Understanding Chromosome & Gene Disorders

Autosomal Recessive Single Gene Disorders

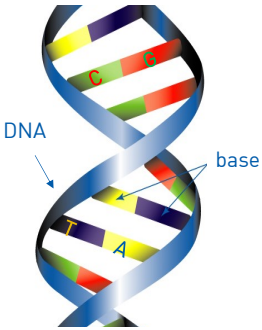
rarechromo.org

This guide aims to provide detailed information about autosomal recessive (AR) genetic disorders associated with developmental delay and learning disability. *Unique* also provides an introductory quick-read guide to AR inheritance.

In order to better understand the nature of autosomal recessive disorders it's important to have a bit of background knowledge about chromosomes, DNA, genes and proteins.

What are genes and what is DNA?

Genes are the instructions that our bodies use for many functions including the control of growth, development and function. 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 and 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.

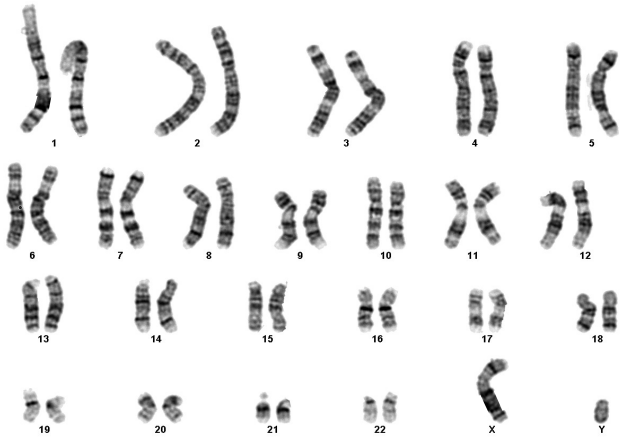
DNA sequences are incredibly long and include all the information for the thousands of genes included in our genome (our complete set of genetic material). However, they need to fit inside the microscopic cells that make up our bodies. Therefore, DNA is tightly compacted into organised structures called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



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

The size of each chromosome varies as does the number of genes located in each (from less than a hundred to a few thousand).

What are single gene disorders?

A single gene disorder occurs when a change to a specific gene sequence (meaning a change of one or more of the bases G, A, T or C), alters the 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 it is found to be associated with a genetic condition (also called a disorder). Sometimes it's difficult to establish if a variant is causing symptoms observed in some people, the variant is then named a 'variant of unknown significance' (VUS) until further evidence is found that can help clarify the variants possible effects.

What are autosomal recessive disorders?

Chromosomes 1-22 are known as autosomes. If a single gene disorder is referred to as autosomal it means that the gene responsible for the disorder can be found on one of these chromosomes. If the disorder is classified as autosomal recessive it means that both gene copies must be altered for symptoms and features to be seen. If only one gene copy is altered, the person with the variant is called a carrier.

Chromosomes X and Y are not autosomes and so are not involved with autosomal recessive gene disorders.

Where do single gene variants come from?

We all carry variants in our DNA, they occur when changes are incorporated into DNA sequences when our chromosomes are copied as new cells are formed. It has been estimated that each of us has about 3-4 million DNA variants that we have accumulated during evolution, most of which have little or no effect (these are called benign variants). Variants that are passed on by our parents are called inherited variants. It has also been estimated that each child has approximately 75 new variants that they did not inherit from a parent, these are known as *de novo* variants.

Inherited variants

Single gene variants can be inherited from unaffected or affected parents. For autosomal recessive disorders, it is possible for each parent to pass on an altered copy of the gene. This situation is more common in families where parents are biologically related or in isolated populations where there is a 'founder' variant that has been passed on to many people in the same population. Parents who carry an autosomal recessive variant on one copy of a pair of genes are called carriers. Carriers do not usually have any symptoms or features associated with the genetic change; they are commonly unaware of it's existence. In extremely rare situations, one parent may have mosaicism (see page 5) or the second variant may occur by chance (it may be *de novo*) in the child.

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 change the function of a gene.

Compound heterozygosity

This is where children and adults are identified as having a recessive genetic variant in both copies of a particular gene, but the genetic changes are different.

Some individuals may carry a gene variant in one copy of a gene and the other copy may be affected in a different way, such as a different change in the code, or the gene being partially or fully absent due to a deletion or altered due to a chromosomal rearrangement or duplication.

It is also possible for children to inherit both copies of the same gene from one parent when both copies of an entire chromosome, or part of a chromosome, are passed on by one parent and no copy is passed on by the other; this is known as uniparental disomy (UPD). Unique provides separate quick read guides to UPD; deletions and microdeletions; duplications and microduplications.

There are many different types of variants

Genes that code for proteins

The majority of genes identified to date (2022) as causing single gene disorders associated with developmental delay and learning disabilities, code for proteins. Genes are made from long sequences of DNA bases A, G, T and C that code for long sequences of amino acids that form proteins. Amino acid sequences bend and fold into functional three dimensional proteins that carry out a multitude of complex and specific tasks within our body.

The coding information of genes uses a triple base system to specify which amino acids to use during the construct a protein. For example, the base sequence CTA codes for an amino acid called Leucine, whereas the base sequence CCA codes for an amino acid called proline. It's easy to see how a small DNA base change can alter the amino acid in a protein. Since proteins are highly complex structures, the smallest of changes can seriously affect their form and function.

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 autosomal recessive disorders, there is no fully functional gene copy or protein to compensate for loss or altered function since both gene copies are affected.

■ Loss of function (LOF) variants

Variants that prevent the formation of a functional protein are called loss of function (LOF) variants.

■ Altered function variants

Altered function variants cause the gene to produce a protein that functions, but not as expected. 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** causes a change in one of the letters of the genetic code that alters which amino acid is selected. The addition of an incorrect amino acid can affect the function of the resulting protein. If we liken this to changing a letter in written instructions, we can see how 'make some rice' would provide different instructions to 'make some mice'.

A **nonsense variant** causes a 'full stop' to appear in the genetic code and amino acids are not added to the amino acid sequence after that point. This means the resulting protein will be shorter than expected and it's function will be altered or lost. If we liken this to a full stop being introduced into the middle of a written instruction, 'make some rice' could be changed to 'make some.'

A **frameshift variant** causes a 'shift' in the genetic code so the information is misread and the protein is not made as expected. Frame shifts occur when one or more bases in the DNA sequence are deleted or added. The code becomes out of sync and the wrong amino acids are selected to make the protein. This means the resulting protein will not function or may function differently. If we liken this to written instructions, removing the 's' from 'make some rice' could change the instructions to 'make omer ice '.

Not everyone with the same genetic condition is affected in the same way

Doctors and scientists call this variable expressivity and reduced penetrance. Different individuals with the same or similar genetic variant may have variable symptoms. There are lots of explanations for this and the complex and varied genetic background of each individual may play a role. Some variants may have variable expressivity which means symptoms can vary between people with the same variant, and reduced or incomplete penetrance which means not everyone with the same variant will have the same symptoms. Unique provides a separate guide to variable expressivity and reduced penetrance.

Mosaicism

The word mosaicism is used in genetics to describe when not all the cells in a person's body carry a genetic change. There are two basic types of mosacism as described below.

■ Germline (gonadal) mosaicism

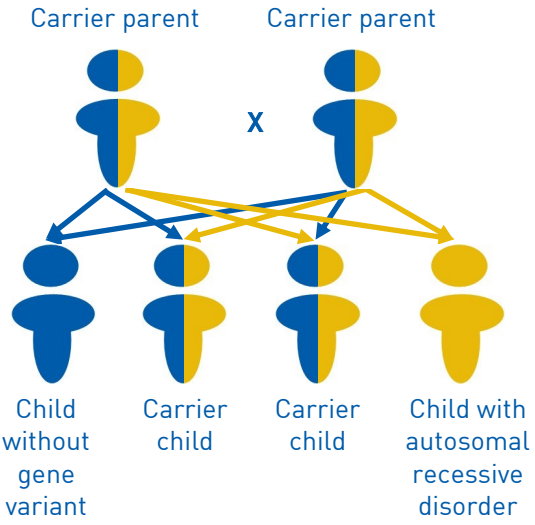
Gondal cells are the cells that make eggs and sperm. Very rarely, parents are identified as not having the genetic variant found in their child, when DNA from a blood test is analysed, but they actually have a few egg or sperm cells that carry the genetic variant. This is called germline or gonadal mosaicism and it means that parents can have more than one child with the same genetic change, even if their blood test does not show that they are carriers for the genetic variant. It is extremely rare but children have been found to have a change to one copy of a gene (either inherited or *de novo*) and the other copy has a variant that is inherited due to germline mosaicism so it initially appears to not be inherited. We cannot test all the cells that produce eggs and sperm in parents since it would make them infertile, so the chance of having germline mosaicism is estimated when a genetic variant appears to have arisen *de novo*.

■ 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 in autosomal recessive disorders is possible but not commonly reported and is complicated by the fact that it's difficult to detect all of the parts of the body involved. If this is suspected in a family then a consultant geneticist or genetic counsellor can explain in more detail.

Can it happen again?

The chance of having another child affected by a rare autosomal recessive gene disorder depends on the genetic code of the parents. If both parents carry the gene variant, theoretically one child in four would have the associated disorder, two would be unaffected carriers and one would not have the gene change. This chance resets for each pregnancy. A clinical geneticist or genetic counsellor can provide more specific advice for each family.



Is there a cure?

The effects of single gene autosomal recessive disorders vary between individuals and are dependent on which gene has been altered as well as how it has been altered and when the alteration(s) occurred. Advances in genetics are enabling the identification of new genes that, if altered, can cause a particular condition but identifying a cure is more complicated. Whilst we cannot currently change our genetic code, symptom specific treatments as well as diet and lifestyle modifications can help each child reach their full potential.

Inform Network Support

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Understanding Chromosome & Gene Disorders

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Unique mentions other organisations' message boards and websites to help families looking for information. This does not imply that we endorse their content or have any responsibility for it.

This information guide is not a substitute for personal medical advice. Families should consult a medically qualified clinician in all matters relating to genetic diagnosis, management and health. Information on genetic changes is a very fast-moving field and while the information in this guide is believed to be the best available at the time of publication, some facts may later change. *Unique* does its best to keep abreast of changing information and to review its published guides as needed. This guide was compiled by Unique (AP), Makaela Jacobs-Pearson, Genetic Counsellor and Dr Emma Baple, Consultant in Clinical Genetics, Royal Devon and Exeter NHS foundation trust.

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