The Inheritance Patterns of Some Rarer Forms of Spinal Muscular Atrophy

This information sheet explains why there are different inheritance patterns for different genetic conditions and what this pattern is for these rarer forms of SMA:

➢ Distal Spinal Muscular Atrophy type V (DSMA-V)

➢ Spinal and Bulbar Muscular Atrophy (SBMA) - also known as Kennedy’s Disease

➢ Spinal Muscular Atrophy with Lower Extremity Predominance (SMA-LED)

➢ Spinal Muscular Atrophy with Progressive Myoclonic Epilepsy (SMA-PME)

➢ Spinal Muscular Atrophy with Respiratory Distress 1 (SMARD1)

➢ X-linked Infantile Spinal Muscular Atrophy

Includes
What are genetic conditions?

Autosomal dominant inheritance

Autosomal recessive inheritance

X-linked recessive inheritance

Other genetic changes

Genetic counselling

Spinal Muscular Atrophy UK
Help for today, hope for tomorrow

Health & care information you can trust
The Information Standard Certified Member
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\textsuperscript{1-2}. 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.
**Autosomal dominant conditions**

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

Conditions described as autosomal are those in which the faulty gene (mutation) that causes the condition is located on one of the autosomes, and not on one of the two sex chromosomes. Autosomal conditions affect both males and females.

Autosomal dominance is the inheritance pattern most often seen in:

- Distal Spinal Muscular Atrophy Type V (DSMA-V)
- Spinal Muscular Atrophy with Lower Extremity Predominance (SMA-LED)

Having a single faulty copy of a gene is enough to cause the condition, even though a healthy copy of the gene is also present. This means that parents with the condition can pass it directly to their children.

The following two diagrams show what the chances are of parents passing on their rare form of SMA to their children if the inheritance pattern is **autosomal dominant**. For each pregnancy, these chances are the same.
Autosomal dominant family 1: one parent has SMA and the other doesn’t

For each pregnancy, the chances are:

➢ Child will have SMA: 2 in 4 chance (50%)
➢ Child won’t have SMA: 2 in 4 chance (50%)

Autosomal dominant family 2: both parents have SMA

If both parents have SMA and their child inherits two dominant genes, one from each parent, this can cause a very severe form of SMA and possibly other difficulties for the child as well.

For each pregnancy, the chances are:

➢ Child will have SMA: 3 in 4 chance (75%)
➢ Child won’t have SMA: 1 in 4 chance (25%)
Autosomal recessive conditions

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

Conditions described as autosomal are those in which the faulty gene (mutation) that causes the condition is located on one of the autosomes, and not on one of the two sex chromosomes. Autosomal conditions affect both males and females.

This is the inheritance pattern most often seen in:

- Spinal Muscular Atrophy with Progressive Myoclonic Epilepsy (SMA-PME)
- Spinal Muscular Atrophy with Respiratory Distress (SMARD).

In an autosomal recessive pattern of inheritance, both copies of the gene must be faulty for the condition to occur. People who have one healthy copy and one faulty copy of a gene are called carriers. They don’t usually have any symptoms themselves, but the faulty gene can be passed on to their children. The chances of children being carriers or having a rare form of SMA will depend on whether their parents have the condition or are carriers.

The following five diagrams show what the chances are of parents passing on their rare form of SMA to their children if the inheritance pattern is autosomal recessive. For each pregnancy, these chances are the same. For the purpose of the diagrams, a ‘non-carrier’ means a person who doesn’t carry the faulty gene and doesn’t have a rare form of SMA.
Autosomal recessive family 1: both parents are carriers

For each pregnancy, the chances are:

➢ Child will have SMA: 1 in 4 chance (25%)
➢ Child won’t have SMA but will be a carrier: 2 in 4 chance (50%)
➢ Child won’t have SMA and is not a carrier: 1 in 4 chance (25%)

Autosomal recessive family 2: one parent is a carrier, the other doesn’t have SMA & is a non-carrier

For each pregnancy, the chances are:

➢ Child will have SMA: not possible (0%)
➢ Child won’t have SMA but will be a carrier: 2 in 4 chance (50%)
➢ Child won’t have SMA and won’t 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 (0%)
➢ Child won’t have SMA and won’t be a carrier: not possible (0%)
➢ 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 (0%)
➢ Child will have SMA: 2 in 4 chance (50%)
➢ Child won’t have SMA but is a carrier: 2 in 4 chance (50%)
Autosomal recessive family 5: both parents have SMA

For each pregnancy, the chances are:

➢ All the children will have SMA: 4 in 4 chance (100%)
X-linked recessive conditions

In an X-linked recessive pattern of inheritance, the faulty gene is on the X chromosome, but isn’t found on the shorter, male-specific Y chromosome. Males only have one X chromosome and therefore only one copy of the gene. This means that if they have one faulty copy then they have no other healthy copy. Males are therefore much more frequently affected by X-linked disorders than females.

Females with one healthy copy and one faulty copy of the gene don’t usually have any symptoms, although some have a very mild form of the condition. However, the faulty gene can be passed on to their children. As a result of this they are called carriers.

This is the inheritance pattern most often seen in:

- Spinal and Bulbar Muscular Atrophy (SBMA) – also known as Kennedy’s Disease
- X-linked Infantile Spinal Muscular Atrophy.

The chances of children being carriers or having a rare form of SMA will depend on whether their parents have the condition or are carriers. The chances stay the same for each pregnancy that a couple has.

The following five diagrams show what the chances are of parents passing on their rare form of SMA to their children if the inheritance pattern is X-linked recessive. For each pregnancy, these chances are the same. For the purpose of the diagrams, a ‘non-carrier’ means a person who doesn’t carry the faulty gene and doesn’t have a rare form of SMA.
X-linked recessive family 1:
the mother is a carrier, the father isn’t a carrier and doesn’t have SMA

For each pregnancy, the chances are:

- Daughters will have a 1 in 2 chance (50%) of not having SMA and not being a carrier
- Sons will have a 1 in 2 chance (50%) of not having SMA and not being a carrier
- Daughters will have a 1 in 2 chance (50%) of being a carrier
- Sons will have a 1 in 2 chance (50%) of having SMA

X-linked recessive family 2:
the mother is a carrier, the father has SMA

For each pregnancy, the chances are:

- Daughters will have a 1 in 2 chance (50%) of being a carrier
- Sons will have a 1 in 2 chance of not having SMA and not being a carrier
- Daughters will have a 1 in 2 chance (50%) of having SMA
- Sons will have a 1 in 2 chance (50%) of having SMA
X-linked recessive family 3:
the mother doesn’t have SMA and isn’t a carrier, the father has SMA

For each pregnancy, the chances are:
➢ Daughters will have a 2 in 2 chance (100%) of being a carrier
➢ Sons will have a 2 in 2 chance (100%) of not having SMA and not being a carrier

X-linked recessive family 4:
the mother has SMA, the father doesn’t have SMA and isn’t a carrier

For each pregnancy, the chances are:
➢ Daughters will have a 2 in 2 chance (100%) of being a carrier
➢ Sons will have a 2 in 2 chance (100%) of having SMA
X-linked recessive family 5: both parents have SMA

For each pregnancy, the chances are:

➢ All the children will have SMA
Is SMA always inherited from one or both parents?

In most cases of SMA, the gene change or changes are inherited from one or both parents, who may themselves have no symptoms of SMA (particularly in autosomal recessive or X-linked recessive forms). In rarer cases however, the genetic change responsible for SMA may not be present in either parent. In other words, it may be a new gene change in the affected individual. 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 due to an error in the making of the egg or sperm cell. This is called a de novo or sporadic mutation. The de novo mutation may only have been present in a single egg or sperm cell that went on to make the affected person, in which case the chance of the same couple having a future pregnancy affected by SMA would be low. However, there remains a chance that more than one egg or sperm cell could carry the gene change - a situation called gonadal mosaicism.

The genetics of any form of SMA is complex. Also, for a small number of people, their SMA genetics aren’t clear. For example, for a small number of people, a diagnosis of ‘adult onset SMA’ is made even though the genetic cause of their SMA symptoms hasn’t been conclusive.

What is genetic counselling?

Genetic counselling is with a healthcare professional who has expert training in genetics. They will 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 a rarer form of SMA, you should be offered a referral for genetic counselling. You can also request a referral from your General Practitioner (G.P.).
Further information and resources

More Information about Genetics and Genetic Testing:

Genetic Alliance UK
Phone: 0207 704 3141
Website: www.geneticalliance.org.uk/information

Support:

SMA UK
Phone: 01789 267520
Email: supportservices@smauk.org.uk
Website: www.smauk.org.uk

Provides information and support for anyone in the UK affected by any form of SMA.

Version: 1.1
Author: SMA UK Information Production Team
Published: September 2018
Last updated: March 2019
Next full review due: September 2021

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

Whilst every effort is made to ensure that the information in this publication is complete, correct and up to date, this cannot be guaranteed and Spinal Muscular Atrophy UK shall not be liable whatsoever for any damages incurred as a result of its use. SMA UK does not necessarily endorse the services provided by the organisations listed in our information sheets.

If you have any feedback about this information, please do let us know at supportservices@smauk.org.uk