

# The Genetics of 5q Spinal Muscular Atrophy

Many families want to learn more about the genetics that have led to Spinal Muscular Atrophy (SMA) in their family. They want to better understand the condition, what it means for future pregnancies and for other family members, and what genetic treatment options might be available in the future.

This information sheet covers the genetics of 5q SMA which includes childhood onset SMA Types 1, 2 and 3 and adult onset SMA Type 4.

You can always ask your child's medical team to go over any of this information with you. They should be able to provide you with genetic information that applies to your individual situation.

There are other rarer forms of SMA with other genetic causes. Our information sheets about these can be found on our website: [www.smauk.org.uk/rarer-forms-of-sma](http://www.smauk.org.uk/rarer-forms-of-sma)

For more information about the causes and effects of 5q SMA please see:

- 'What is Spinal Muscular Atrophy?'
- 'Symptoms, diagnosis & effects of 5q Spinal Muscular Atrophy'

You can find these at:

[www.smauk.org.uk/about-sma](http://www.smauk.org.uk/about-sma)

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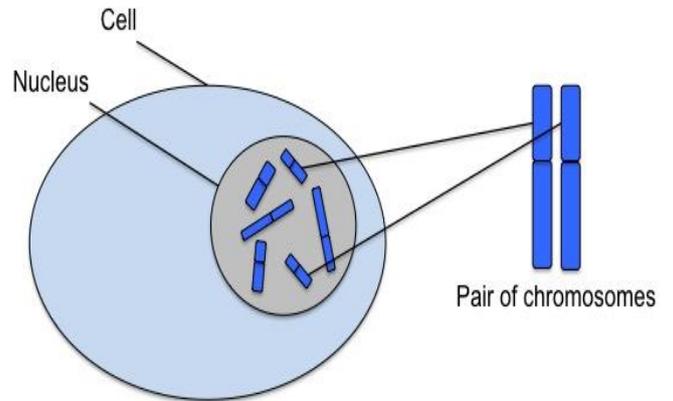
## What are genetic conditions?

Genetic conditions are generally caused by differences or 'faults' in our genes.

Our bodies are made up of many millions of cells. Nearly all cells have a structure called the nucleus, which contains chromosomes.

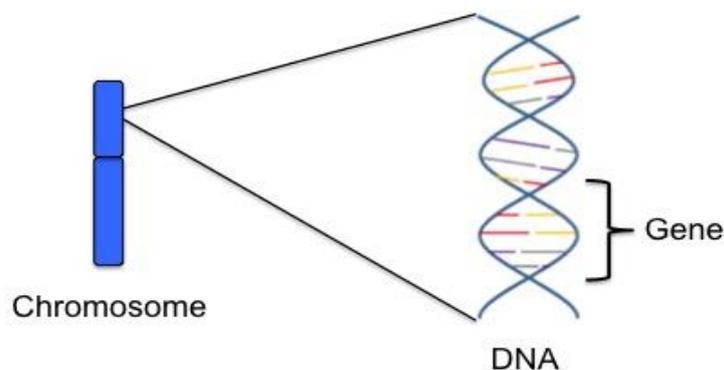
Body cells usually have two copies of each chromosome.

We all have 46 chromosomes in each cell in our body and these are arranged in 23 pairs.



Chromosomes are compact bundles of DNA. (See Box 1 for an explanation of DNA.)

A gene is a specific section of DNA. Genes are packaged into chromosomes.



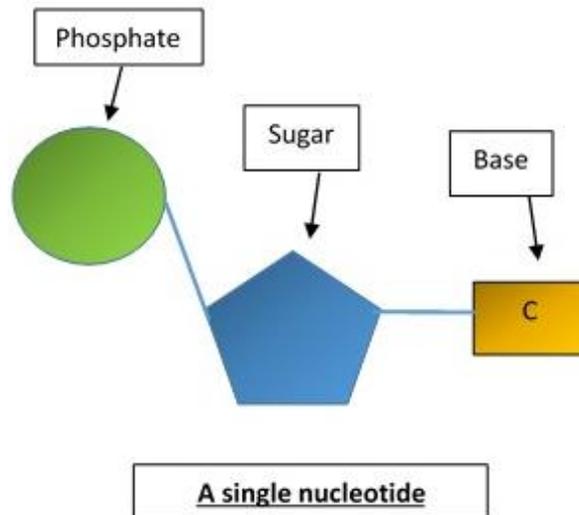
Genes carry the information needed to make proteins. Our cells need protein for their structure, survival and to work correctly. We each have approximately 20,000 different genes making different proteins in our bodies<sup>1-2</sup>. Each protein made by a different gene has its own unique function. The structure of the protein, and therefore its function, is determined by the order in which the base pairs are arranged in that particular gene. Usually, there are two copies of each gene on each chromosome pair: one inherited from each parent.

Sometimes a gene can contain an unusual change or 'fault', known as a mutation. Genetic conditions occur when a mutation within a gene affects how the protein in our bodies is produced and how it works.

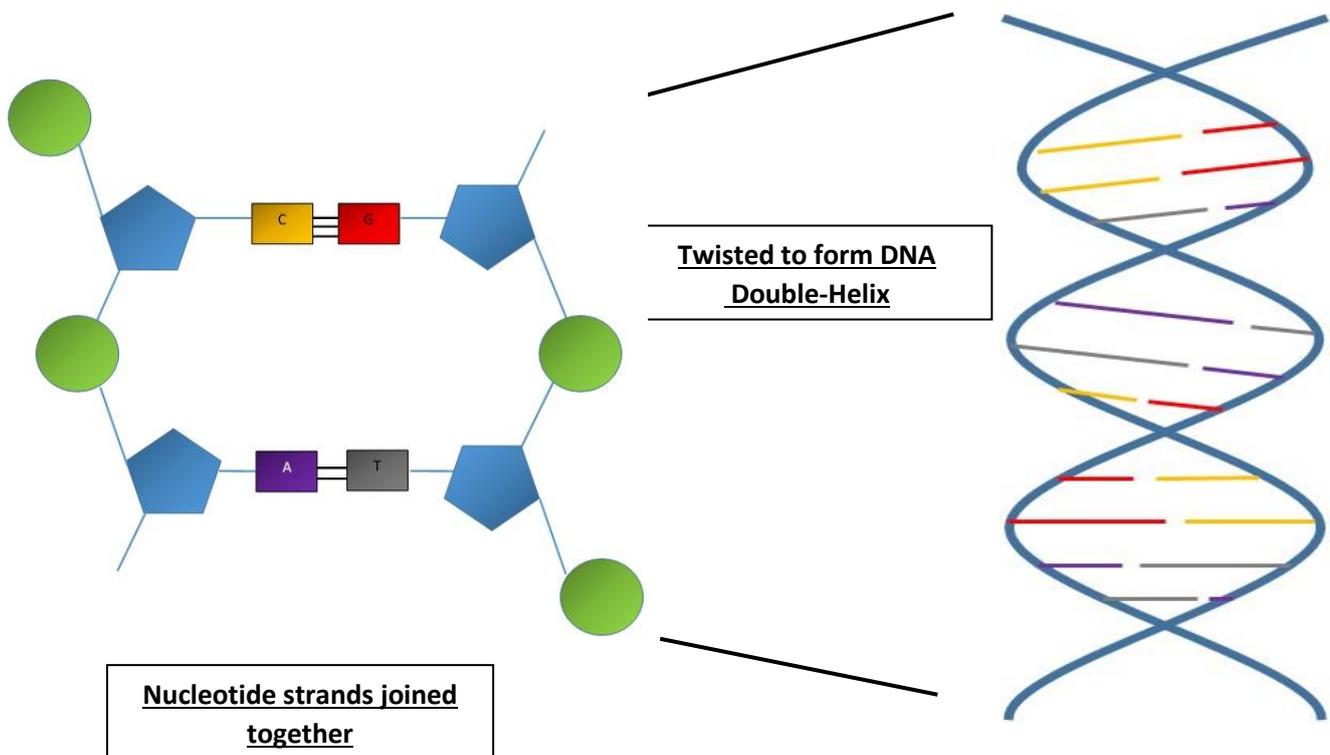
### **Box 1 – an explanation of DNA**

DNA is often described as a recipe book, or a set of instructions, because it contains the information needed for a person to grow and develop.

DNA is made up of lots of nucleotides joined together. Each nucleotide contains a phosphate, a sugar and a base. The phosphate and sugar are always the same but the base varies in each nucleotide. The base can be one of four: adenine (A), guanine (G), cytosine (C), or thymine (T).



These bases pair up: A with T, C with G. The order in which these pairs of bases are arranged affects how the 'recipe book' information is read. The joined base pairs hold the nucleotides together in strands that twist together to form the DNA double-helix shape.



## What genes are involved in 5q SMA?

### ➤ The *SMN1* gene

Most people have two copies of the *SMN1* gene. People with 5q SMA have two faulty copies of the *SMN1* gene. This means they are unable to produce enough SMN protein to have healthy lower motor neurons<sup>4</sup>.

### ➤ The *SMN2* gene

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

*SMN2* has an important single base (nucleotide) difference from *SMN1*. This causes a small chunk of the gene, called **Exon 7**, to be excluded in the majority of SMN protein that the *SMN2* gene makes. It’s estimated that only about 10% of the SMN protein made from *SMN2* is functional<sup>5</sup>.

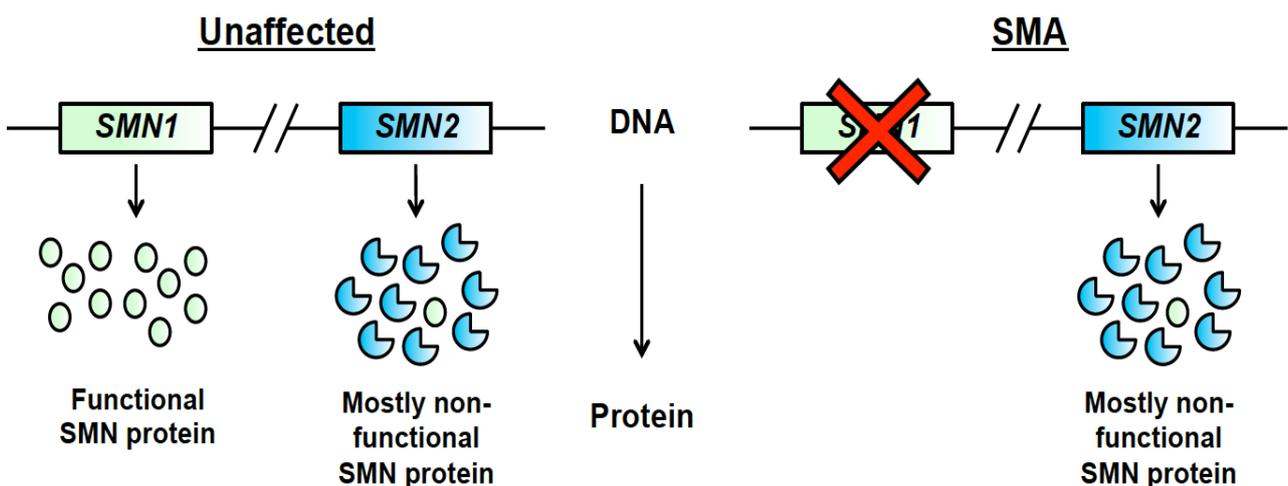


Figure 1. People possess two genes able to produce SMN protein. *SMN1* produces all the functional SMN protein we need and is the gene affected in SMA. *SMN2* only makes a small fraction of functional protein (about 10%). The large majority (about 90%) of protein produced from *SMN2* is lacking an essential part and is consequently non-functional. Figure adapted from Burghes, A.H and Beattie, C.E<sup>6</sup>.

Unlike most genes, the number of copies of *SMN2* on each chromosome can vary from one person to the next<sup>7</sup>.

As the severity of a person’s SMA has been linked to how much SMN protein a person makes<sup>8-10</sup>, there is therefore a broad relationship between the number of *SMN2* copies a person has (“*SMN2* copy number”) and the likely severity of their symptoms. Having more *SMN2* copies is generally

associated with less severe SMA symptoms. However, accurate predictions can't be made about the Type or severity of SMA based on the *SMN2* copy number alone. This is likely to be because other genetic factors also have a modifying influence.

*SMN2* copy number isn't essential for a diagnosis of SMA or for carrier testing. However, as it's often used in clinical trials to group patients to try to identify whether copy number affects the effectiveness of the drug being tested, it's often collected and recorded as part of the diagnosis.

## ➤ Deletion and point mutations

A **deletion** describes a type of mutation or fault when a small section of DNA is missing. When part or all of a gene is missing, it can no longer make healthy protein. Instead, a shorter, often less functional (less useful) protein is made, or in some instances no protein at all.

About 95% of people with 5q SMA have a deletion mutation in both copies of the *SMN1* gene. This is called a **homozygous deletion**.

The other 5% of people with SMA have a **point mutation**. This is when a single base (**nucleotide**) within the DNA is altered. Often, these people will have the more common deletion mutation in one of their copies of *SMN1* and the point mutation in the other copy.

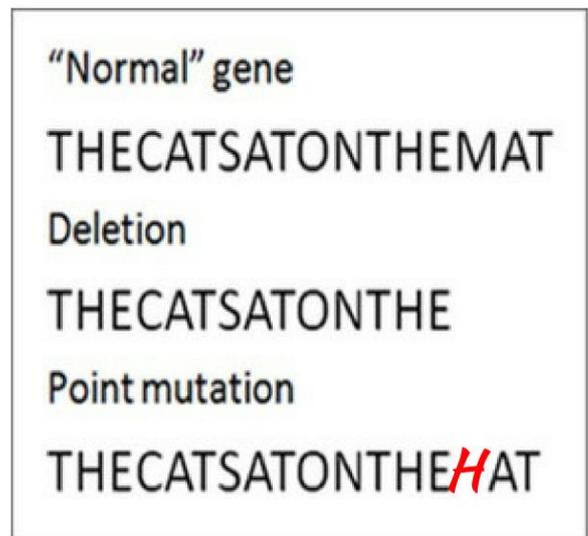


Figure 2. Deletion and Point Mutations. Taken from Skirton, H. and Patch, C. (2009) *Genetics for the Health Sciences*. Oxford: Scion Publishing.

## How are these genes inherited?

People have 23 pairs of chromosomes. 22 of the pairs are non-sex chromosomes, known as autosomes, and which are found in both males and females. The 23rd pair consists of two sex chromosomes, which determine your sex. Females usually have two X chromosomes (XX), and males an X and a Y chromosome (XY).

SMA is an **autosomal recessive condition**. This means that the gene (mutation) causing the condition is located on one of the autosomal chromosomes<sup>3</sup>, and not one of the two sex chromosomes. More specifically, for 5q SMA, the *Survival Motor Neuron 1 (SMN1)* gene is located on the fifth autosomal chromosome, in the region labelled 'q'.

Autosomal conditions affect both males and females equally.

In an autosomal recessive condition like 5q SMA:

- a person will only have SMA if they inherit two faulty copies of the *SMN1* gene
- a person who carries one faulty copy of the gene and one healthy copy won't have the condition but is a carrier. They don't have any symptoms, but the faulty gene can be passed on to their children.

## How will this affect my children?

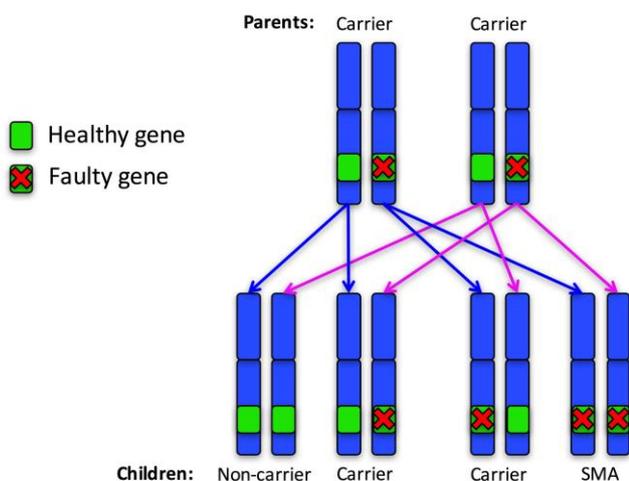
The chances of your children being carriers or having 5q SMA due to the way autosomal recessive genetic conditions are passed on will depend on whether you or your partner have 5q SMA, or are carriers. The chances stay the same for each pregnancy; having one child who has 5q SMA or is a carrier doesn't change the chances for any further children.

Each copy of the gene (healthy or faulty) has the same chance of being passed on. This happens randomly, like the result of a coin toss.

The following diagrams show what the chances are in different families.

For the purpose of the diagrams, a 'non-carrier' means a person who doesn't carry the faulty gene and doesn't have SMA.

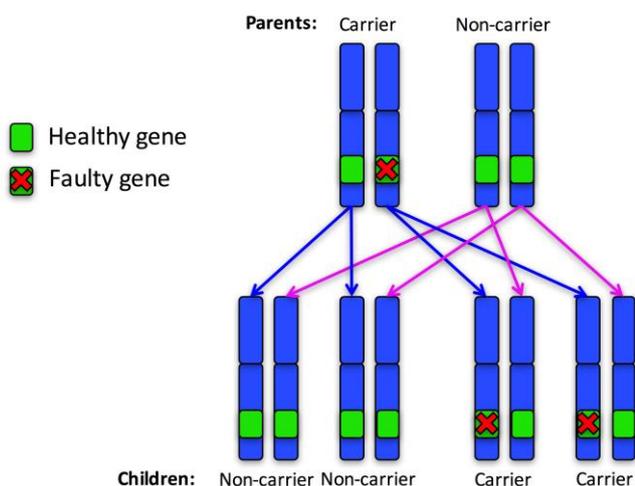
## Autosomal recessive family 1: Both parents are carriers



For each pregnancy, the chances are:

- Child won't have SMA and won't be a carrier: 1 in 4 chance (25%)
- Child won't have SMA but will be a carrier: 2 in 4 chance (50%)
- Child will have SMA: 1 in 4 chance (25%)

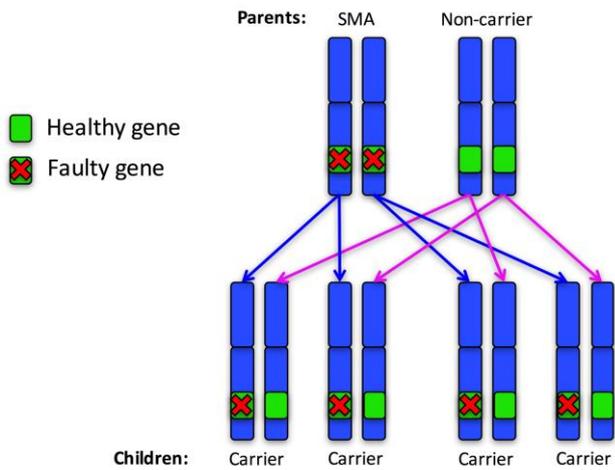
## Autosomal recessive family 2: One parent is a carrier, the other doesn't have SMA and is a non-carrier



For each pregnancy, the chances are:

- Child will have SMA: not possible
- Child won't have SMA and won't be a carrier: 2 in 4 chance (50%)
- Child won't have SMA but will be a carrier: 2 in 4 chance (50%)

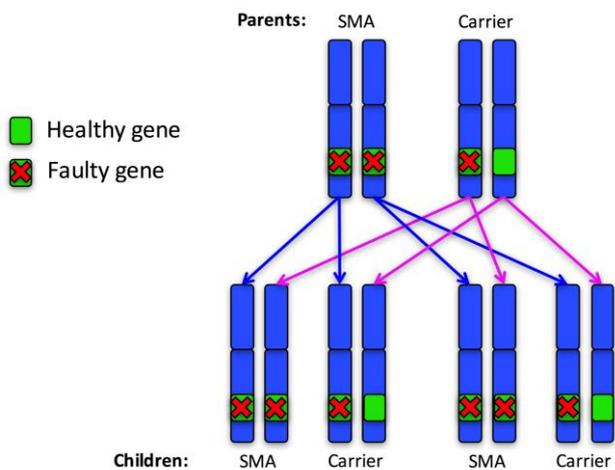
### Autosomal recessive family 3: One parent has SMA, the other doesn't have SMA and is a non-carrier



For each pregnancy, the chances are:

- Child will have SMA: not possible
- Child won't have SMA and won't be a carrier: not possible
- Child won't have SMA but will be a carrier: 4 in 4 chance (100%)

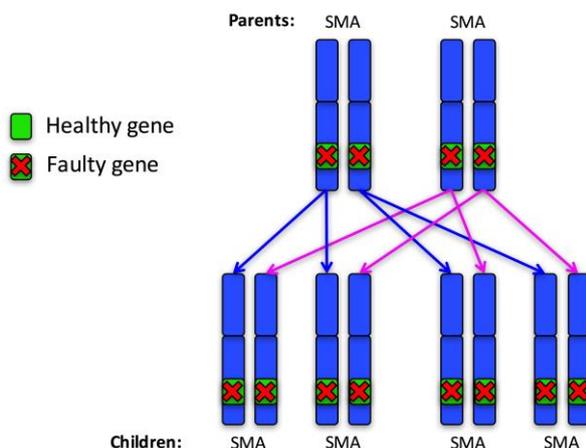
### Autosomal recessive family 4: One parent has SMA, the other is a carrier



For each pregnancy, the chances are:

- Child won't have SMA and won't be a carrier: not possible
- Child will have SMA: 2 in 4 chance (50%)
- Child won't have SMA but will be a carrier: 2 in 4 chance (50%)

### Autosomal recessive family 5: Both parents have SMA



For each pregnancy, the chances are:

- All children will have SMA (100%)

## Can 5q SMA happen in any other way?

### ➤ *De Novo* Mutation

In most cases, mutations in *SMN1* are inherited from a parent who is a carrier. In around 2% of cases of 5q SMA however, the mutation is new in the affected person. This can be due to the mutation occurring for the first time: when a sperm or egg is made; when a sperm fertilises an egg; when cells are dividing after fertilisation. The most likely reason is an error in the making of the egg or sperm cell. This is called a ***de novo or sporadic mutation***. This can have implications for the chance of 5q SMA affecting a future pregnancy, and so emphasises the importance of having genetic counselling specific to your own circumstances.

### Genetic counselling

Genetic counselling is with a healthcare professional who has expert training in genetics. They'll aim to explain results from your genetic testing in an easily understandable way, and answer any questions you might have about the genetic aspects of the diagnosis.

If you or your child have recently been diagnosed with 5q SMA you should be offered a referral to a clinical genetics service for genetic counselling. You can also request a referral from your General Practitioner (G.P.).

Common issues to discuss in genetic counselling might include implications or options for a future pregnancy, and whether there is a need to discuss the diagnosis with other family members, who might wish to seek genetic counselling.

### Frequently asked questions

***Q. We don't have 5q SMA ourselves, but have had one child with SMA. How can we find out if our next child will also have SMA?***

**A:** It's most likely that you and your partner are both carriers of the faulty gene that causes 5q SMA. A referral to a Clinical Genetics Service for genetic counselling is important so that you can get advice specific to your own circumstances and consider your future options (see below). If you have another pregnancy together, the chance that your next child will have 5q SMA will be 1 in 4 (25%), as shown in Family 1 diagram. The copy of each gene inherited from each parent is random and can't be predicted. Some couples who are both carriers decide to take that chance, while others want to consider alternative options when having children.

Our information sheet '**Future Options in Pregnancy**' tells you more about these options. You can also discuss what's possible with the healthcare professionals involved who should be able to help you make this very personal decision:

**[www.smauk.org.uk/future-options-in-pregnancy](http://www.smauk.org.uk/future-options-in-pregnancy)**

***Q. I'm a carrier, should I suggest that other family members get tested?***

**A:** As genes are inherited from parents, and passed on from generation to generation, you share many of your genes with members of your extended family. It's therefore possible that your blood relations may also be carriers of the same faulty gene. You might want to tell your relations about this so that they have the option of asking for genetic counselling to obtain more information, and to have carrier testing if they wish to do so. This can be particularly relevant if they are considering a pregnancy in the future.

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***Q: My partner is a carrier of SMA and we are thinking of having children. Where can I get tested to see if I'm a carrier too?***

**A:** Ask your G.P. to refer you to your regional clinical genetics centre. The main genetics clinics are usually in large cities, but outreach clinics may be held in other smaller hospitals across the region.

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***Q: In a family with 5q SMA, who will be able to have genetic testing?***

**A:** Staff at your regional genetics centre can give you specific advice about who might need to be tested. Close family members will be seen first to identify who might be carriers. The staff might work with you to draw a family tree.

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***Q: There's a history of 5q SMA in my family. When should my partner and I have genetic testing?***

**A:** Genetic counselling before pregnancy will give you and your partner more time to think about genetic testing and the possibly difficult decisions this can raise. But, you can still seek genetic counselling if you're already pregnant – just make sure to say you are and ask to be seen urgently.

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***Q: What's the waiting time for a genetics appointment?***

**A:** You'll usually be offered an appointment within 18 weeks.

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***Q: A member of my family has been diagnosed with 5q SMA. I'm pregnant and I don't know if I'm a carrier. How do I get a quick referral to genetic services?***

**A:** Contact your G.P. to ask for an urgent genetic counselling referral. If this isn't possible you can contact your local genetic service directly (there is a list of centres on the British Society for Genetic Medicine website: [www.bsgm.org.uk](http://www.bsgm.org.uk)). You and your partner may be offered testing.

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***Q: I've no family history of 5q SMA, can I still be tested?***

**A:** Genetic testing isn't usually available on the NHS to people with no personal family history or connection to 5q SMA.

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***Q: Can I have a genetic test for 5q SMA without having genetic counselling?***

**A:** This is generally not possible via the NHS. Genetic counselling will give you the most up-to-date and accurate information enabling you to make informed choices about the options available to you.

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***Q: How long will it take to get the results of a genetic test for 5q SMA?***

**A:** The test result is usually available within 2 – 4 weeks, but can sometimes take longer. Testing can be completed more urgently in certain situations (for example, in pregnancy or a very unwell baby).

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***Q: I've been tested for 5q SMA and the test has come back negative but my consultant still thinks I have SMA. Is this possible?***

**A:** In a small number of cases the genetic basis is more complex and further genetic and / or other testing may be necessary. Your doctor will advise you depending on your symptoms and the tests you've had so far.

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***Q: My son has SMA symptoms but the test has come back negative. Is it possible that he has SMA?***

**A:** Routine testing for 5q SMA will confirm the diagnosis in the majority of people but sometimes further genetic and / or other testing may be needed. Your doctor will advise you depending on your son's symptoms and the tests he's had so far. This may include investigations for other conditions that can present in a similar way to SMA.

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***Q: My daughter's been diagnosed with 5q SMA. I'm worried that her brother and sister might develop 5q SMA too. Should they be tested?***

**A:** It's important for you to discuss this with the healthcare professionals involved and your family. Your decision may be influenced by the Type of 5q SMA your daughter has and whether you already have worries about the health of your other children.

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***Q: My sister's son's been diagnosed with 5q SMA. I have a 4-year-old daughter and I'm worried that she might develop SMA too. Should I have her tested?***

**A:** You could request carrier testing at a genetic centre to see whether you're a carrier of 5q SMA. Once you have your own result you can discuss with your healthcare professionals and your family whether to test your daughter. Genetic centres don't always offer carrier testing in childhood as it removes the child's right to make an informed decision when they're older.

## Further information and resources

### *More information about Genetics and Genetic Testing:*

**Genetic Alliance UK**

Phone: 0207 704 3141

[www.geneticalliance.org.uk/information](http://www.geneticalliance.org.uk/information)

### *Clinical trials information:*

**How Clinical Trials Work**

[www.smauk.org.uk/clinical-trials](http://www.smauk.org.uk/clinical-trials)

**Current clinical trials in SMA:**

[www.clinicaltrials.gov/](http://www.clinicaltrials.gov/)

**The UK SMA Patient Registry**

Phone: 0191 241 8604

[www.treat-nmd.org.uk/registry](http://www.treat-nmd.org.uk/registry)

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

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