HKU Med
LKS Faculty of Medicine
Department of Medicine
香港大學內科學系

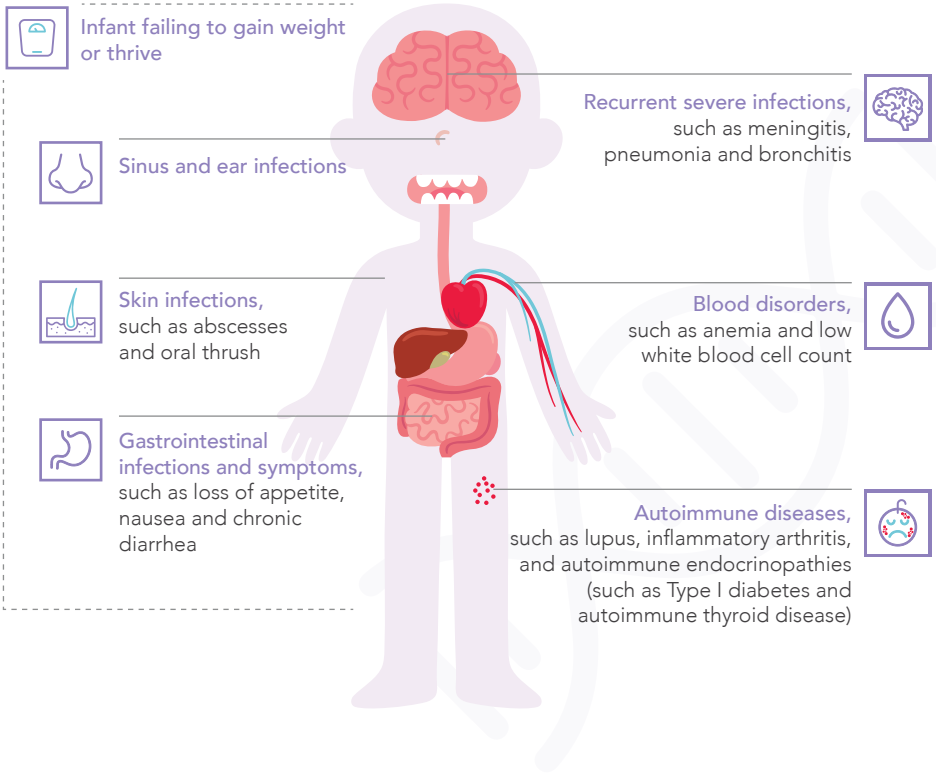
Genetic Testing for Immunodeficiencies

An Introduction

What is Primary Immunodeficiency?

Primary immunodeficiency (PID) refers to a group of inherited genetic disorders that causes immune system defects.[1] Most PID patients become vulnerable to infections caused by bacteria, viruses and fungi.[2] Early diagnosis and treatment of PID lower the risk of exacerbations and complications.[3]

Patients presenting with the following recurrent or severe symptoms (disproportionate to their medical history) may have PID.[2,3] Please consult your immunologist for further evaluation if there is any suspicion.



PID=primary immunodeficiency.

Current PID Treatment Options:[2]

1 Immunoglobulin Replacement Therapy

Provides immunoglobulin (antibodies) to replace patients with antibody deficiencies.

2 Anti-microbial Prophylaxis

Preventive measures against infections, including using antibiotics, antifungal medications and vaccines

3 Hematopoietic stem cell transplantation

Some patients with potentially fatal PID may require transplantation for long-term survival and recovery of the immune system.

How Does Genetic Testing Assist in PID Diagnosis and Treatment?[4]

Improve Treatment Plan

Find the Right Treatment

The diagnosis of PID may be challenging and an exact genetic defect may not be found using conventional testing.

Genetic tests may help to provide more detailed disease information to enable your immunologist to accurately diagnose and manage your disease.

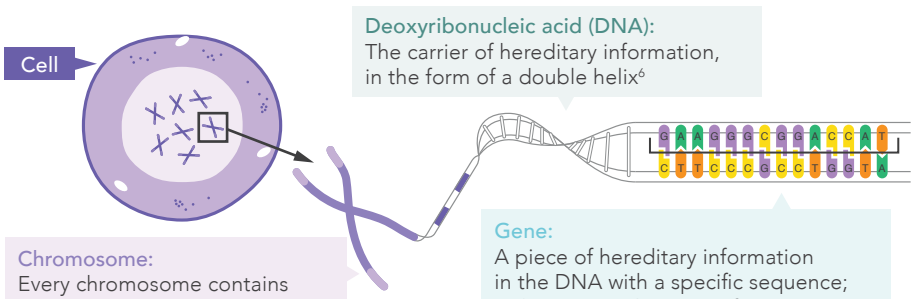
To better understand how genetic testing can benefit PID patients, we must first learn about genes.

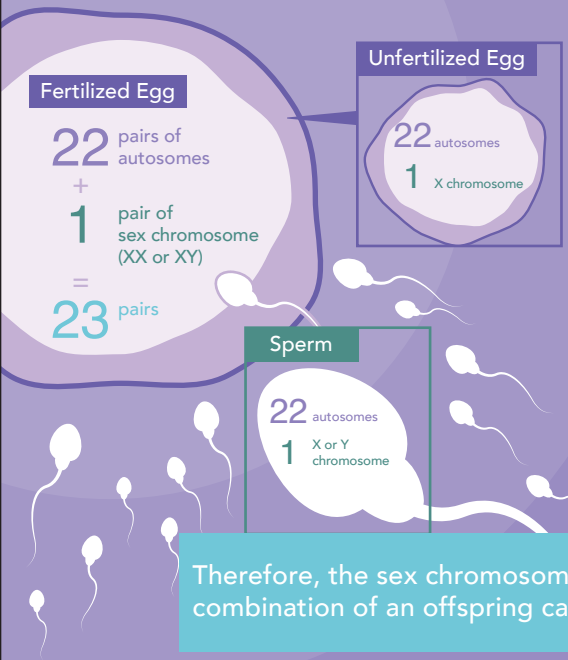
PID=primary immunodeficiency.

What are Genes?

PID includes disorders that result from various genetic mutations,[2] but what is the principle and function of the genes?

Genes are the hereditary information that is passed on from parents to their children. It determines all the traits of the offspring, from their height, skin colour and sex, to the number of various proteins in the body. More importantly, some hereditary diseases can also be passed on from generation to generation.[5]





Normal human cells have 46 chromosomes. The sperm from the father and the egg from the mother each provides 23 of them to form 23 pairs of chromosomes. Among those are 22 pairs of autosomes and one pair of sex chromosome, which determines the sex of the offspring.[6]

Sex chromosomes are divided into X and Y chromosomes. An egg always has an X chromosome, but a sperm has either an X or Y chromosome.[6]

Therefore, the sex chromosome combination of an offspring can be:[6]

XX for female ♀

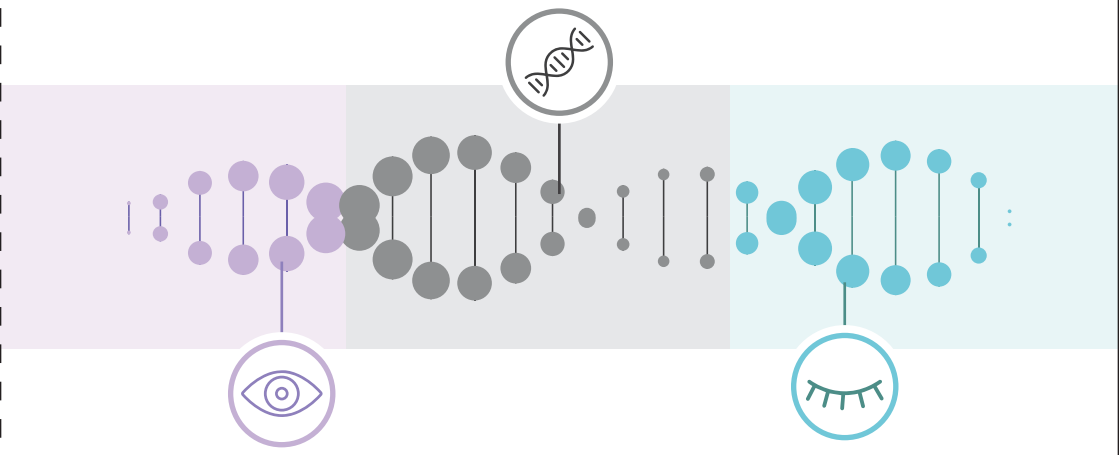
XY for male ♂

DNA=deoxyribonucleic acid; PID=primary immunodeficiency.

Dominant and Recessive Gene[7]

If the sperm and egg each provides genes from the father and mother respectively, then which genetic traits will the offspring show? Let's take a look at the comparison below.

Genes can be classified as dominant or recessive.



Dominant traits can be expressed when at least one dominant gene is inherited.

Recessive traits can only be expressed when both of the inherited genes are recessive.

How genes are matched directly affect the characteristics of the offspring. Here is an example: if the gene for black hair is dominant (D) and that for blonde hair is recessive (d), all the gene pairing combinations are shown in the table below.

	Dominant Gene D (Black hair)	Recessive gene d (Blonde hair)
Dominant Gene D (Black hair)	D + D = DD The offspring inherits two dominant genes and has black hair	D + d = Dd The offspring inherits one dominant gene and has black hair
Recessive gene d (Blonde hair)	d + D = dD The offspring inherits one dominant gene and has black hair	d + d = dd The offspring inherits two recessive genes and has blonde hair

How is PID Inherited?[8]

PID can be inherited through three different ways.

1 X-linked Disorders

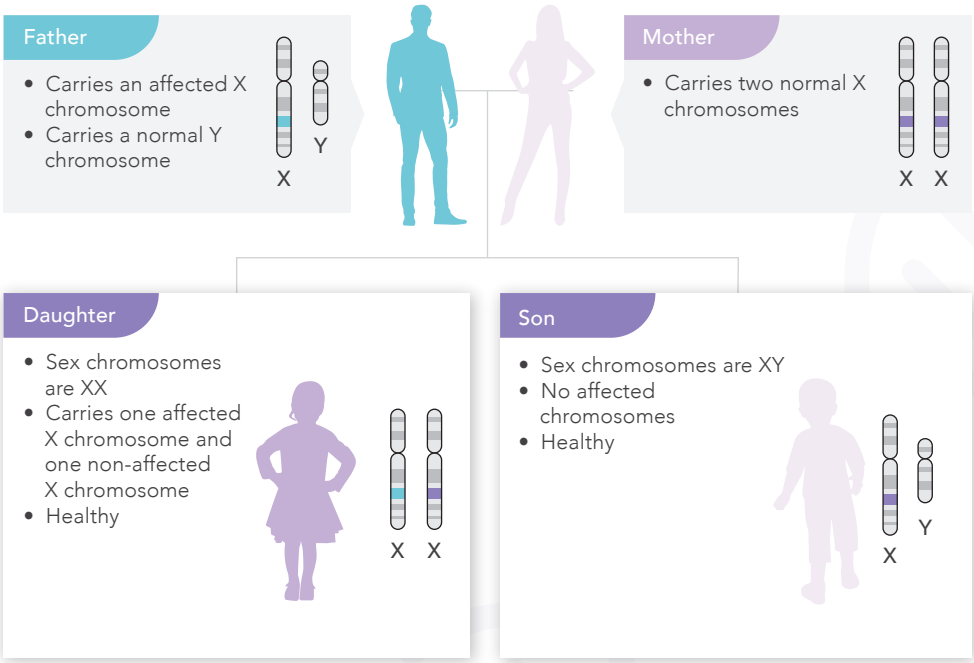
Male and female have different sex chromosomes. Some PID may be inherited in genes found on the X-chromosome.

If the father is a carrier of an affected X-chromosome, neither the son nor the daughter will inherit PID, but the daughter is definitely carrying the gene mutation.

100%
chance of the daughter carrying the mutated gene

0%
chance of the son carrying the mutated gene

If the father is a carrier of an affected X chromosome



PID=primary immunodeficiency.

Since the combination of male sex chromosomes is XY, sons will always inherit their Y chromosome from their father, and the X chromosome from the mother.

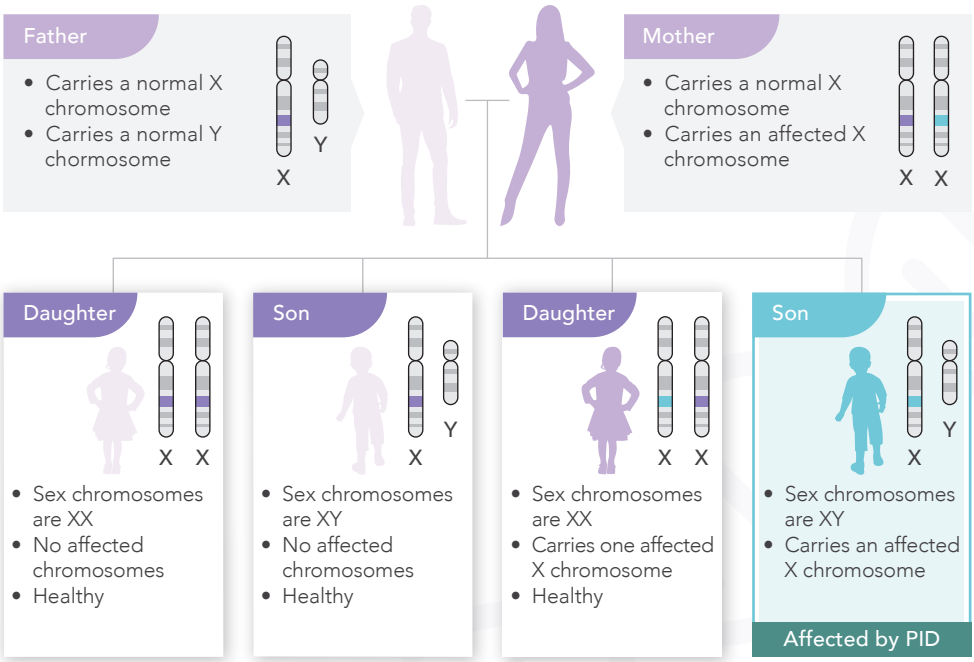
In most cases, if the mother carries an affected X chromosome, the daughter will stay healthy, but the son will have a 50% chance of inheriting PID.

50% of sons inherit the affected gene and have a PID

50% of daughters carry the affected gene

50% chance of the offspring not inheriting the affected gene

If the mother is a carrier of an affected X chromosome



PID=primary immunodeficiency.

2 Autosomal Recessive Inheritance

Both parents must have the same recessive gene mutation for their offspring to potentially be affected by PID. This type of mutation is unrelated to sex chromosomes, so offspring of either gender have equal chances of inheriting the affected gene.

25%
chance of inheriting the affected gene and having a PID

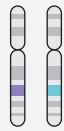
50%
chance of carrying the recessive affected gene

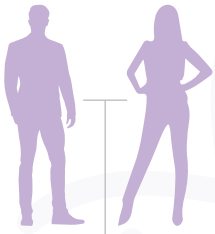
25%
chance of not inheriting the affected gene

If both parents have the same recessive affected gene

Father

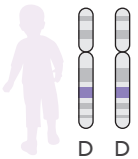
- Carries a normal gene D
- Carries a recessive affected gene d



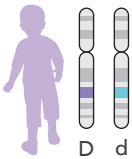


Mother

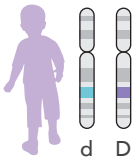
- Carries a normal gene D
- Carries a recessive affected gene d



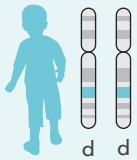
- Gene combination is DD
- No affected genes
- Healthy



- Gene combination is Dd
- Carries one recessive affected gene d
- Healthy



- Gene combination is dD
- Carries one recessive affected gene d
- Healthy



- Gene combination is dd
- Carries two recessive affected genes d

Affected by PID

PID=primary immunodeficiency.

3 Autosomal Dominant Inheritance

Unlike recessive inheritance, offspring will be affected by PID once they inherit a signal mutated gene.

If either parent has a dominant affected gene, there is a risk of passing it down to their offspring. This type of mutation is unrelated to sex chromosomes, so offspring of either gender have equal chances of inheriting the gene and having a PID.

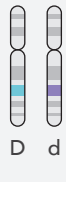
50%
chance of inheriting
the affected gene and having a PID

50%
chance of not inheriting
the affected gene

If the father is a carrier of a dominant affected gene

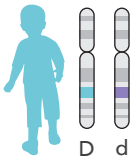
Father

- Carries a normal gene d
- Carries a dominant affected gene D



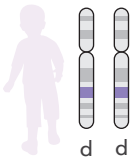
Mother

- Carries two normal genes d

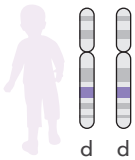


- Gene combination is Dd
- Carries one dominant mutated gene D

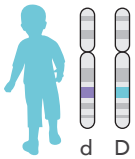
Affected by PID



- Gene combination is dd
- No affected genes
- Healthy



- Gene combination is dd
- No affected genes
- Healthy



- Gene combination is dD
- Carries one dominant affected gene D

Affected by PID

PID=primary immunodeficiency.

How will my genome be examined?

There are several methods of looking at your genome:

Some tests look at a single gene, some look at a panel of genes (a few selected genes), and some look at your entire genome (all the genes). For your immunological condition, it is likely that a genetic test will be done on a selected group of genes only, also known as a gene panel.[4]

The results of genetic tests are rarely straightforward, which often makes them challenging to interpret.[4] Discussing your results with your doctor can help you understand them better.

What Do Genetic Test Results Mean?[4]

Positive Result

- Confirms a pathogenic genetic mutation in targeted genes
- Confirms PID or increased risk of having PID
- Results are not predictions for PID severity
- Sometimes a mutation may be found in unexpected genes. These are called incidental findings

Negative Result

- The laboratory did not find any changes in your genes that are likely contributing to your immunological condition
- Not a carrier of specific mutated genes
- Keep in mind that diseases can also be affected by factors that are not genetic

Uncertain Result

Natural and harmless genetic variations in our bodies could affect the results. However, having a variation does not necessarily mean that you have a disease, or show symptoms of a disease. Most variations are not supported by enough evidence to conclude whether they are disease-causing or not. Having an immediate family member or patient with similar symptoms take the same tests might provide more accurate results.

PID=primary immunodeficiency.

What are the Benefits and Limitations of Genetic Testing?

Genetic testing has its advantages and limitations.

Benefits[4]

- Easy sampling
- Potential information for more accurate diagnosis
- Provides disease information for suitable treatment plans
- Negative test results can prevent unnecessary workup and further tests
- Provides information for the family members who may be at risk

Limitations[4,8]

- It can take up to months before you receive a result
- Testing may not result in definitive answers. Results may not be clear-cut and your diagnosis can remain uncertain
- Your test will only focus on certain genes of interest and cannot detect all genetic changes that may potentially cause diseases or disorders
- Results may not always help directly with treatment. For example, there may be a lack of treatment strategies despite your immunological diagnosis

Considerations Before Taking a Genetic Test?[4,9]

Genetic testing is completely voluntary.

We encourage communication between you and your doctor, as well as your family members before making an informed decision to undergo genetic testing. It is important to consider what the test results might mean for you and your family.

Consider the Following Factors

Is the test necessary?

Do you want to take the test?

How will the results affect the management of your medical, financial, and insurance plans?

Mental preparation

Are you mentally prepared for the emotional and psychological impact of your results?

Are you prepared to handle any incidental findings?

Effect on family members

Be mindful that results of your test can reveal genetic information about other family members as well as yourself.

Family planning

If you are planning to have children, knowing whether you are a carrier for a genetic variant may be helpful. Your doctor or a genetic counsellor can explain the risk of your future children potentially inheriting the disease.

HKU Med LKS Faculty of Medicine
Department of Medicine
香港大學內科學系

Genetic testing is beneficial for the

Understanding **Diagnosis** **Treatment**

# of primary immunodeficiencies

The content of this booklet is for reference only.

To learn more about primary immunodeficiency and genetic testing, please consult your physician.

References:
1. Meyts I, Bousfiha A, Duff C, et al. Primary immunodeficiencies: a decade of progress and a promising future. Front Immunol. 2021;11:625753. 2. Stiehm ER, Chin TW, Haas A, Peerless AG. Infectious complications of the primary immunodeficiencies. Clinical Immunology and Immunopathology. 1986;40(1):69-86. 3. McCusker C, Warrington R. Primary immunodeficiency. All Asth Clin Immun. 2011;7(S1):S11. 4. Genetic Testing. MedlinePlus Genetics. Accessed November 17, 2021. https://medlineplus.gov/download/genetics/understanding/testing.pdf 5. Inheritance. Immune Deficiency Foundation. Accessed November 17, 2021. https://primaryimmune.org/about-primary-immunodeficiencies-diagnosis-information/inheritance 6. Finegold D. Genes and Chromosomes. MSD Manual Consumer Version. Accessed November 17, 2021. https://www.msdmanuals.com/home/fundamentals/genetics/genes-and-chromosomes 7. Talking Glossary of Genetic Terms - Recessive. National Human Genome Research Institute. Accessed November 17, 2021. https://www.genome.gov/genetics-glossary/Recessive 8. Heimall JR, Hagin D, Hajjar J, et al. Use of genetic testing for primary immunodeficiency patients. J Clin Immunol. 2018;38(3):320-329. 9. Genetic Counseling. CDC. Accessed November 17, 2021. https://www.cdc.gov/genomics/gtesting/genetic_testing.htm.

Courtesy of Dr Valerie Chiang,
Division of Clinical Immunology, Department of Pathology, Queen Mary Hospital
And Dr Philip Li,
Department of Medicine, The University of Hong Kong