There are different types of variants

Genes that code for proteins

The majority of genes identified to date (2019) as causing single gene disorders associated with learning disabilities and developmental delay, code for proteins. This type of gene can be described as carrying the instructions to make a functional 3D structure (a protein) that carries out specific tasks within our body. A pathogenic variant in a protein coding gene can result in no protein being made, or a smaller (truncated protein) or altered protein being produced. For genes located on chromosomes 1 to 22 and the X chromosome in females (XX), there is usually a second unaffected copy of the gene on the other paired chromosome that should produce the expected protein.

Loss of function (LOF) variants

Some variants prevent the formation of a functional protein, these are called loss of function (LOF) variants.

Altered function variants

Some variants cause the gene to produce a protein that functions, but not as expected, the proteins have an altered function. Such proteins may behave in different ways and cause different symptoms depending on how their function has been changed.

Different gene variants can have different effects on a protein.

A **missense variant** is like a 'spelling mistake' in the genetic code that can alter the way a protein is made.

A **nonsense variant** causes a 'full stop' to appear in the genetic code, meaning the part of the protein coded for after the stop signal will not be made.

A **frameshift variant** causes a 'shift' in the genetic code so the information is misread and the protein is not made properly.

RNA genes

Not all genes code for proteins. When a protein is made, DNA transfers its information to a similar structure called RNA, which is then used to make the protein. Some DNA sequences however code for RNAs that have distinct functions and do not code for proteins. Variants in these non-coding RNAs have been identified but are less common.

Variants in non-coding DNA

Some sequences of DNA do not code for RNA or proteins but have other important functions. Many of these sequences are used to control the activity of genes, for example to switch them 'on and off'. Variants in these sequences are not easy to identify but are known to exist.

Is there a cure?

The effect of a single gene disorder varies between individuals and is dependent on which gene has been altered as well as how it has been altered and when the alteration occurred. Advances in genetics are enabling the identification of new disorder causing genes and variations but identifying a cure is more complicated. Usually this is because the effects take place during early fetal development. Immediate cures are not available but symptom specific treatments as well as diet and lifestyle modifications may help each child reach their full potential.

Inform Network Support

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Single Gene Disorders

learning disability & developmental delay

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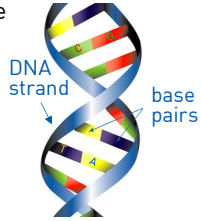
What are genes and what is DNA?



Genes are the 'instructions' that our bodies use for many functions including the control of growth and development. We have approximately 23,000 genes in total, and each has a distinct role in different parts of the body at different stages of development.

Genes are made from a complex structure called DNA. DNA, and therefore genes, can be described as a sequence of letters but unlike an alphabet, the sequence (or code) only uses 4 letters (G, A, T, C).

More technically, a single sequence or 'strand' of DNA is made from building blocks (called nucleotides), each containing one of four bases; A (adenine), T (thymine), G (guanine) or C (cytosine). DNA exists as a double stranded structure (called a double helix, as shown in the image above). Two strands of DNA coil around each other and are held together by bonds between the base pairs; A always pairs with T and G always pairs with C.

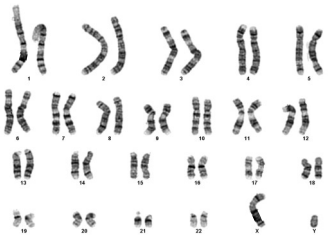
DNA sequences are incredibly long and include all the information for the thousands of genes included in our 'genome' (our complete set of genetic material). However, they need to fit inside the microscopic cells that make up our bodies. Therefore, DNA is tightly compacted into organised structures called chromosomes.

Chromosomes

Most cells in our body have 23 pairs of chromosomes, so a total of 46. Eggs and sperm, however, have a single copy of each chromosome pair, so that when these cells join together at conception, the chromosomes pair up to make a total of 46.

There are 22 chromosomes called autosomes, numbered 1-22 roughly according to decreasing size, and two sex chromosomes, X and Y, that determine the characteristics associated with biological sex. Males usually have one X chromosome and one Y chromosome (XY), and females usually have two X chromosomes (XX).

If cells are prepared in a specific way, chromosomes can be stained and viewed under a microscope. The size of each chromosome varies as does the number of genes on each chromosome (from less than a hundred to a few thousand).



Chromosomes pairs 1-22, X and Y (male)

What are single gene disorders?

A single gene disorder occurs when a change to a single gene sequence (meaning a change of one or more of the bases G, A, T or C), alters a gene in such a way that health and development are affected. The change in sequence is known as a variant and is described as pathogenic, meaning 'disease causing' if a disorder occurs. Sometimes it's difficult to establish if a variant is associated with symptoms observed in some people, the variant is then named a 'variant of unknown significance' (VUS) or likely pathogenic.

Where do single gene variants come from?

We all carry variants in our DNA, they occur when errors are made as our chromosomes are copied when new cells are formed. It has been estimated that each of us has approximately 3-4 million DNA variants that we have accumulated during evolution, most of which have little or no effect (these are called benign variants). It has also been estimated that each child has approximately 75 new variants that they did not inherit from a parent.

De novo variants

When a variant is described as *de novo*, it means that the DNA variant has occurred as a new event in a child and is not present in either parent. This is confirmed by testing the DNA in parent's blood samples and finding neither has the same genetic change as their child. *De novo* variants arise in either sperm or eggs and every child will have many, but most are benign (have no effect) since they do not damage a gene. When a *de novo* variant disrupts the correct functioning of an important gene, then a genetic condition is diagnosed.

Inherited variants

Some single gene variants can be inherited from unaffected or mildly affected parents. The severity of symptoms will determine the possibility of having children and passing on the altered gene.

It is not fully understood why some genetic variants can cause symptoms in a child but be inherited from healthy or mildly affected parents, or why siblings with the same genetic variant can have a difference in symptom severity. Possible explanations are numerous and the complex and varied genetic background of each individual may play a role.

For some variants, the variable symptoms may be explained by 'reduced or incomplete penetrance' meaning not everyone who has the variant will have symptoms. Another common explanation is 'variable expressivity' which means symptoms can vary between people with the same variant.

Single gene variants on chromosomes 1 to 22

Chromosomes 1-22 are known as autosomes. If a single gene disorder is referred to as autosomal it means that the gene can be found on one of these chromosomes. If a single gene disorder is referred to as dominant it means that symptoms will be seen if only one of the two gene copies is altered. A recessive disorder requires both gene copies to be altered for symptoms to be seen.

Single gene variants on chromosome X or Y

Genes located on the X chromosome are commonly referred to as X-linked. X-linked disorders are also identified as dominant or recessive. If a variant causes significant symptoms in a female, it is described as dominant. If a male shows significant symptoms but female family members do not, it is described as recessive.

Girls and women usually have two X chromosomes; boys and men usually have an X and a Y chromosome. If a variant is located on an X chromosome, the outcome can be quite different for males (XY) since they do not have a second functional X chromosome to compensate for any altered or loss of gene function. Females (XX) do have another X chromosome, and it is more common for females to have no outcome, or a milder outcome with an X-linked disorder compared to males. However, one X chromosome is 'switched off' in females so this is not always the case, please read our X-inactivation guide for further information.

Y-linked disorders are caused by mutations on the Y chromosome, they are incredibly rare, and commonly cause infertility. The Y chromosome is passed on from father to son, girls and women do not have a Y chromosome.

Mosaicism

Germline mosaicism

Very rarely, parents are identified as not having the variant found in their child when DNA from a blood test is analysed, but they actually have a few egg or sperm cells that carry the genetic change. This is called germline mosaicism and it means that parents can have more than one child with the same genetic disorder even if their blood test is 'normal'.

Somatic mosaicism

Somatic cells are the cells that form our body. Somatic mosaicism for a gene variant means that some cells in the body will contain the variant and some will not, this is because the variant occurred during fetal development rather than within an egg or sperm. Somatic mosaicism can result in less severe symptoms but predicting an outcome is complicated since it's difficult to detect all of the parts of the body involved.