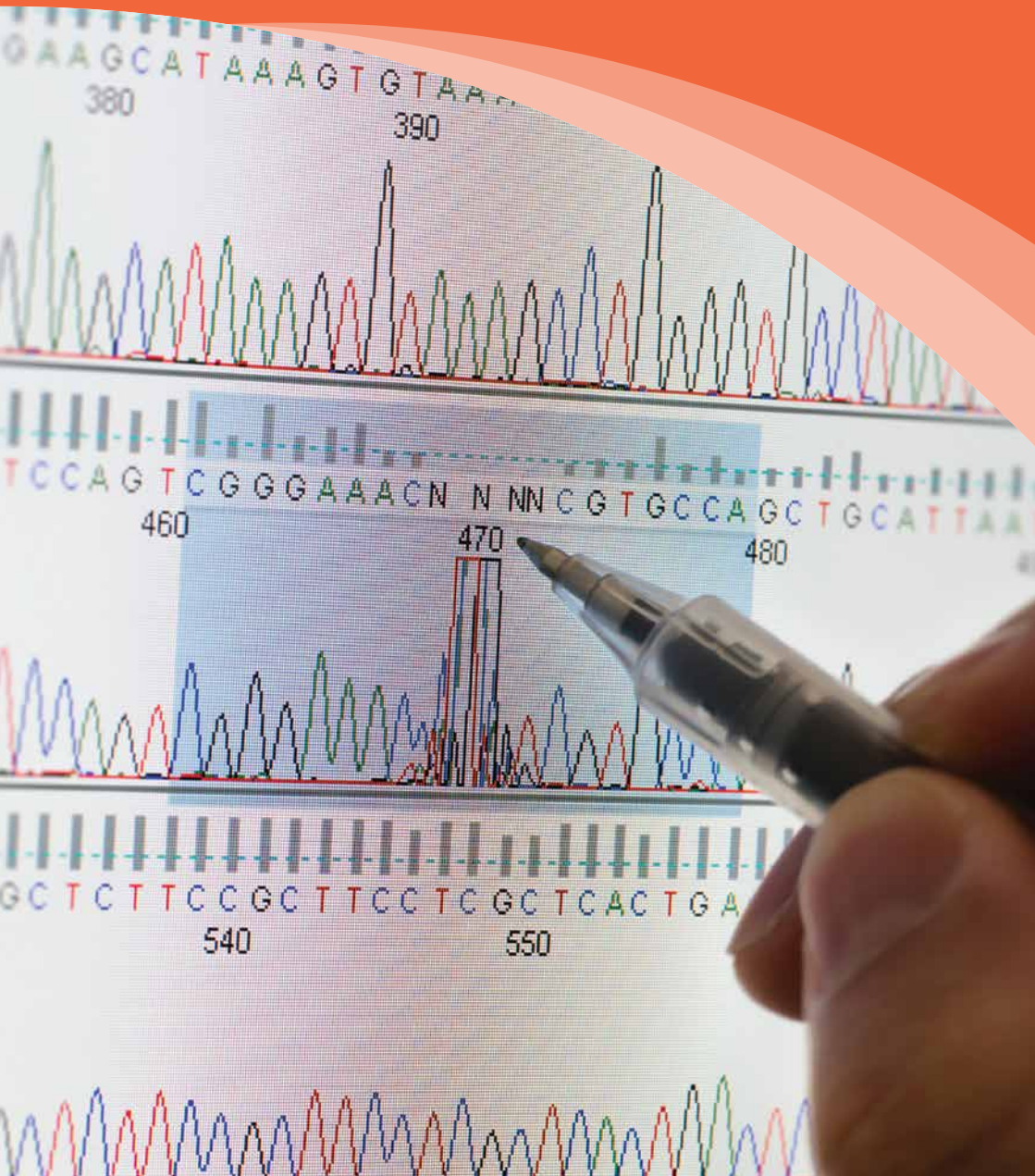
IPOPI
INTERNATIONAL
PATIENT ORGANISATION
FOR PRIMARY IMMUNODEFICIENCIES

PRIMARY **IMMUNODEFICIENCIES**

GENETIC DIAGNOSIS OF PIDs



ABBREVIATIONS

APDS	Activated phosphoinositide 3 kinase delta syndrome
CGD	Chronic granulomatous disease
IPOPI	International Patient Organisation for Primary Immunodeficiencies
PID	Primary immunodeficiency
SCID	Severe combined immunodeficiency

Genetic diagnosis of primary immunodeficiency disorders (1st edition).

© International Patient Organisation for Primary Immunodeficiencies (IPOPI), 2020

Published by IPOPI: www.ipopi.org

INTRODUCTION

This booklet explains how genetic analysis can be used to diagnose primary immunodeficiencies.

Primary immunodeficiencies (PIDs) are rare diseases that occur when components of the immune system are either not present or are not functioning normally, rendering the patient susceptible to potentially life-threatening infections.

PIDs arise due to changes (mutations) in specific genes that encode proteins involved in the functioning of the immune system. The specific genes and mutations that are associated with an increasing number of PIDs are now known making it possible to undertake a genetic analysis to confirm a PID diagnosis and ensure patients get the optimal treatment. Genetic analysis can also help to trace mutations within close family members so that they can receive screening tests, for example during pregnancy, if they wish.

The following sections provide an overview of how genetic analysis contributes to the diagnosis and treatment of PIDs.

HOW DO GENETIC CHANGES IN PIDs ARISE AND HOW ARE THEY INHERITED?

PIDs arise due to changes (mutations) in specific genes that encode proteins involved in the functioning of the immune system. Some PIDs arise sporadically (meaning that mutation randomly occurred during egg formation), while other PIDs already exist in the chromosomes of one or both parents and are inherited.

Chromosomes and genes come in pairs. Inheriting a specific disease, condition, or trait depends on the type of chromosome that is affected. There are two types of chromosomes: autosomal chromosomes (22 pairs) and sex chromosomes (one pair: the X and Y). It also depends on whether the trait is dominant or recessive.

Most of PIDs are inherited in one of two different modes of inheritance: autosomal recessive or X-linked recessive; rarely, the inheritance is autosomal dominant.

- **Autosomal recessive:** a PID can only occur if two abnormal genes (one from each parent) are present. If an individual inherits only one gene for the PID, then he or she carries the gene for the disorder but does not have the disorder itself. In this form of inheritance, males and females are affected with equal frequency. Both parents carry the gene for the disease although they themselves are healthy.
- **Autosomal dominant:** a PID can emerge when just one mutated copy of the gene is present. In rare situations, a normal gene in the presence of a mutated gene cannot compensate for the defective gene; in this situation, the abnormal gene is said to exert a “dominant negative effect”.
- **X-linked:** here the mutation occurs on a gene present in the X chromosome. X-linked disorders almost exclusively affect males. Women have two X chromosomes while men have one X and one Y chromosome. Since women have two X chromosomes, they usually do not have problems when a gene on one X chromosome does not work properly because the second X chromosome usually carries a normal gene and compensates for the abnormal gene on the affected X chromosome. Men have only one X chromosome, which is paired with their male-determining Y chromosome. The Y chromosome does not carry much active genetic information so if there is an abnormal gene on the X chromosome, the paired Y chromosome has no normal gene to compensate for the abnormal gene on the affected X chromosome, and the boy (man) has the disorder.

  In this type of inheritance, the disease is passed on from females (mothers) to males (sons). While the males are affected with the disease, the females are generally asymptomatic and healthy even though they carry the gene for the disease because they carry a normal gene on the other X chromosome. However, an abnormal skewing of X inactivation can occur, rendering the carrier sick with partial to full blown PID phenotype (only seen in approximately 1% of female carriers).

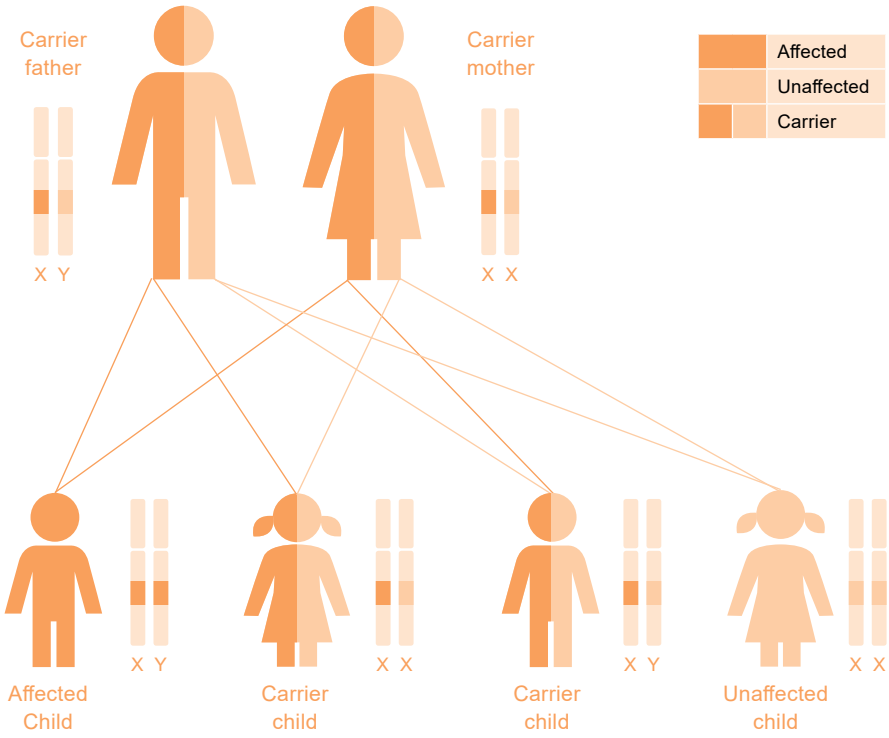
The specific genes and mutations associated with an increasing number of PIDs are now known making it possible to undertake a genetic analysis to confirm a PID diagnosis and ensure patients get the right treatment.[1]

AUTOSOMAL RECESSIVE PIDs

Most autosomal recessive disorders are very rare as the frequency of mutations in the general population is usually very low.

If both parents have a copy of an abnormal gene there is a 1 in 4 (25%) chance that any baby will be affected by the disorder and a 50% chance that the baby will be a (healthy) carrier of the mutated gene.

AUTOSOMAL RECESSIVE



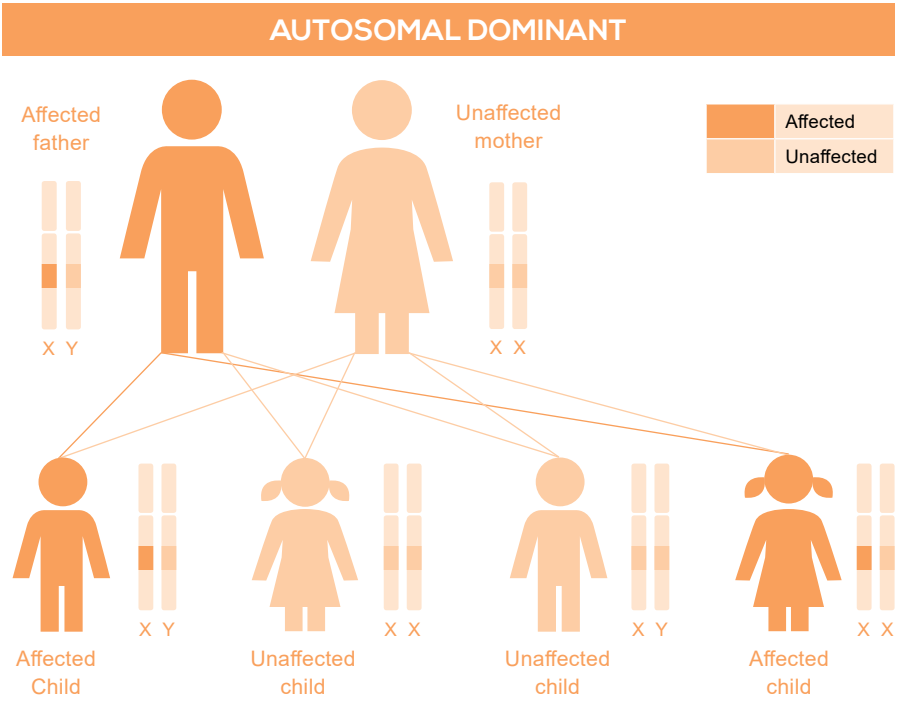
[1] Mahlaoui N, et al. Advanced in the care of primary immunodeficiencies (PIDs): from birth to adulthood. J Clin Immunol 2017;37:452-460.

Some of the more frequently recognised types of autosomal recessive PIDs are:

- Various forms of severe combined immunodeficiency (SCID; it is worth noting that half of the patients with SCID will have X-linked SCID), such as adenosine deaminase deficiency, purine nucleoside phosphorylase deficiency, recombinase activating gene deficiency or Janus kinase 3 deficiency
- Ataxia telangiectasia
- Major histocompatibility complex class II deficiency
- Chronic granulomatous disease (CGD; again, at least half of patients with CGD will have X-linked CGD)
- Leucocyte adhesion deficiency
- Chediak-Higashi syndrome
- Familial forms of haemophagocytic lymphohistiocytosis.

AUTOSOMAL DOMINANT PIDs

Babies born to a parent with an autosomal dominant disorder will have a 1 in 2 (50%) chance of inheriting the disorder; the risk is the same for every pregnancy.



An example of an autosomal dominant PID is activated phosphoinositide 3 kinase delta syndrome (APDS), which causes a common variable immunodeficiency-like disorder. It is likely that more will be identified with further genetic research.

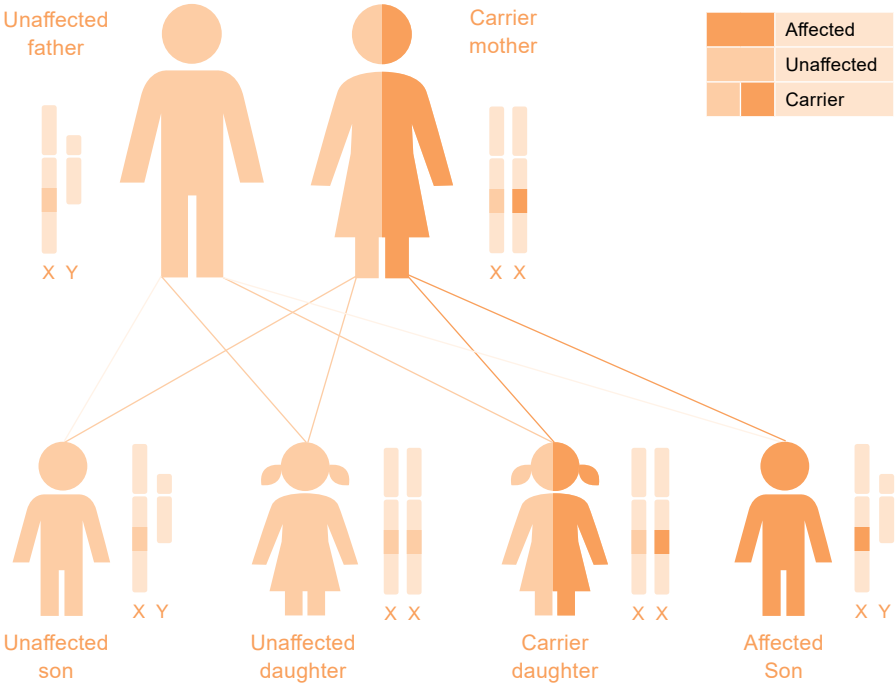
X-LINKED PIDs

As already mentioned, X-linked disorders almost exclusively affect males. A female with an abnormal gene 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.

There is a 1 in 2 (50%) chance that the abnormal X chromosome will be inherited from the mother, which means that 1 in 2 (50%) daughters (XX) will be carriers and 1 in 2 (50%) sons (XY) will be affected by the disorder. The risk is the same in every pregnancy.

In extremely unusual cases, a female may inherit two abnormal X chromosomes, in which case she will also be affected by the disorder.

X-LINKED RECESSIVE, CARRIER MOTHER



Affected sons' offspring:

- In case of a girl: she would be a carrier.
- In case of a boy: unaffected or a 50% chance of being a carrier if the mother is a carrier.

X-linked PIDs include:

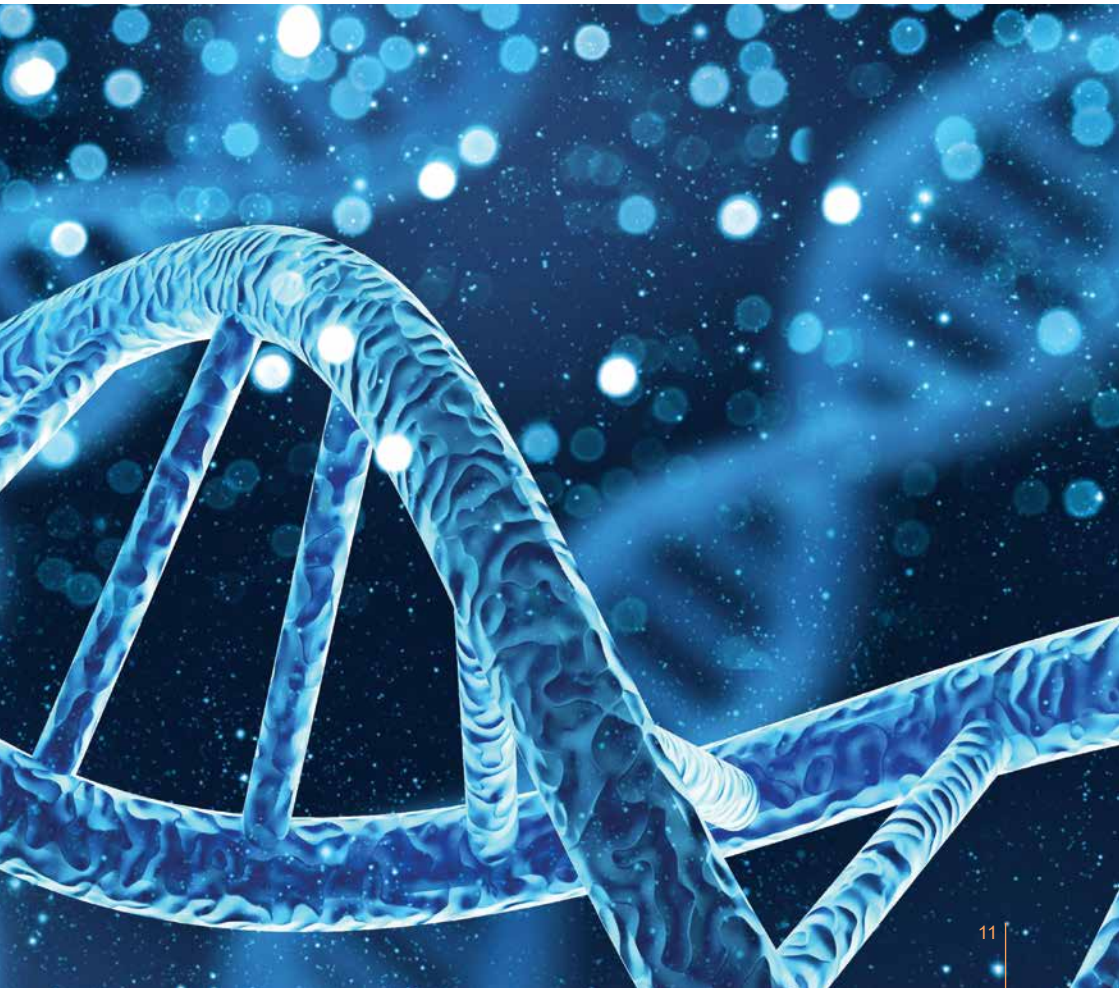
- X-linked agammaglobulinaemia (XLA or Bruton's disease)
- X-linked severe combined immunodeficiency (X-SCID)
- X-linked hyper-IgM syndrome (CD40 ligand deficiency)
- X-linked lymphoproliferative disease 1 or 2 (XLP1 or 2)
- X-linked chronic granulomatous disease (X-CGD)
- Wiskott-Aldrich syndrome
- Properdin deficiency.

GENETIC DIAGNOSIS OF PID

The genetic defect underlying an increasing number of PIDs is now known making is possible to confirm a suspected diagnosis using standard genetic analysis and allow optimal treatment for patients. All that is usually required is a sample of blood.

In some difficult to diagnose cases where the precise genetic defect is not known or does not fit a usual pattern, newer techniques such as whole genome sequencing (WGS), whole exome sequencing (WES) or microarrays (panel) may be needed to confirm a genetic diagnosis.

Prenatal diagnosis may be possible in families where a genetically defined PID has been identified should the parent request it. Newborn screening may identify babies with a PID before symptoms emerge and permit early therapeutic intervention.



FURTHER INFORMATION AND SUPPORT

This booklet has been produced by the International Patient Organisation for Primary Immunodeficiencies (IPOPI). Other booklets are available in this series. For further information and details of PID patient organisations worldwide, please visit **www.ipopi.org**.

GRIFOLS Takeda

Supported by an educational grants from Grifols and Takeda.