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Classification of primary immunodeficiency diseases by the International Union of Immunological Societies (IUIS) Expert Committee on Primary Immunodeficiency 2011

H. Chapel
Nuffield Department of Medicine, University of Oxford, John Radcliffe Hospital, Oxford, UK

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Correspondence: H. Chapel, Nuffield Department of Medicine, University of Oxford, Level 7, John Radcliffe Hospital, Headley Way, Oxford OX3 9DU, UK.
E-mail: helen.chapel@ndm.ox.ac.uk

Helen Chapel for the IUIS PID Expert Committee in 2011

Traditionally the International Union of Immunological Societies (IUIS) Expert Committee on Primary Immunodeficiency has revised the classification of primary immunodeficiency diseases (PIDs) every 2 years since 1973. The aim is to provide a document that not only demonstrates the scientific basis of these conditions, but assists clinicians in diagnosing patients with this rare group of diseases. In addition, the PID committee has recently advised, based on the latest tables, the revision of the World Health Organization International Disease (ICD) codes as relating to PIDs, due for publication in 2015. The ICDs form the basis on which funding for health care is provided in many, if not most, countries around the world, so the new classification has particular relevance for health-care providers this year.

The IUIS PID Expert committee met in New York City, 31 May–1 June 2011 and the updated document has been published in *Frontiers in Immunology*, the IUIS journal [1]. It can be downloaded directly from the website for Frontiers in Immunology: Primary Immunodeficiencies http://www.frontiersin.org/primary_immunodeficiencies, as well as the IUIS PID website (http://www.iuisonline.org/iuis/index.php/primary-immunodeficiency-expert-committee.html).

The rate of identification of new PIDs continues to rise, alongside increasing knowledge of the genes involved and the mechanisms that govern immune system development and function. Studies of individuals with recurrent or severe infections provide further evidence of new types of immune defects that, in turn, inform basic mechanisms of protection against infections. There are 31 newly described defects in this year's tables; these are listed at the end of each relevant table.

As in previous years, there are eight tables; these conform to the various immunopathogenic defects of the diseases and the cell types involved. The tables have also been re-ordered, starting with Table I: combined immunodeficiencies, then Table II: well-defined syndromes with immunodeficiency, Table III: predominantly antibody defects, Table IV: defects of immune dysregulation, Table V: phagocytic defects, those of innate immunity (Table VI) including complement (Table VIII) and autoinflammatory conditions (Table VII). Each table is subdivided further into groups of diseases according to the relative proportions of cell types or the nature of the proteins affected, which accounts for the DNA repair gene defects being listed together in Table II.

Where there is more than one defective mechanism, disorders might well belong to more than one group. Hyperimmunoglobulin (Ig)E syndromes (HIES) have been studied in detail during the last 2 years by investigators in several centres, showing considerable variation, and the different forms of this disease are listed in Tables I and II. Autosomal recessive (AR)-HIES, caused by DOCK8 (dedicator of cytokinesis 8) deficiency, is included in Table I (combined immunodeficiencies), as there are striking T and B cell abnormalities, as well as Table II, alongside autosomal-dominant-HIES (job syndrome) and AR-HIES due to Tyk2 deficiency. However, Tyk2 deficiency could also be listed in Table VI (defects in innate immunity), because of its association with atypical mycobacterial disease resulting in Mendelian susceptibility to mycobacterial disease (MSMD). CD40 ligand deficiency is reported both in Table I (combined immune deficiencies) and Table III ('predominantly antibody deficiencies'), as this may be a severe defect with opportunistic infections in early childhood, although many patients survive to adulthood without significant opportunistic infections and do well for many years with Ig replacement therapy alone.

As this can be confusing, there are extensive footnotes to aid clinicians and others in situations when symptoms or immune findings do not appear to fit with basic immune concepts; there are also more detailed aids in the literature [2]. These apparent discrepancies can be due to clinical diversity within an individual, or can be used as a reminder that different mutations within a single gene may have differing effects on immune functions. An example is signal transducer and activator of transcription 1 (STAT1) mutations: a loss of function mutation results in failure of the

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interferon-gamma signalling pathway and increased susceptibility to mycobacteria and salmonella (Table V). However, gain-of-function mutations in the same gene impair the development of interleukin-17-producing T cells, resulting in chronic mucocutaneous candidiasis (Table VI).

A new feature is the addition of the gene number for the relevant disorder in the Online Mendelian Inheritance in Man (OMIM) database, to those conditions in which a gene has been shown to have an effect. Thus the tables can be linked to the publicly accessible database (http://www.omim.org) of human genetic disorders, which is updated regularly and is a fully referenced resource. Readers should be aware that the multiplicity of gene function and gene interactions may become even more extensive in the future, given the advent of new genetic technologies and the increasing accessibility of exome or even genome sequencing. This, combined with greater awareness of disease-modifying genes and susceptibility genes contributing to defective immune mechanisms, will continue to make PIDs an exciting field of study.

Over the last few years, with the publication of many national PID registries [3–7], it has become apparent that the prevalence of the PIDs varies in different countries and continents. The new classification no longer comments on the relative frequency of PID disorders, but an asterisk has been placed in the first column after the disease name, in order to identify disorders for which fewer than 10 unrelated cases have been reported so far in the literature. While this may change for some of the newly described conditions, others may be so severe that they are not usually compatible with life. An example is Ikaros deficiency, observed in a single case, a prematurely born infant, who died at the age of 87 days.

The scope of the IUIS Expert Committee on Primary Immunodeficiency is to increase awareness, facilitate recognition and promote optimal treatment for patients with primary immunodeficiency disorders worldwide. For this reason, as well as revising the Classification of Primary Immunodeficiencies periodically, the Expert Committee is also involved actively in the revision of diagnostic criteria in conjunction with the IUIS Clinical Immunology Committee and the European Society for Immune Deficiencies (ESID). In addition, the committee will provide, upon request, support for existing management and therapeutic guidelines. There are templates for the more common primary antibody deficiencies on the IUIS website, produced by the Jeffrey Modell Foundation, to assist national or regional bodies that wish to develop these for local use. The widening role of the IUIS PID committee includes support for all patient organizations, so that health-care professionals can work together to improve facilities and care for patients with primary immune deficiencies.

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