

Genetic aspects of

**PID**

# Genetic aspects of primary immunodeficiency

## Information for families

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Supporting families affected  
by primary and secondary  
immunodeficiency

## About this booklet

This booklet has been produced jointly between Immunodeficiency UK, Great Ormond Street Hospital (GOSH) and the Great North Children's Hospital. It is designed to help answer the questions that families may have about the genetic aspects of primary immunodeficiencies (PID).

The information has been reviewed by the Immunodeficiency UK Medical Advisory Panel and Patient Representative Panel and by families affected by PID but should not replace advice from a clinical immunologist or a geneticist.

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## Introduction

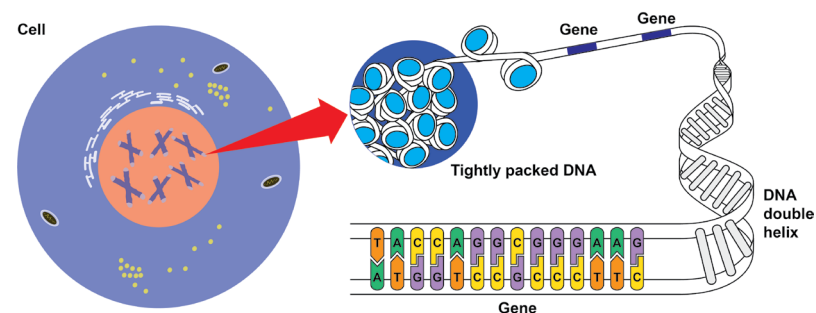
Primary immunodeficiency disorders are the result of defects in an individual's genetic make-up. These defects are mistakes that occur in genes and are passed from generation to generation. Sometimes a genetic mistake (mutation) can occur for the first time in an infant or child when no one else in the family has had the problem, but in other situations there may be family members who have suffered from the same or similar problems. There are several ways in which mutations can be inherited and these are explained below. In an increasing number of immunodeficiency disorders, the precise mistake in the relevant gene can now be identified in the laboratory, and this not only helps to determine the best treatment but also means that accurate counselling can be offered to the family, and screening tests can be offered in pregnancy if requested.

## What are genes?

Genes are complicated chemical units. Made of DNA (deoxyribonucleic acid), they contain the coding information that determines all the characteristics of an individual. They are carried on structures known as chromosomes, of which every cell in a human body contains 46, in 23 pairs. Thousands of genes are essential for normal development and functioning of an individual. A mistake in the coding sequence of a gene may cause serious malfunction and potentially result in one of many genetic diseases.

Of these 23 pairs of chromosomes, one pair are the 'sex' chromosomes. A female has two X chromosomes, a male has one X and one Y chromosome; it is the Y which confers 'maleness'. All the cells in the body, therefore, have 22 pairs of chromosomes known as 'autosomes' and either XX sex chromosomes in a female or XY sex chromosomes in a male. During reproduction, each egg and each sperm receives one copy of each pair of chromosomes. The resultant offspring will thus receive one copy of each of the 22 autosomes from each parent and one X chromosome from the mother, and either an X or a Y from the father. An X chromosome from the father will result in a female, a Y chromosome will develop into a male. Genetic disorders can arise from mistakes on both autosomes and sex (X and Y) chromosomes.

The structure of chromosomes, genes and DNA

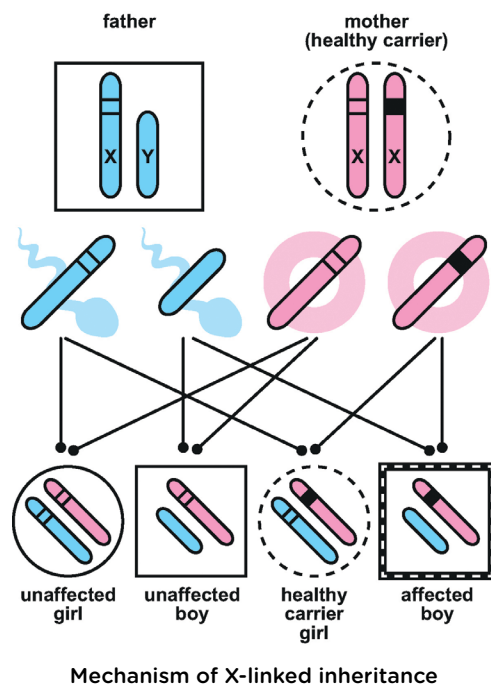


## How can genetic disorders be inherited?

There are two main types of inheritance pattern for immunodeficiency disorders: X-linked and autosomal recessive. A small number of disorders are inherited in an 'autosomal dominant' pattern. Some conditions can be caused by several different genes so that there may be X-linked forms and autosomal recessive forms that clinically can be very similar but have different genes involved.

### X-linked disorders

X-linked disorders are the result of mutations in genes on the X chromosome and almost exclusively affect males. A female who has a mistake on one of her two X chromosomes also has a normal X, which compensates for the abnormal one; so, in almost all such situations the female is healthy, but is a 'carrier'. A male who inherits an X chromosome carrying a mutation does not have a second X to compensate, so may be affected by an 'X-linked recessive' disorder. In extremely unusual cases, a female may inherit two abnormal X chromosomes, in which case she will also be affected by the disorder.



The child of a female carrier of an X-linked disorder will inherit only one of the mother's X chromosomes, and will also inherit either an X or a Y chromosome from the father. There is a 50 per cent (1 in 2) chance that the abnormal X chromosome will be inherited from the mother. This means that 50 per cent (1 in 2) of daughters (XX) will be carriers, and 50 per cent (1 in 2) of sons (XY) will be affected by the disorder. It is important to remember that the risk is the same in every pregnancy. Any affected male who has children will pass on the abnormal X to all his daughters, and the healthy Y to all his sons. Therefore, all his daughters will be carriers and all his sons will be healthy.

Mutations on the X chromosome occur spontaneously with a relatively high frequency. This means that an X-linked disorder can occur in a family with no previous history of the disorder, and this is the case in approximately 30 per cent of newly diagnosed males. The mutation may have arisen for the first time in the boy, or in his mother's ovary, or in a grandparent - in which case his mother would be a carrier.

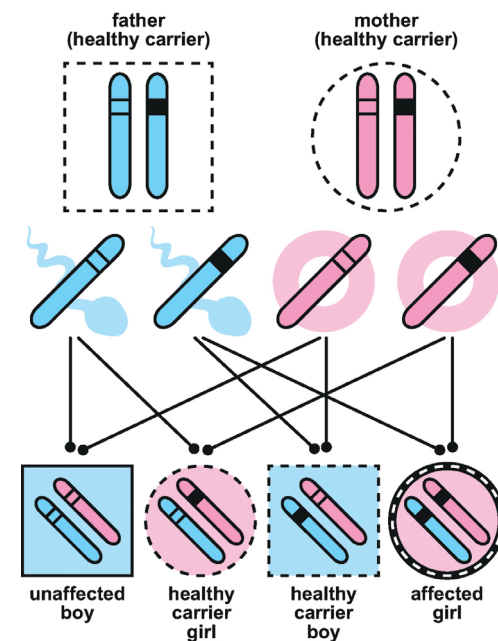
### X-linked immunodeficiencies

A number of genes on the X chromosome are important for normal development and functioning of the immune system. Examples of X-linked immunodeficiencies are:

- X-linked agammaglobulinemia (XLA; Bruton's disease)
- X-linked severe combined immunodeficiency (X-SCID)
- X-linked hyper IgM syndrome (CD40 ligand deficiency)
- X-linked lymphoproliferative disease (XLP)
- X-linked inhibitor of apoptosis (XIAP) deficiency
- X-linked chronic granulomatous disease (X-CGD)
- Wiskott-Aldrich syndrome (WAS)
- Properdin deficiency
- Dyskeratosis congenita.

### Autosomal recessive inheritance

A gene carried on one of the 22 pairs of autosomes is known as 'autosomal'. In most cases a mutation in an autosomal gene does not cause a clinical disorder if the equivalent gene on the other of the pair of autosomes is normal. However, if an individual is unlucky enough to inherit a gene containing a mutation from both mother and father, they may be affected by a disorder. These are known as 'autosomal recessive' disorders.



If both parents have one copy of an abnormal gene, they are carriers and there is a 25 per cent (1 in 4) chance that any baby will be affected by the disorder. This is the same for boys and girls. There is a 50 per cent (1 in 2) chance that the offspring will be a carrier, and a 25 per cent (1 in 4) chance that the baby will not inherit the faulty gene, so will not be affected by the condition or be able to pass it on to their children. The chances are the same for each pregnancy.

Most autosomal recessive disorders are very rare. The incidence depends on the frequency of mutations in the general population, which is usually very low. In most infants diagnosed with an autosomal recessive disorder, there is no history of the problem in previous generations. However, in families where cousins or other relatives are married to each other, there is a higher chance of these disorders occurring, and in these families there may be affected infants in earlier generations or in cousins.

## Autosomal recessive immunodeficiencies

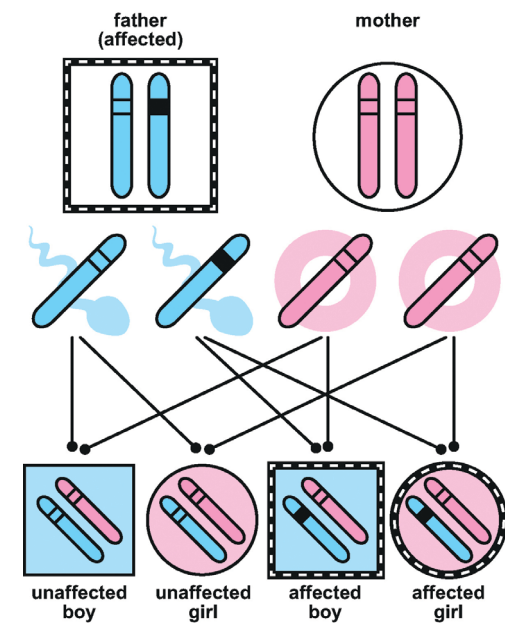
As new genes are identified, increasing numbers of autosomal recessive forms of immunodeficiency are being defined. Some of the more frequently recognised forms are:

- Various forms of severe combined immunodeficiency (SCID)
- Adenosine deaminase (ADA) deficiency
- Purine nucleoside phosphorylase (PNP) deficiency
- Recombinase activating gene (RAG) deficiency
- Jak3 deficiency
- MHC class II deficiency
- Chronic granulomatous disease (CGD) - three forms
- Leucocyte adhesion deficiency (LAD)
- Chediak-Higashi syndrome
- Familial forms of hemophagocytic lymphohistiocytosis (HLH).

## Autosomal dominant inheritance

Sometimes a mutation in an autosomal gene can cause a disorder even if the copy of the gene on the other of the pair of autosomes is normal. This is known as 'autosomal dominant inheritance'. These disorders can affect males and females. All offspring of an affected individual have a 50 per cent (1 in 2) chance of inheriting the abnormal gene and being affected by the disorder. The risk is the same for every pregnancy.

Recently it has been recognised that some primary immunodeficiencies are inherited as autosomal dominant disorders. One example is activated phosphoinositide 3 kinase delta syndrome (APDS), which causes a common variable immunodeficiency-like disorder. It is likely that many more will be identified with further genetic research.



Mechanism of autosomal dominant inheritance

## Is it always possible to make a genetic diagnosis?

Increasing numbers of immunodeficiencies are being defined at a molecular or genetic level. Currently there are over 300 known disorders, and it is now possible to determine the underlying cause in many cases. In cases where the immunological abnormalities fit a well-defined and recognised pattern, it may be possible to make a molecular diagnosis by analysis of the proteins known to be absent or abnormal in that particular disorder. Once an immunodeficiency has been defined and a specific protein abnormality confirmed, then DNA analysis can be carried out to try to identify the precise mistake in the gene. This is successful in approximately 80 to 90 per cent of such cases. Once a mutation has been found it is relatively easy to analyse DNA samples from other family members to determine if they are carriers of the disorder.

In cases that do not fit a typical pattern or where initial genetic testing does not make a diagnosis, there are now other sophisticated techniques that may identify the underlying genetic cause. These include several techniques that fall within the umbrella term 'next generation sequencing' (NGS) or high throughput sequencing: (i) whole genome sequencing (WGS) involves reading an individual's entire DNA sequence, (ii) whole exome sequencing (WES) involves reading the sequences of all the protein-coding genes, and (iii) NGS panel is sequencing a particular group of disease genes. WES and WGS are currently performed as part of a number of research studies underway both locally and nationally. Your immunology team will be able to provide you with up-to-date information regarding these studies.

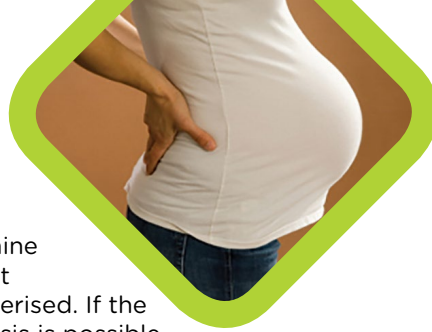
These techniques allow precise diagnosis in increasing numbers of families, although there are still a few cases where a cause cannot be defined. Full analysis of genes in WES or WGS can take a long while, and it is sometimes necessary to ask for further samples so that checks or further investigations of discoveries can be carried out. This is important to ensure that your family is given absolutely the correct information. It is very frustrating and depressing for families who do not know the cause of their child's disorder, and who cannot be offered any genetic testing, but continuing progress means that such cases are becoming fewer all the time.

## Indirect gene tracking

Sometimes a mutation cannot be found in the relevant gene, even though all the evidence suggests that there should be one. If the evidence is strong enough, and there are several affected family members, it may be possible to use indirect methods to track the abnormal gene through the family, even where the identity of the gene is not known. This is known as linkage analysis, and it can be used to determine carrier status in other family members, but carries a small risk of inaccuracy - usually of the order of five per cent.

## Prenatal diagnosis

In families where an immunodeficiency has been recognised, some parents may wish to know whether future babies are affected by the disorder, particularly if it is one of the more severe forms. Testing to determine whether unborn babies are affected is possible in most situations where the immunodeficiency is well characterised. If the responsible mutation has been found, prenatal diagnosis is possible in all cases. In other situations, there may be methods for prenatal diagnosis but these may be less accurate.



### Why should prenatal diagnosis be performed?

There are several reasons why prenatal diagnosis might be requested. In situations where the immunodeficiency is known to be severe, and treatment cannot be guaranteed to be successful, couples may decide to terminate the pregnancy. However, this is not the only reason. Sometimes couples may wish to know whether or not the baby is affected before birth, so that plans can be made for appropriate management of the baby after birth. If haematopoietic stem cell transplantation (HSCT) or gene therapy is required, this can be performed soon after birth if the diagnosis is known beforehand.

### Methods of prenatal diagnosis

#### DNA analysis

DNA from the foetus can be obtained in several ways.

A tiny sample of the developing placenta – known as a ‘chorionic villus sample’, or CVS – can be taken at around 11 weeks into pregnancy. DNA is prepared from this, and, provided that the sample is adequate, and that there is no contamination of the sample with DNA from the mother, this is a reliable method of analysing DNA from the unborn baby.

Another method of collecting foetal DNA is by amniocentesis. This involves sampling of the fluid surrounding the baby at around 14 to 16 weeks into pregnancy.

A newer technique is isolation of foetal DNA from maternal blood (‘free foetal DNA’). The advantage of this technique is that it is non-invasive and carries no risk to the pregnancy.



The two techniques of DNA analysis are:

- Mutation analysis: If the mutation is known, then mutation analysis can be performed, and is 100 per cent reliable.
- Linkage analysis: If the disease is very well characterised and the diagnosis is definite, but the mutation is not known, prenatal diagnosis may be possible using linkage analysis. This will be slightly less reliable than mutation detection.

In X-linked conditions where the mutation is not known, it is possible to determine the sex of the foetus. Female foetuses will be unaffected.

#### Foetal blood analysis

In situations where the precise cause of an immunodeficiency is not known, but there is a very high likelihood that it has a genetic basis, it is sometimes possible to perform prenatal testing by analysis of foetal blood, taken from the umbilical cord. This is not genetic testing but involves analysis of the numbers and function of immune cells in foetal blood. This type of testing can only be done if there is a clearly recognisable pattern of abnormalities that has been seen in a previously affected child. If an abnormal pattern is seen, this means the foetus is affected. However, if the results are normal, it may not be possible to exclude the possibility that the problem will emerge later in foetal development. This type of testing is therefore less reliable than genetic testing.

Additionally, foetal blood sampling cannot be safely or reliably performed before about 19 to 20 weeks gestation, and, although results are usually available very quickly, a termination of pregnancy at that stage would involve a mini-labour. For all these reasons, foetal blood analysis is not performed very frequently.

#### Enzyme analysis

In certain specific immunodeficiencies, prenatal testing can be done by measuring the concentration and/or function of the enzyme that is known to be defective. Examples of this are adenosine deaminase and purine nucleoside phosphorylase, deficiencies of which both cause forms of severe combined immunodeficiency (SCID). Both of these enzymes can be analysed in a chorionic villus sample taken at 11 to 12 weeks gestation.



## Who should be tested for carrier status?

Once a genetic diagnosis has been established in a family, it becomes possible to test all at-risk family members to determine whether they are carriers of the abnormal gene. This may be particularly important for female relatives on the maternal side of a family where a male baby has an X-linked immunodeficiency. However, it can also be important in autosomal recessive disorders, especially in cultures where marriage between cousins or other family members is common.

Nevertheless, it is very important that the decision to test for carrier status is made by the individual concerned. It should be an informed decision, and should be preceded by counselling to ensure that the implications are fully understood. In the case of inherited immunodeficiencies, counselling may be done by both a geneticist and an immunologist so that all aspects of the diagnosis can be explained.

The question of carrier testing for children is more difficult. Many parents wish to know whether their children are carriers, particularly where the disorder is X-linked. However, the general principle that is recommended is that the child should be old enough to understand the implications, and to be able to decide for his/herself whether they wish to be tested. There may be exceptional circumstances that mean that younger children are tested, but generally testing children is not considered before they are 16.

## Pre-implantation diagnosis

In some situations families may wish to be certain that a foetus is not affected by a genetic disorder, even before the embryo is implanted in the womb. This may be because there have been several previous terminations of pregnancy, or because there are religious objections to termination.

Detection of genetic abnormalities before implantation is theoretically possible provided that the mutation is known, but it is a highly complex procedure that has only been successfully carried out and followed by a normal pregnancy in a small number of cases. It involves in vitro fertilisation (IVF) of a number of eggs, followed by genetic testing by analysis of a single cell from each embryo, and subsequent implantation of one to three normal embryos. At present these techniques are available in only a few centres in the UK, for specific disorders, and are not offered routinely.

For X-linked disorders the option of foetal sexing is available more easily. This is essentially the same procedure but only female embryos are returned to the womb, since females will not be affected by X-linked disorders.

Any family wishing to discuss any of these possibilities would be referred to a specialist unit, who would provide much more extensive information and counselling.

## Umbilical cord blood storage

Blood collected from the umbilical cord at the time of delivery of a new baby is a very rich source of haematopoietic stem cells - the cells that give rise to all the different cells of the blood and immune system. Stem cells from an unaffected baby can be used as an alternative to bone marrow to transplant an affected child. Stem cells from a baby who is affected by an immunodeficiency may in the future also be used to perform gene therapy. For these reasons, it is often recommended that umbilical cord blood is collected at the time of delivery in families known to carry genetic disorders. This can then be stored frozen in the Cord Blood Bank until such time as it may be needed.

## Further support

You can contact the umbrella organisation for support groups in the UK at Contact a Family. Ring the helpline on 0808 808 3555 or visit the website at [www.cafamily.org.uk](http://www.cafamily.org.uk)



## Glossary of terms

**amniocentesis** removal and genetic testing of a small sample of cells from amniotic fluid, which surrounds the foetus in the womb (uterus).

**autosomal dominant** a type of inheritance. If a faulty gene is dominant, it will show an effect even though there is a working copy of the gene on the other chromosome. A person only needs to inherit one faulty gene from one parent to develop a disease in a dominantly inherited condition. The risk of having a child with the condition is 50 per cent (or 1 in 2) for each pregnancy.

**autosomal recessive** a type of inheritance where the presence of one copy of a faulty gene does not affect the individual him or herself. However, when two carriers of the same faulty gene have children, there is a 25 per cent (or 1 in 4) chance of a child inheriting two copies of the faulty gene (one from each parent) for each pregnancy. If this happens, the child is affected by the disorder.

**autosome** any chromosome other than the sex chromosomes.

**carrier** an individual who carries the faulty gene for a specific condition, usually without symptoms.

**chorionic villous sampling** a test performed during early pregnancy to check for genetic disorders. It involves removing and testing a small sample of cells from the placenta.

**chromosomes** thread-like structures located inside the nucleus of cells. Each chromosome is made of protein and DNA.

**coding sequence** sequence of molecular building blocks (nucleotides) of DNA that determines the function of a gene.

**cord blood bank** storage bank for umbilical cord blood collected at the time of delivery. Cord blood is a rich source of stem cells that can be used for transplantation.

**DNA (deoxyribonucleic acid)** complex helix-shaped molecule that contains the specific instructions that make each type of living creature unique.

**enzymes** biological molecules (proteins) that act as catalysts and help complex reactions everywhere in life.

**exome** all the expressed genes in a genome.

**foetal blood analysis** laboratory testing of blood collected from the umbilical cord of a foetus, for inherited disorders.

**free foetal DNA** foetal DNA circulating freely in the maternal blood stream.

**gene** section of DNA on a chromosome that codes for a functional RNA molecule and thus a protein. Put another way, a word rather than a letter in the genetic code. Genes are the fundamental units of inheritance that carry the instructions for how the body grows and develops.

**gene therapy** attempting to cure genetic diseases by placing a normal 'healthy' gene into cells that have a faulty version of that gene.

**genetic counselling** advice from a specialist geneticist regarding the implications of carrying or being affected by a genetic disorder.

**geneticist** an expert in the study of genes and heredity.

**genome** the genetic material of an organism.

**haematopoietic stem cells** cells from which all blood cells and immune cells are derived.

**haematopoietic stem cell transplantation (HSCT)** transfer of stem cells from a donor – either related or unrelated – to a recipient. Stem cells may be obtained from bone marrow (by aspiration usually from the hip bones), peripheral blood (PBSCs), or from stored umbilical cord blood. The donor stem cells replace the recipient bone marrow, giving him/her a new immune system and curing the immunodeficiency.

**immune system** the structures and processes that protect the body against infection and disease.

**inheritance** passing down of genetic information from parents to children.

**linkage analysis** a method of genetic testing that relies on the tendency for genes and other genetic markers to be inherited together because of their location near one another on the same chromosome.

**mutation** a change in the structure of a gene or group of genes. Such changes can be passed on to the next generation. Many mutations cause no harm, but others can cause genetic disorders, such as primary immune deficiencies.

**next-generation sequencing (NGS)** also known as high-throughput sequencing, the catch-all term used to describe a number of different modern DNA sequencing technologies.





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## About Immunodeficiency UK

**Immunodeficiency UK is a national organisation supporting individuals and families affected by primary and secondary immunodeficiency.**

We are the UK national member of IPOPI, an association of national patient organisations dedicated to improving awareness, access to early diagnosis and optimal treatments for PID patients worldwide.

Our website has useful information on a range of conditions and topics, and explains the work we do to ensure the voice of patients with primary and secondary immunodeficiency is heard. If we can be of any help, please email us or call on the number above, where you can leave a message.

Support us by becoming a member of Immunodeficiency UK. It's free and easy to do via our website. Members get monthly bulletins.

Immunodeficiency UK is reliant on voluntary donations. To make a donation, please go to [www.immunodeficiencyuk.org/donate](http://www.immunodeficiencyuk.org/donate)



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Supporting families affected  
by primary and secondary  
immunodeficiency

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