

How did this happen?

There are a number of different ways that UPD can occur. It can happen due to a random event during the formation of egg and sperm cells, or after conception (when an egg is fertilised by a sperm).

Formation of eggs and sperm

Eggs and sperm are usually produced with a single copy of each chromosome. Occasionally an egg or sperm are produced that are missing a chromosome or have an extra copy of a chromosome (or part of a chromosome). The extra chromosome copy can be identical to an existing chromosome or it can be slightly different since we inherit slightly different chromosomes from each parent. When chromosome pairs come together during the formation of eggs and sperm, they exchange genetic material and therefore are not an exact replica of either grandparental chromosome but a combination of both.

Conception

There are different ways that UPD can occur.

Trisomic rescue: Sometimes an egg or sperm with an extra copy of a chromosome joins with an egg or sperm with a single copy of that chromosome. This results in the presence of three copies of a specific chromosome. If one chromosome is then lost, the expected number of chromosomes is restored. UPD occurs if both the remaining chromosomes come from the same parent.

Monosomic rescue: Sometimes an egg or sperm with a missing chromosome joins with an egg or sperm with a single copy of that chromosome. If the single copy chromosome is duplicated, a pair of identical chromosomes with the same parental origin are formed.

Complementation: Sometimes an egg or sperm cell with two copies of a chromosome joins with an egg or sperm cell that is missing that particular chromosome. In this situation, both chromosomes come from a single parent but are not necessarily identical.

If UPD occurs slightly later in fetal development, for example if a chromosome from one parent is duplicated by error and the matching chromosome from the other parent is lost during trisomic rescue, UPD **mosaicism** can occur. This means that not all cells of the body will have UPD.

UPD test UPD cannot be identified by looking at chromosomes under a microscope since the number and appearance of chromosomes will not be affected. A molecular test is used to establish the inheritance pattern of each chromosome (or part of a chromosome) such as **microsatellite** analysis or **SNP** (single nucleotide polymorphism) genotyping. These techniques make use of the fact that each chromosome of each individual contains small DNA sequence variations. A set of markers for each chromosome are analysed. The presence of the same markers across entire chromosome pairs suggests UPD with identical chromosomes. If different variations are identified along the length of each chromosome in a pair, it suggests that one chromosome has been inherited from each parent. The same tests are used to identify UPD with non-identical chromosomes and partial UPD, when a section of a chromosome has UPD. Another technique that looks at the activity of a chromosome (**methylation** test) can also be used.

Inform Network Support



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Understanding Chromosome & Gene Disorders

Uniparental disomy (UPD)

rarechromo.org

What are chromosomes?

Our bodies are made up of different types of cells, most of which contain our chromosomes. Chromosomes are made from DNA and contain genes. They usually come in pairs; one member of each chromosome pair is usually inherited from each parent. All chromosome containing cells have 23 pairs of chromosomes (a total of 46) except the egg and sperm cells which have a single copy of each chromosome pair. At conception (when an egg is fertilised by a sperm), the chromosome number is restored to 46.

We normally have 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).

Chromosomes can't be seen with the naked eye but if cells are prepared in a specific way, the chromosomes can be stained and viewed under a microscope. This image shows the chromosomes present in a typical male cell.



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

What is uniparental disomy (UPD)?

UPD is a rare chromosomal event that occurs when both copies of a specific chromosome (or part of that chromosome) are inherited from one parent and no copy is inherited from the other parent.

When both chromosomes (or part of a chromosome) of a pair are inherited from the mother it is known as maternal UPD (or mUPD / UPDmat). When both copies are inherited from the father it is known as paternal UPD (or pUPD / UPDpat).

How does UPD affect me or my child?

The consequences of UPD vary considerably from no obvious effect on health and development to more serious disorders (UPD can also in some cases cause spontaneous miscarriage). Symptoms depend on which chromosome (or part of a chromosome) has UPD, especially if **imprinted** genes or **recessive gene variants** are involved.

■ UPD and imprinted genes

Each chromosome in a pair contains the same genes (apart from the sex chromosomes). For the majority of genes, both copies are active. In such cases, it doesn't appear to be of any significance if both copies of a gene are inherited from the same parent. However, some genes are **imprinted**, which means only one copy of the gene is active and activity depends on which parent the chromosome is inherited from.

Imprinting is a normal process that results in some genes being 'switched off' on chromosomes inherited from the father (**paternal imprinting**) and others being switched off on chromosomes inherited from the mother (**maternal imprinting**).

If UPD includes a chromosome (or part of a chromosome) that contains imprinted genes, symptoms will depend on the parental origin of the chromosome in question. For example, inheriting two copies of a chromosome from a father that contains paternally imprinted genes means that both gene copies are switched off. When there are no active copies of an important gene, health and development can be affected. If both copies of a chromosome (or part of a chromosome) with maternally imprinted genes are inherited from the mother, both copies will be active, and this can also cause symptoms since appropriate gene activity is important for regular health and development.

■ UPD and recessive gene variants

UPD can affect health and development if both copies of the chromosome (or part of the chromosome) with UPD carry a gene with a **pathogenic** (disease causing) **variant**. Some pathogenic gene variants are inherited in a dominant manner, which means having only one copy of the variant can result in symptoms.

Other gene variants are inherited in a **recessive** manner, which means both copies of the gene must be altered in order for symptoms to occur.

We all unknowingly carry recessive gene variants, but since only one gene is affected, we have no symptoms. These variants can be passed on to children who will also have no symptoms unless both copies of their genes are affected.

Recessive gene disorders more commonly occur when both parents carry a recessive gene variant on the same gene and pass it on to their child. However, recessive gene disorders can also occur when both copies of a gene with a pathogenic variant are inherited from the same parent due to UPD, and no unaffected gene copy is inherited. Symptoms will depend on which gene or genes are involved.

Why did this happen?

UPD occurs naturally, it is not due to a parents' lifestyle or anything they did before, during or after pregnancy.

When a child is conceived their parents' chromosomes are usually passed on as a single copy from each parent. Each chromosome is then copied into the new cells that form as a child grows and develops. These biological processes are not perfect and random, rare changes can occur that result in an unexpected distribution of chromosomes (or parts of chromosomes) that results in UPD.

Occasionally UPD occurs if a parent carries a chromosomal translocation (when parts of two different chromosomes fuse together and act as a single chromosome). It is also thought that some UPDs may be associated with maternal age.

How common is UPD?

The incidence of UPD has recently been estimated to be roughly 1 in 2000 (Nakka 2019). The occurrence of UPD is higher than previously estimated since more people are taking molecular genetic tests, and UPD has been identified as an incidental finding in healthy individuals.