies of the SMN1 gene, which means they are unable to produce enough SMN protein to have healthy lower motor neurons. This means these specialist nerve cells in the spinal cord deteriorate. This restricts the delivery of signals from the brain to their muscles, making movement difficult. The muscles then waste due to lack of use - this is known as muscular atrophy.

In summary:

- Brain sends signals along the spinal cord via nerve cells called lower motor neuron
- In SMA, lower motor neurons in the spinal cord deteriorate
- Signals cannot efficiently get through to the muscles making movement difficult
- Muscles waste (atrophy) due to lack of use

The SMN1 gene is on the fifth chromosome in the region labelled ‘q’. This is why the main types of SMA are often referred to as ‘5q SMA’.

There are other rarer forms of SMA with different genetic causes. For more information on these, please see: www.smauk.org.uk/rarer-forms-of-sma
The *SMN2* gene

A second gene also has a role in producing SMN protein. This is the *Survival Motor Neuron 2* gene (*SMN2*), sometimes referred to as the SMA “back-up gene”.

However, most of the SMN protein produced by *SMN2* lacks a key building block that is usually produced by *SMN1*. This means that while *SMN2* can make some functional SMN protein, it cannot fully make up for the faulty *SMN1* gene in people with SMA.

Unlike most genes, the number of copies of *SMN2* on each chromosome can vary from one person to the next\(^6\); this can be between 0 – 8 copies. At the population level, the severity of SMA is linked to how much SMN protein is made \(^1,8,9\); there is therefore a general relationship between the number of *SMN2* copies (“*SMN2* copy number”) and the likely severity of SMA symptoms\(^1,8,9\). Having more *SMN2* copies is generally associated with less severe SMA symptoms. However, at the individual level, accurate predictions cannot be made about the Type or severity of SMA based on the *SMN2* copy number alone\(^1\). This is likely to be because other genetic and possibly environmental factors have an influence on the disease.

Bearing this in mind, the following table gives a summary of:

- how many *SMN2* copies the majority of people within each type of SMA may have (see ‘usual’ column)\(^3\) *and*

- the possible range of copy numbers that people within each type of SMA may have (see ‘range’ column)\(^10\)

<table>
<thead>
<tr>
<th>SMA Type</th>
<th>Usual age of symptoms (^1^0)</th>
<th><em>SMN2</em> copies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>‘usual’ number(^1)</td>
</tr>
<tr>
<td>Type 1</td>
<td>Younger than 6 months</td>
<td>2</td>
</tr>
<tr>
<td>Type 2</td>
<td>6 – 18 months</td>
<td>3</td>
</tr>
<tr>
<td>Type 3a</td>
<td>Under 3 years</td>
<td>3</td>
</tr>
<tr>
<td>Type 3b</td>
<td>Over 3 years</td>
<td>4</td>
</tr>
<tr>
<td>Type 4</td>
<td>Over 18 years</td>
<td>4</td>
</tr>
</tbody>
</table>

Table adapted from Tillmann et al. 2018\(^1^0\)
How do people inherit 5q SMA?

5q SMA is passed from parents to their children through faulty *SMN1* genes. It usually follows an autosomal, recessive pattern of inheritance. This means that:

- People who have inherited two faulty copies of the *SMN1* gene (one from each parent) have SMA.

- People who have inherited one faulty copy and one healthy copy of the *SMN1* gene (one from each parent) are carriers of SMA. Carriers do not have SMA or any symptoms of SMA.

- People who have inherited two healthy copies of the *SMN1* gene (one from each parent) do not have SMA and are not carriers.

When two SMA carriers have a child together, for each pregnancy there is a:

- 1 in 4 (25%) chance that the child will inherit both faulty copies of the *SMN1* gene and will have SMA.

- 1 in 2 (50%) chance that the child will inherit one faulty copy and one healthy copy of the *SMN1* gene and will be a carrier.

- 1 in 4 (25%) chance that the child will inherit two healthy copies of the *SMN1* gene and will not be a carrier or have SMA.

In around 2% of cases of SMA, the mutation is new in the affected person, most likely due to an error in making the egg or sperm cell from which they were conceived. This is called a *de novo* mutation.

For more detailed information, please see our information sheet, ‘The Genetics of 5q SMA’

[www.smauk.org.uk/the-genetics-of-5q-sma](http://www.smauk.org.uk/the-genetics-of-5q-sma)

There are other rarer forms of SMA with different genetic causes and different patterns of inheritance. For more information on these, please see:

[www.smauk.org.uk/rarer-forms-of-sma](http://www.smauk.org.uk/rarer-forms-of-sma)
How many people are affected by SMA?

Approximately 1 in 40 people carry the faulty \textit{SMN1} gene\textsuperscript{11} - that means there are around 1.6 million carriers in the UK.

The \textit{incidence} is the number of new cases of a condition or disease at any one time. Recent studies indicate that approximately one in every 10,000 babies worldwide are born with a Type of SMA, and that Type 1 SMA accounts for approximately 60\% of cases\textsuperscript{11,12}.

In the UK in 2017, there were 755,043 live births\textsuperscript{13-15}. This suggests that in that year approximately 76 babies were born with a type of 5q SMA.

The \textit{prevalence} is how many people are living with a condition or disease in a population at any one time. Recent studies suggest between 1 and 2 people in every 100,000 worldwide have a type of SMA\textsuperscript{11,12}.

Is there a treatment or cure for 5q SMA?

Although there is currently no cure for SMA, this does not mean that nothing can be done. There are a range of options aimed at managing symptoms, reducing complications of muscle weakness and maintaining the best quality of life. These are outlined in the internationally agreed Standards of Care for SMA \textsuperscript{1,2}.

➢ \textbf{Nusinersen / Spinraza\textsuperscript{TM}}

The first (and currently, the only) potentially available drug treatment for SMA is called nusinersen. Essentially, the drug is designed to modify the product of the \textit{SMN2} gene to produce more functional SMN protein.

In collaboration with researchers, nusinersen was developed by Ionis Pharmaceuticals and Biogen Idec, which have run clinical trials with infants and children affected by SMA Types 1, 2 or 3. There have not yet been any clinical trials of nusinersen with anyone with SMA Type 4. On June 1\textsuperscript{st} 2017, the European Commission (EC) approved nusinersen for marketing under its brand name Spinraza\textsuperscript{TM} as a treatment for those with \textit{5q SMA}\textsuperscript{17}. Following any EC marketing approval, it’s up to each country to decide who can be prescribed the drug.
Currently in the UK, nusinersen is only available in Scotland if the medical team and family agree that an infant with SMA Type 1 is eligible and may potentially benefit from the treatment.

➢ **Research and further developments**

There is a considerable amount of research into SMA taking place around the world. This research will not only improve our understanding of the condition, but will also help to develop effective treatments.

One area of extensive research is the genetics of SMA and the underlying mechanisms that lead to damage of the nerve cells. The UK is a significant contributor to this, with several UK centres involved in clinical trials and international collaborations. This has led to encouraging breakthroughs in developing treatments.

For the latest developments with drug treatments, the science behind them, and what clinical trials and other research is going on, please go to:

[www.smauk.org.uk/treatments-research](http://www.smauk.org.uk/treatments-research)
Resources and support

The International Standards of Care for Spinal Muscular Atrophy (2017) can be read / downloaded from here: www.smauk.org.uk/international-standards-of-care-for-sma

SMA UK

Phone: 01789 267 520
Email: supportservices@smauk.org.uk
Website: www.smauk.org.uk

We provide free information and support to families in the UK affected by SMA. Our outreach workers are able to visit you at home. They offer personalised support and information and are available to answer questions. They can discuss with you the support you and your family can access. Please note, we don’t give medical advice.

Our monthly E-news will keep you informed about developments in services and research, campaigns and surveys, social and fundraising events and other general information and news. Each time we send this, you have the option to unsubscribe. You can opt in to receive this here: www.smauk.org.uk/sign-up-for-mailings

Our Route Maps for SMA have other information about day-to-day life with SMA and signpost to possible sources of support and advice. At the moment they are organised according to Type of SMA. You can find these at: www.routemapforsma.org.uk

We are currently re-organising this information so that it’s more accessible. It will be located on a new part of our website which we will call ‘Living with SMA’. As soon as it’s ready we’ll let people know via our monthly E-news.

Muscular Dystrophy UK

Phone: 0800 652 6352
Website: www.musculardystrophyuk.org

MDUK provide information, support, advocacy services and grants towards specialist equipment for people affected by a range of neuromuscular conditions.
References


We are grateful to the writers and reviewers who assist us in our information production. A list of who this includes may be viewed on our website: www.smauk.org.uk/our-writers-and-reviewers-panel or requested from supportservices@smauk.org.uk.

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