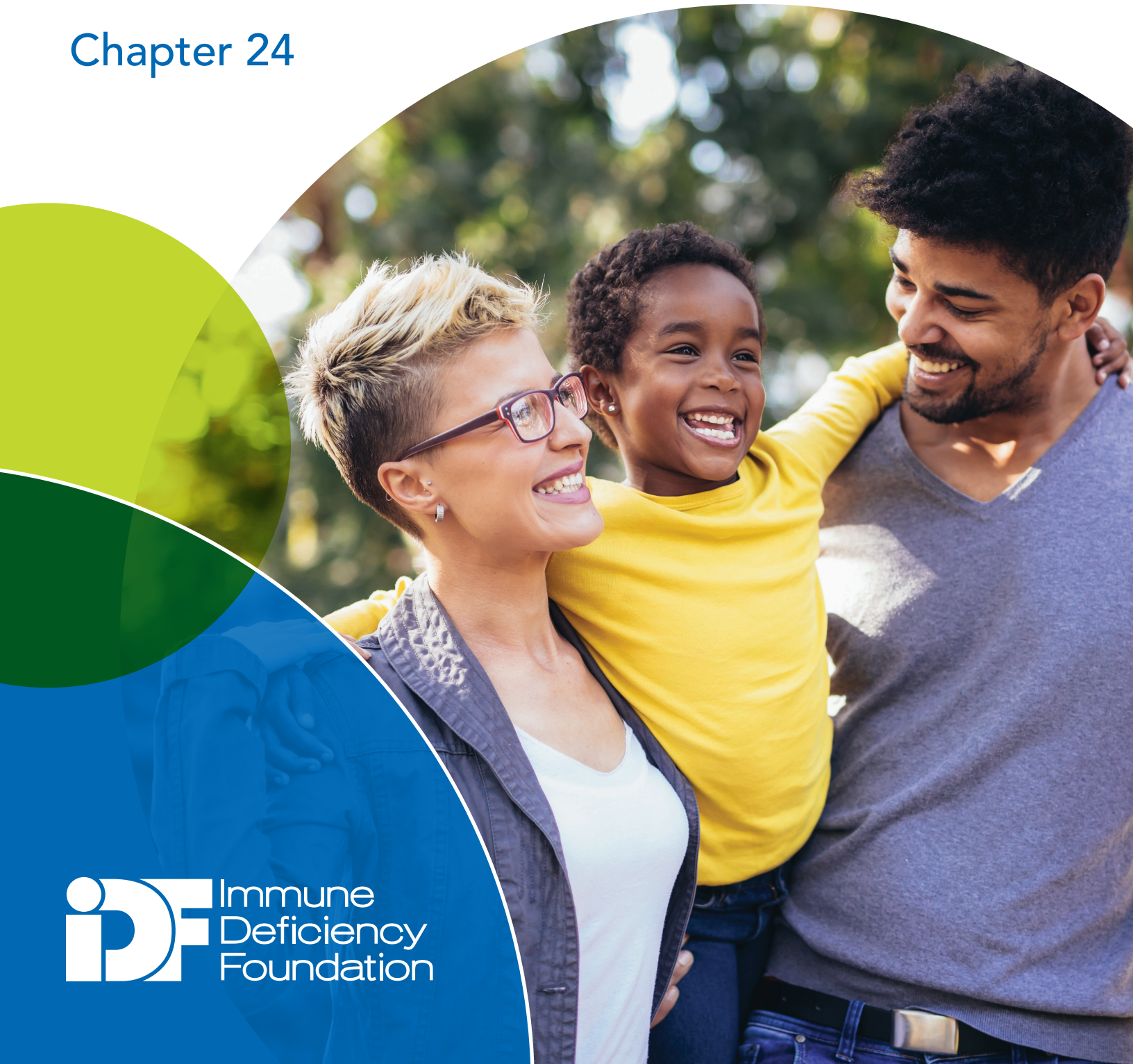
Immune Deficiency Foundation

Patient & Family Handbook

For Primary Immunodeficiency Diseases

Chapter 24



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Chapter 24
Inheritance

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Primary immunodeficiency diseases (PI) are mostly caused by genetic abnormalities that lead to weaknesses in the immune system. To understand the inheritance in PI, it's good to understand a few basic concepts in genetics.

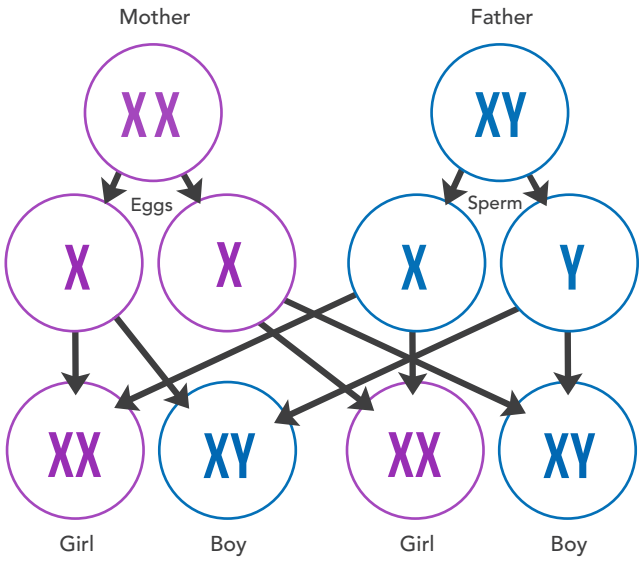
Inheritance of Primary Immunodeficiency Diseases

Every cell in the human body contains genetic material that instructs the job of that cell. This genetic material is packaged into 23 pairs of chromosomes (22 numbered chromosomes, and one pair of sex chromosomes (XX for females and XY for males). Children inherit one chromosome in each pair from their mother, and one chromosome of each pair from their father.

During fertilization, the egg which consists of 23 chromosomes (haploid) fuses with 23 chromosomes of the sperm and the resulting zygote has 46 chromosomes (diploid). This way each parent contributes half of their genetic information and physical characteristics, such as hair color, eye color, blood type, etc., onto the offspring. The sex of the offspring is determined by which chromosome (X or Y) of the sperm (X or Y) fuses with the egg (only X). An X chromosome results in a female offspring and a Y chromosome in a male offspring. (Figure 24:1)

The genetic material packaged in these chromosomes is made up of DNA, which is composed of individual molecules called nucleotides. Four nucleotides make up the DNA, these are Adenine (A), Thymidine (T), Guanine (G), and Cytosine (C). The DNA is made up of long chains of codons comprised of three nucleotides (letters) that are arranged in a specific way, similar to the arrangement of alphabetical letters to form words and sentences. Errors in the spelling of the words (because of misplacement of one or more letters) lead to genetic mutations, now called variants. Some spelling errors might not lead to a significant change in the word, and those variants do not cause disease, while other spelling errors can cause diseases, such as PI. If these errors occur in the egg or sperm of one of the parents, it can cause disease in the child. Occasionally, the errors occur in the fertilized egg, and neither of the parents actually carry that variant.

Figure 24:1 X-Linked Recessive Inheritance - Carrier Mother



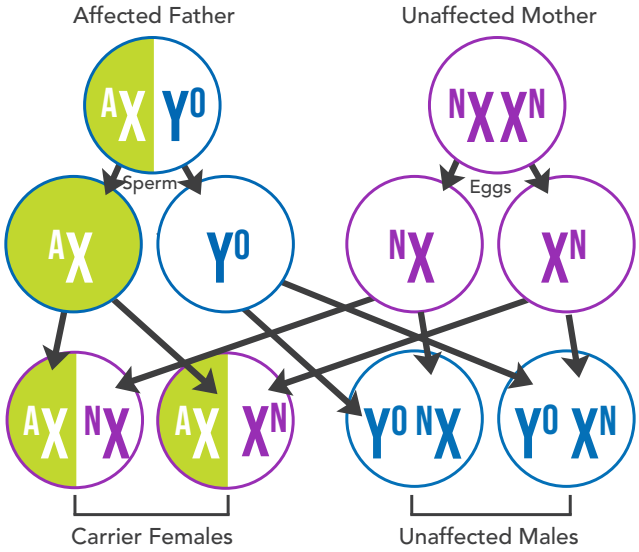
Types of Inheritance

PI can be inherited in one of three different ways: X-linked recessive, autosomal recessive or autosomal dominant. Family history and laboratory studies can be helpful in establishing the possible role of genes or chromosomes in a particular PI and may be useful to identify a particular pattern of inheritance.

X-linked Recessive Inheritance

X-linked recessive is a mode of inheritance where the gene causing disease is present on the X chromosome, mainly affecting males. Males have only one X chromosome. If the inherited X chromosome carries the mutated gene in a male, this will lead to disease expression, as there is no additional X chromosome to compensate and the Y chromosome does not carry information that duplicates that of the X chromosome. An affected male will pass on the defective gene to all his female offspring. All of his daughters will be carriers, and all of his sons will carry the healthy Y chromosome and will therefore not be affected by the disease. Females have two X chromosomes and must inherit both mutated genes – one from each parent to develop the disorder. Therefore, females are carriers if they inherit one faulty X gene, while the second normal X gene continues to carry out its function and consequently prevents the abnormal gene from expression. Females with one affected X and one healthy X appear to be a healthy carriers. However, at times, female carriers could present with symptoms similar to males with X-linked disease due to a process called X-inactivation. In this process, some cells shut down (inactivate) the X chromosome coming from the mother, and other cells inactivate the X chromosome from the father. In the case of X-linked disease carrier, if the inactivation happened to the X chromosome coming from the mother, then the only active chromosome will be the X chromosome coming from the father, which carries the disease-causing variant, leading to symptoms similar to the affected males. Carriers can pass on the mutated gene to their children.

Figure 24:2 X-Linked Recessive Inheritance - Affected Father



Mothers who are carriers can pass on the disease to their sons if the sons inherit the affected X, and in this type of inheritance, a family history may show multiple males affected with the disease. Mothers who are carriers can also pass on the affected X to their daughters, who then become carriers of the disease themselves.

Mutations in X chromosomes may occur spontaneously and may occur in individuals with no previous family history.

The following are examples of PI with X-linked recessive inheritance:

- Bruton's or X-Linked Agammaglobulinemia (XLA)
- Wiskott-Aldrich Syndrome
- Severe Combined Immunodeficiency (SCID), caused by mutations in the common gamma chain
- Hyper IgM Syndrome, due to mutations in CD40 ligand
- X-linked Lymphoproliferative Disease, two forms
- Chronic Granulomatous Disease (CGD), the most common form
- Properdin Deficiency
- Dyskeratosis Congenita

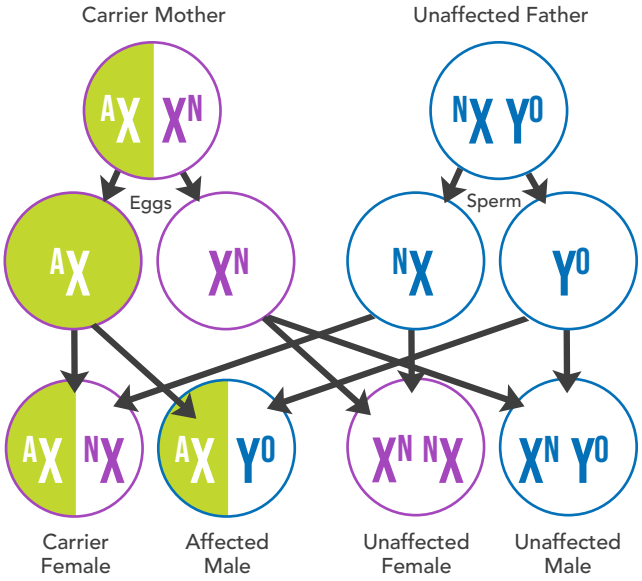
The chances of a woman who carries the faulty gene having an affected child is different based on the gender of the child. If the father is a non- carrier, there are four possible combinations in every pregnancy (See Figure 24:3).

- 1 chance in 4, (25% chance) that a son will inherit the Y chromosome from his father and X-linked recessive gene mutation from his mother. He will, therefore, be affected.
- 1 chance in 4, (25% chance) that a son will inherit the Y chromosome from his father and the working copy of the X-linked gene from his mother. He will not be affected by the condition.
- 1 chance in 4, (25% chance) that a daughter will inherit both working copies of the X-linked genes: one copy from her father and one from her mother. In this case, she will not only be unaffected by the condition, but she will also NOT be a carrier of the X linked recessive gene mutation.

- 1 chance in 4, (25% chance) that a daughter will inherit from her father the working copy of the X-linked gene and the faulty X-linked recessive gene mutation from her mother. She will be a genetic carrier of the condition like her mother and will usually be unaffected.

To summarize, if the offspring is a boy, there is 50% chance he will be affected by the disease. If the offspring is a girl, there is a 50% that she will be a genetic carrier of the disease. The outcome of future pregnancies will not be affected by previous pregnancies, meaning that it is possible for all (100%) of the boys in a family where the mother is a carrier to be affected with X-linked conditions.

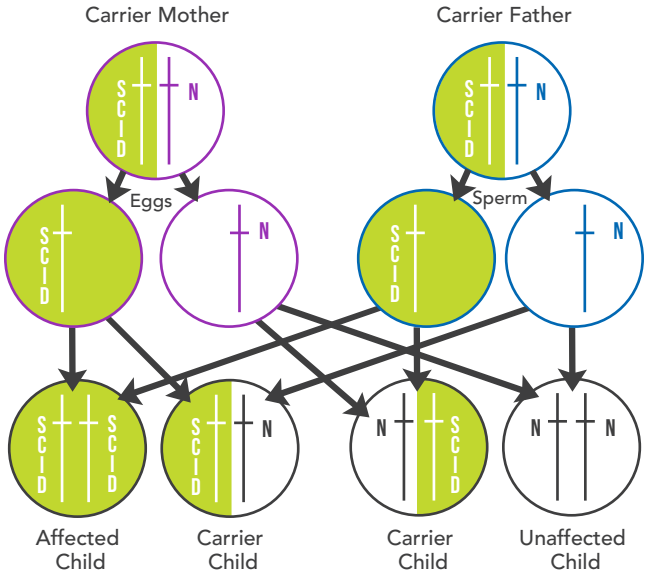
Figure 24:3 X-Linked Recessive Inheritance - Carrier Mother



Autosomal Recessive Inheritance

Genes present on one of the 22 pairs of chromosomes/autosomes are known as autosomal. In autosomal recessive disease, two abnormal copies of the gene, typically one from each parent, must be inherited to cause symptoms of the condition. Usually, parents of the child affected by an autosomal recessive condition carry one copy of an abnormal gene and are unaffected because of normal functioning of the other gene. In this scenario, where both parents are carriers of an abnormal autosomal recessive gene, there is a 25% chance (1 in 4) that any offspring, irrespective of gender will be affected by the disorder. There is a 50% chance (1 in 2) that the offspring will be a carrier (have one abnormal gene), and a 25% (1 in 4) that the baby will not inherit the faulty gene, and therefore will not be affected by the condition or be able to pass it on to their children (See Figure 24:4). Chances remain the same for all future pregnancies, and the outcome of each pregnancy is not affected by previous pregnancies.

Figure 24:4 Autosomal Recessive Inheritance - SCID Example



The following are frequently recognized autosomal recessive deficiencies:

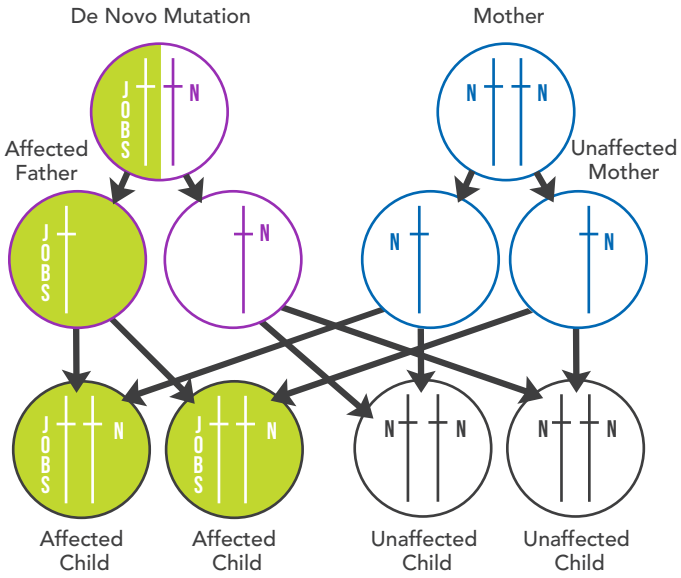
- Various forms of Severe Combined Immunodeficiency (SCID)
  - Adenosine deaminase (ADA) deficiency
  - Recombinase activating gene (RAG) deficiency
  - Jak3 deficiency
  - ARTEMIS SCID
- MHC class II deficiency
- Chronic Granulomatous Disease (CGD), three forms
- Leucocyte adhesion deficiency (LAD)
- Chediak-Higashi syndrome
- Familial forms of hemophagocytic lymphohistiocytosis (HLH).

The incidence of autosomal recessive diseases is rare. Most affected infants do not have any previous family history. However, consanguineous marriages and increased frequency of asymptomatic carriers of mutations in certain populations (such as ARTEMIS SCID in Navajo populations) increase the incidence of such diseases.

Autosomal Dominant Inheritance

Autosomal dominant inheritance is a mode of inheritance where only one copy of the faulty gene is needed for the disease to occur irrespective of the normal gene inherited from the other parent. This affects both males and females, and there is a 50% chance (1 in 2) of the offspring of an affected parent to have the disease. The risk is the same in every pregnancy (See Figure 24:5). Many times, a patient affected with a condition associated with autosomal dominant disease will be the first affected person in their family. In this case, the faulty gene developed after the joining of egg and sperm during fertilization.

Figure 24:5 Autosomal Dominant Inheritance - Jobs Syndrome Example



Examples of Autosomal Dominant Inheritance:

- Hyper IgE Syndrome, due to mutations in STAT3 (Jobs syndrome)
- Warts, Hypogammaglobulinemia, Infections, and Myelokathexis (a form of neutropenia – low neutrophil counts), also known as WHIM syndrome
- Some rare forms of defects in the IFN-γ/IL-12 pathway
- STAT1 and STAT3 gain of function disorders of immune regulation

Carrier Testing

With increasingly well-defined immunodeficiencies, it has now become possible to make a molecular diagnosis by analyzing recognized patterns and proteins present or absent in a particular disorder. DNA analysis can be performed to identify the presence of an abnormal gene. Once the diagnosis is confirmed, DNA samples from family members can be analyzed to establish if they are carriers or not.

In cases that do not fit a typical pattern or where initial genetic testing does not make a diagnosis, there are now other advanced techniques that may identify the underlying genetic cause. These include next-generation sequencing (NGS) or high throughput sequencing:

- Whole genome sequencing (WGS) involves reading an individual's entire DNA sequence,
- Whole exome sequencing (WES) involves reading the sequences of all the protein-coding genes, and
- NGS panel is sequencing a particular group of disease genes.

These techniques allow precise diagnosis in increasing numbers of families. Consult with your physician or genetic counselor to learn if carrier detection is available in your specific situation.

Prenatal Diagnosis

In families where an immunodeficiency has been recognized, some parents may wish to know whether future babies are affected by the disorder. Testing to determine whether unborn babies are affected is possible in most situations where the immunodeficiency has a known genetic cause, such as XLA or RAG1 SCID. However prenatal testing is not possible if the genetic cause has not been defined despite a well characterized clinical immunodeficiency, such as most cases of Common Variable Immune Deficiency (CVID).

Methods of prenatal diagnosis include:

- Chorionic villus sampling (CVS) or amniocentesis associated laboratory techniques for prenatal diagnosis: DNA (deoxyribonucleic acid) from the fetus can be obtained by CVS or amniocentesis. These procedures can be performed to obtain a fetal sample for chromosome, gene or biochemical testing. CVS is usually scheduled at 10-13 weeks of pregnancy and involves the retrieval of a tiny sample of the developing placenta from the womb. Amniocentesis is typically performed at 16 to 17 weeks of pregnancy and involves the withdrawal of fluid

containing fetal cells that surrounds the fetus. Both procedures have a small risk of miscarriage that should be balanced against the benefits of the testing. Two techniques of DNA analysis are:

1. Mutation analysis: This method is 100% reliable if the mutation is known
2. Linkage analysis: If the mutation is unknown, but the diagnosis is definite, prenatal diagnosis may be possible using linkage analysis. This will be slightly less reliable than mutation detection.

- Noninvasive prenatal testing (NIPT), sometimes called noninvasive prenatal screening (NIPS), is a method of determining the risk that the fetus will be born with certain genetic abnormalities. This testing analyzes small fragments of DNA that are circulating in a pregnant woman's blood. Unlike most DNA, which is found inside a cell's nucleus, these fragments are free-floating and not within cells, and so are called cell-free DNA (cfDNA). These small fragments usually contain fewer than 200 DNA building blocks (base pairs) and arise when cells die off and get broken down and their contents, including DNA, are released into the bloodstream.
- During pregnancy, the mother's bloodstream contains a mix of cfDNA that comes from her cells and cells from the placenta. The placenta is tissue in the uterus that links the fetus and the mother's blood supply. These cells are shed into the mother's bloodstream throughout pregnancy. The DNA in placental cells is usually identical to the DNA of the fetus. Analyzing cfDNA from the placenta provides an opportunity for early detection of certain genetic abnormalities without harming the fetus.
- NIPT is a screening test, which means that it will not give a definitive answer about whether or not a fetus has a genetic condition. The test can only estimate whether the risk of having certain conditions is increased or decreased. In some cases, NIPT results indicate an increased risk for a genetic abnormality when the fetus is actually unaffected (false positive), or the results indicate a decreased risk for a genetic abnormality when the fetus is actually affected (false negative). Because NIPT analyzes both fetal and maternal cfDNA, the test may detect a genetic condition in the mother.
- Enzyme analysis: Concentration and/or function of the enzyme that is known to be defective can be measured. Examples are adenosine deaminase (ADA) and purine nucleoside phosphorylase (PNP), deficiencies which both cause forms of SCID. Both of these enzymes can be analyzed in a chorionic villus sample taken at 11 to 12 weeks of gestation.
- Pre-implantation genetic diagnosis (PGD): This is a useful, viable option for couples who are at high risk of bearing a child with a single gene disorder. It involves in vitro fertilization (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. Implantation of an unaffected embryo via IVF in individuals with SCID, LAD, CGD, and XLA have been previously reported. Evidence supporting the efficacy of PGD in the detection of some immunodeficiencies such as Wiskott-Aldrich syndrome, X-linked Hyper IgM Syndrome (HIGM), X-linked hypohidrotic ectodermal dysplasia with immune deficiency (HED-ID); Ataxia-Telangiectasia is also available.

Gamete donation (use of donor egg or sperm) to conceive a child via IVF for infertile couples can be associated with risk of inheritable forms of PI, particularly if the health status of the donor with regard to immunodeficiency has not been established.

In conclusion, PI is a group of inherited diseases caused by genetic abnormalities that weaken the immune system. They could be inherited by one of three modes, X-linked recessive, autosomal recessive, or autosomal dominant. It is undeniable that raising a child with PI places physical, emotional, and financial burden on families, and many families might wish to maintain current family size to avoid the possibility of having another affected child. Those choices are very personal. It is recommended that parents are well-informed by healthcare professionals such as pediatricians, genetic counselors, immunologists and obstetricians on current medical advances relating to the diseases. Lately, there have been new developments in understanding the genetic causes of these rare diseases, and genetic counseling is highly recommended in families with a known history of PI as it allows option for early detection, diagnosis, and treatment.

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