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INTERNATIONAL
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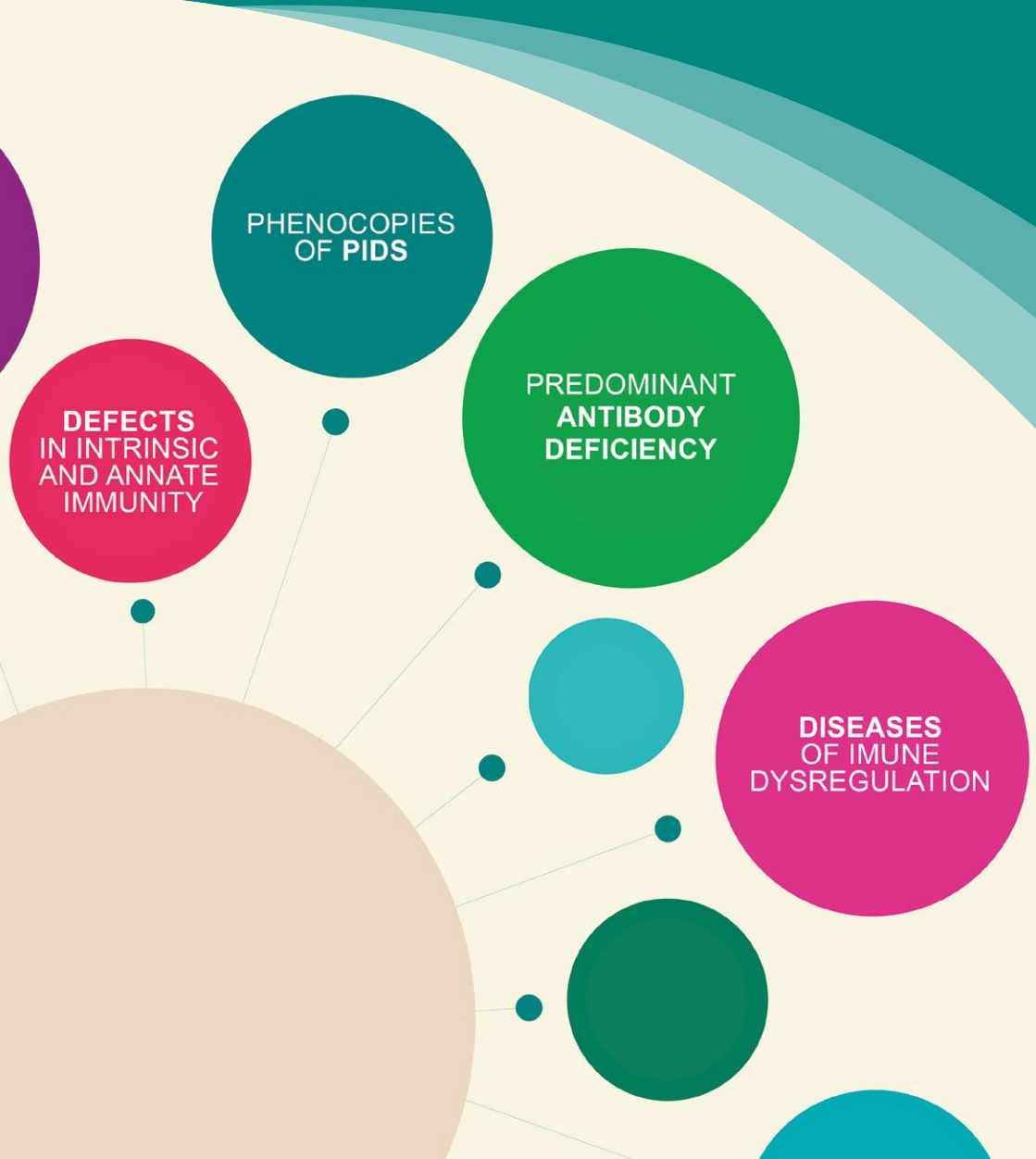
FOR PRIMARY IMMUNODEFICIENCIES

HOW ARE **PRIMARY IMMUNODEFICIENCIES CLASSIFIED?**



KEY ABBREVIATIONS

CGD	Chronic granulomatous disease
CVID	Common variable immunodeficiency
IBD	Inflammatory bowel disease
IgA/D/E/G/M	immunoglobulins A, D, E, G or M
IPOPI	International Patient Organisation for Primary Immunodeficiencies
PID	Primary immunodeficiency
SCID	Severe combined immunodeficiency

How are primary immunodeficiency diseases classified? (1st edition)

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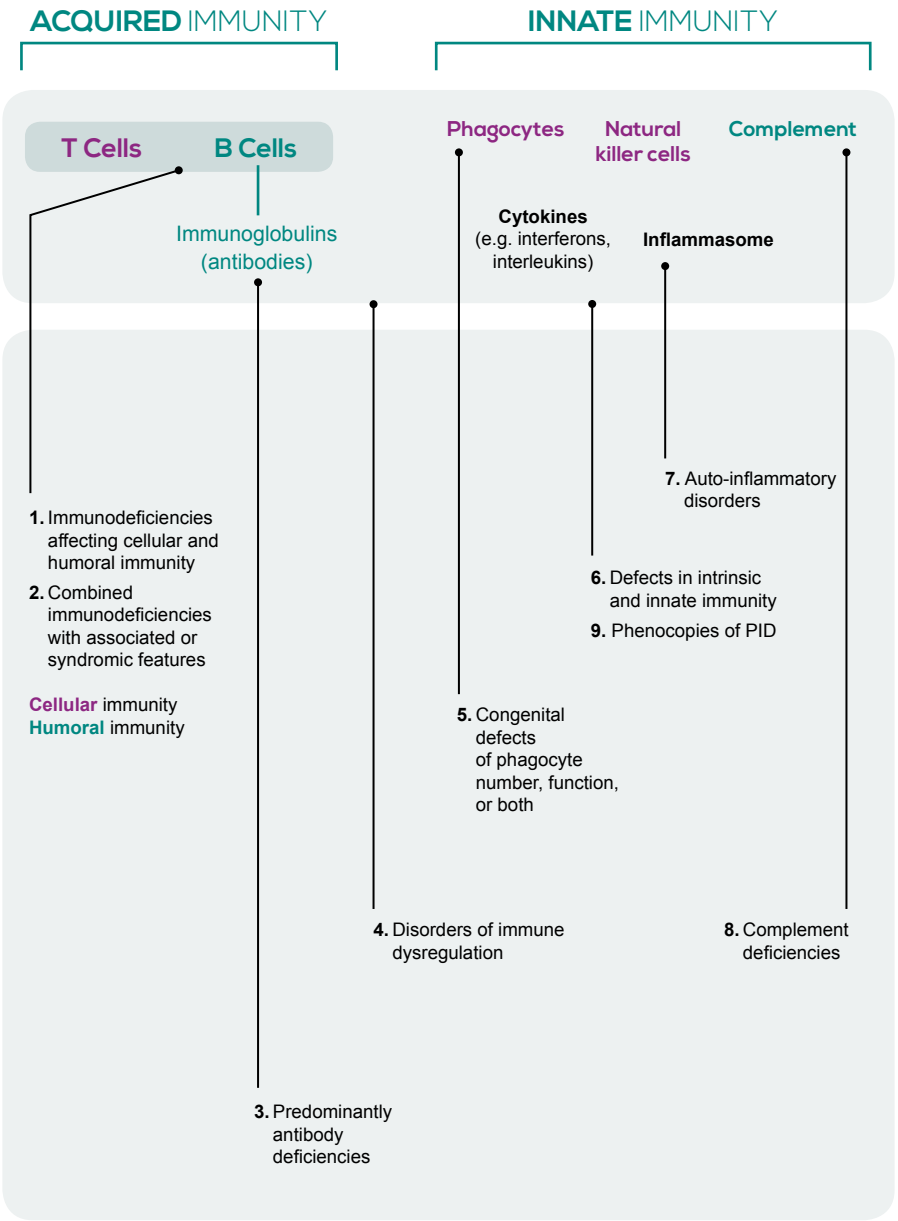
INTRODUCTION

This booklet explains the latest classification system for primary immunodeficiencies (PIDs).

PIDs are rare diseases that occur when components of the immune system are either not present or not working properly. PIDs are caused by defects or abnormalities in the DNA, or genes. In recent years, advances in genetic testing have allowed many of these abnormalities to be identified. Currently, over 280 different P IDs are recognised. In 2015, experts published an updated international PID classification system to increase awareness of PIDs, to help doctors to recognise them, and to promote optimal treatment for patients (see “Further reading” on page 8).

The latest classification system divides PIDs into nine categories (see Figure page 4) according to the components of the immune system affected. PIDs are complex diseases and previously some PIDs were placed in more than one category. In the latest system each PID is assigned to a specific category according to the main genetic and immunological abnormality. The same genetic abnormality can cause different effects in different people, however. To use the scientific terminology, a particular genetic defect (or ‘genotype’) can produce a different clinical disease profile (or ‘phenotype’) in different patients. This variability results from the complicated interactions between genes and other factors related to the patient and his or her environment. The fact that gene defects can have such variable effects has been known for many years, but it has become clearer thanks to improvements in genetic technologies.

This booklet explains how PIDs are now classified and gives examples of diseases from each class, together with some of their particular features. As always, you can obtain further information on PIDs from your healthcare team and from the International Patient Organisation for Primary Immunodeficiencies (**www.ipopi.org**) and other patient organisations.



1. IMMUNODEFICIENCIES AFFECTING CELLULAR AND HUMORAL IMMUNITY

These PIDs cause a combined immune defect affecting both types of 'acquired' immunity, i.e. both cellular and humoral responses. Acquired immunity remembers when it encounters an invading foreign cell or molecule ('antigen') and quickly mounts a specific response on subsequent encounters. Cellular acquired responses are mediated by T cells (also called T lymphocytes), which kill infected cells, help B cells and control the immune response. Humoral immunity is mediated by B cells (B lymphocytes) which produce antibodies (or 'immunoglobulins') that help T cells and other immune cells to recognize and attack antigens.

Severe combined immunodeficiency

Severe combined immunodeficiency (SCID) is a rare and potentially fatal PID usually identified in babies. SCID causes an absence of T and B cell function, leaving patients at high risk of serious infections. SCID can be caused by many genetic abnormalities and is sub-classified according to the levels of B cells in the blood. T^-B^+ SCID causes very low levels of T cells with high or normal levels of B cells that nevertheless do not work properly. This subclass includes γc deficiency, the commonest form of SCID. T^-B^- SCID causes very low levels of both T cells and B cells, e.g. adenosine deaminase (ADA) deficiency.

Combined immunodeficiencies generally less profound than SCID

This large group of PIDs includes CD40 and CD40L deficiencies and major histocompatibility complex (MHC) deficiencies.

CD40 and CD40L are proteins found on B and T cells, respectively. Normally, these proteins help T cells tell B cells when to produce immunoglobulins A (IgA), E (IgE) and G (IgG), rather than immunoglobulin M (IgM). These PIDs result in normal or high levels of IgM (and hence are sometimes called hyper-IgM syndromes), but low levels of the other immunoglobulins.

MHC are molecules normally found on the surface of lymphocytes that present antigens to T cells. These PIDs are divided into MHC Class I and Class II deficiencies according to the type of MHC affected.

2. COMBINED IMMUNODEFICIENCIES WITH ASSOCIATED OR SYNDROMIC FEATURES

This diverse group of PIDs is associated with various T and B cell abnormalities, some of which can be very severe. Its 10 sub-categories include:

- Congenital thrombocytopenias, namely Wiskott-Aldrich syndrome (WAS) and WAS protein-interacting protein (WIP) deficiency. Thrombocytopenia is a lack of platelet cells, which are important for blood clotting, and hence these deficiencies are associated with abnormal bleeding.
- DNA repair defects, including ataxia telangiectasia and immunodeficiency with centromeric instability and facial anomalies (ICF).
- Thymic defects with additional congenital anomalies, e.g. DiGeorge syndrome.

Other categories are: Immune-osseous dysplasias, various hyper-IgE syndromes, dyskeratosis congenita (DKC), vitamin B12/folate metabolism defects, anhidrotic ectodermaldysplasia with immunodeficiencies (EDA-ID, including NEMO deficiency), calcium channel defects and others, such as veno-occlusive disease and immunodeficiency (VODI).

3. PREDOMINANTLY ANTIBODY DEFICIENCIES

The most common PIDs worldwide, antibody deficiencies put patients at risk of infections and autoimmune diseases, where the immune system attacks parts of the patient's own body. These PIDs are categorised according to the specific immunoglobulin deficiency and the B cell level in the blood.

Severe reduction in all serum immunoglobulin isotypes with profoundly decreased or absent B cells

Patients with these PIDs lack all types of immunoglobulin, as well as B cells, and hence are at risk of severe or recurrent bacterial infections. They include Bruton's tyrosine kinase (BTK) deficiency and thymoma with immunodeficiency (Good syndrome).

Severe reduction in at least two serum immunoglobulin isotypes with normal or low number of B cells

This group includes common variable immunodeficiency (CVID). CVID is characterised by low levels of IgG, IgA and/or IgM. Although its effects vary, most patients have recurrent infections and some have enlarged lymph nodes and autoimmune blood disorders.

Severe reduction in serum IgG and IgA with normal/elevated IgM and normal numbers of B cells

This group includes activation-induced deaminase (AID) deficiency (this has nothing to do with the acquired immune deficiency syndrome, or AIDS) and uracil-DNA glycosylase (UNG).

Isotype or light chain deficiencies with generally normal numbers of B cells

These include several relatively mild PIDs that may not cause symptoms, e.g. isolated IgG subclass deficiency, immunoglobulins heavy chain mutation or deletions, immunoglobulin kappa light chain (IGKC) deficiency, and transient hypogammaglobulinaemia of infancy. However, two PIDs affecting the phosphatidylinositol 3-kinase (PI3K) system can be more serious and are associated with viral infections.

4. DISEASES OF IMMUNE DYSREGULATION

This is a large, diverse category of PIDs caused by genetic abnormalities affecting mechanisms that control the immune system. Some of these PIDs have been added in recent years and they are sub-divided into six categories:

- Familial haemophagocytic lymphohistiocytosis (FHL) syndromes: these include Chediak-Higashi syndrome, a rare condition that causes light colouring (hypopigmentation) of the skin, hair and eyes and which can progress to a life-threatening stage.
- T cell regulatory cell genetic defects.
- Autoimmunity with or without lymphoproliferation, e.g. autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy (APECED), a condition that can cause autoimmune disease affecting organs that produce hormones (e.g. the pancreas, thyroid and adrenal glands).
- Autoimmune lymphoproliferative syndrome (ALPS), in which an uncontrolled proliferation of lymphocytes causes autoimmune effects on various organs, e.g. the spleen, lymph system and blood.
- Immune dysregulation with colitis, e.g. interleukin-10 deficiencies, which are associated with inflammatory bowel disease (IBD).
- Type 1 interferonopathies, associated with an abnormally high activity of Type 1 interferons, a type of protein that help to trigger immune immune responses. Many of these PIDs can damage the brain, as well as the blood and other organs.

5. CONGENITAL DEFECTS OF PHAGOCYTE NUMBER, FUNCTION OR BOTH

Phagocytes, which include neutrophils and macrocytes, are immune cells that swallow and kill invading microorganisms. They are important components of the 'innate' or non-specific immune system which (unlike the acquired immune system; see p. 4) is not specific for particular antigens and does not need a prior exposure to identify and attack antigens.

This class of PIDs comprises various 'congenital' defects (i.e. defects present from birth) that affect the number of phagocytes or how they work. They are divided into four sub-classes:

- Congenital neutropenias, e.g. elastase deficiency, Barth syndrome and Cohen syndrome. Neutropenia means a lack of neutrophils in the blood.
- Defects of motility, e.g. in the migration of phagocytes toward antigens. An example is leukocyte adhesion deficiency (LAD).
- Defects of respiratory burst, a process whereby neutrophils and macrophages normally release chemicals (e.g. hydrogen peroxide) to kill invading cells. These PIDs are forms of chronic granulomatous disease (CGD). CGD can be caused by several different genetic defects, with X-linked CGD being the most common. Patients with CGD are susceptible to infections and inflammatory conditions, e.g. IBD.
- Other defects, e.g. GATA2 deficiency (mono MAC syndrome), a PID affecting monocytes (a type of white blood cell) and 'natural killer' cells.

6. DEFECTS IN INTRINSIC AND INNATE IMMUNITY

This class includes various PIDs caused by genetic defects that put patients at risk of serious infections by particular micro-organisms, including Mycobacteria, viruses and fungi. These PIDs are divided into nine sub-classes.

- Mendelian susceptibility to mycobacterial disease (MSMD): 'Mendelian' disorders are those caused by a defect in a single gene. This subclass includes various PIDs that cause patients to be susceptible to infection by Mycobacteria and Salmonella.
- Epidermodysplasia verruciformis, a skin disorder caused by human papilloma virus (HPV) infection.
- Predisposition to severe viral infection, e.g. STAT-1 or -2 deficiency.
- Herpes simplex encephalitis, i.e. inflammation of the brain caused by the herpes simplex virus.
- Predisposition to invasive fungal diseases, i.e. serious infection caused by Candida fungi (CARD9 deficiency).
- Chronic mucocutaneous candidiasis (CMC), a superficial Candida infection of the skin, nails and the lining of the respiratory and digestive tract (known as 'mucous membranes').
- Toll-like receptor (TLR) signalling pathway deficiency, which renders patients susceptible to bacterial infection (e.g. IRAK-4 deficiency).
- Isolated congenital asplenia (ICA): asplenia means an absence of the normal function of the spleen, which normally plays a key role in humoral and cellular immunity.
- Trypanosomiasis, i.e. infection by microorganisms called Trypanosoma (e.g. Chagas disease).

7. AUTO-INFLAMMATORY DISORDERS

Auto-inflammatory disorders are diseases that result from inflammation caused mainly by abnormal stimulation of the innate immune system. This group is divided into two sub-classes.

Defects affecting the inflammasome: Inflammasomes are proteins involved in identifying invading microorganisms and triggering the innate immune response. This class includes familial Mediterranean fever, a rare condition found mainly in people from the south-eastern Mediterranean area.

Other examples include mevalonate kinase deficiency (or hyper IgD syndrome), Muckle–Wells syndrome, familial cold autoinflammatory syndrome and neonatal onset multisystem inflammatory disease (NOMID), which is also called chronic infantile neurologic cutaneous and articular syndrome (CINCA).

Non inflammasome-related conditions: These include tumour necrosis factor receptor-associated period syndrome (TRAPS), pyogenic sterile arthritis/ pyoderma gangrenosum acne (PAPA syndrome) and Blau syndrome.

8.COMPLEMENT DEFICIENCIES

The complement system comprises a group of proteins that help phagocytes find, identify and engulf microorganisms, and which can directly kill bacteria and viruses themselves. These PIDs are divided into two sub-classes:

Integral complement cascade component deficiencies, which include deficiencies in various forms of complement (C1–9). Many of these conditions are associated with systemic lupus erythematosus (SLE), an autoimmune disease. Patients are also susceptible to infection by a group of 'encapsulated' microorganisms (i.e. germs with an outer coating called a capsule), including Neisseria.

Complement regulatory defects: This subclass comprises numerous PIDs caused by deficiencies in factors that control the complement system, e.g. C1 inhibitor and Factors B, D and H.

9. PHENOCOPIES OF PID

This is a relatively new category of PIDs, only added to the classification system in 2014. These conditions do not result from inherited genetic mutations, but instead are acquired during life. They are caused by 'somatic' genetic mutations or by autoantibodies.

Somatic mutations are acquired by cells – unlike other mutations that cause other PIDs, these are not inherited and are not passed on to offspring. This class includes several autoimmune diseases, such as autoimmune lymphoproliferative syndrome (ALPS).

Autoantibodies are antibodies that target the body's own proteins. Antibodies against components of the immune can cause forms of immunodeficiency, e.g. adult-onset immunodeficiency and atypical haemolytic urea syndrome.

Experts expect that many more PID phenocopies are likely to be identified in the future.

FURTHER READING

- Bousfiha A, et al. The 2015 IUIS Phenotypic Classification for Primary Immunodeficiencies. J Clin Immunol 2015;35:727–38 (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4083684/).
- Picard C, et al. Primary Immunodeficiency Diseases: an Update on the Classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency 2015. J Clin Immunol 2015;35:696–726 (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4659841/).

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 in 56 countries worldwide, please visit **www.ipopi.org**.

Provided by

IMMUNO DEFICIENCY UK

Supporting families affected by primary and secondary immunodeficiency

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.

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