

Classification of primary immunodeficiencies: Need for a revised approach?

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Since Bruton described X-linked agammaglobulinemia in 1952, more than 180 different primary immunodeficiencies have been described.¹ As more case reports and descriptions of immunodeficiency were subsequently recognized and published, immunologists grouped similar diseases in a classification system to provide a diagnostic framework.² The structure of the current classification, unchanged in concept since the original attempts at classification, is based on molecular defects and mode of inheritance. The most recently published international classification lists 188 diseases¹; others will be added that have been discovered but not yet reported or are as yet undiscovered disease phenotypes. Many genes involved in immune system development or function are described for which no human (or animal) disease has yet been reported, and all practicing clinical immunologists will have patients with genetically undefined immunodeficiencies. Indeed, if the concept that the majority of severe, life-threatening infection is due to primary immunodeficiency is accepted, then most immunodeficiencies predisposing to infection are yet to be identified and classified.³ Furthermore, many or most non-life-threatening infections might be due to polymorphisms in immune response genes and therefore a symptom of immunodeficiency.⁴

Furthermore, as the definition of immunodeficiency widens to encompass not only clinical phenotypes associated with recurrent multiple infection but also other manifestations of disordered immunologic homeostasis, including periodic fevers caused by inflammasome pathway defects or failure of immunosurveillance leading to lymphoid malignancy, then a rethinking of the current classification is required. This is especially true when considering diseases that present with apparently nonimmunologic phenotypes, such as pulmonary alveolar proteinosis, Cohen syndrome, or the Carnevale, Mingarelli, Malpuech and Michels syndromes (3MC syndrome), a developmental disorder caused by defects in proteins in the mannan-binding lectin serine protease pathway as

a result of mutations in *MASP1* or *COLEC11*. As we move into a new century, the traditional warning signs classically recognized as heralding primary immunodeficiency are being challenged as our concept of disordered immunity broadens.⁵ Perhaps both the classification of primary immunodeficiencies and the purpose served by the current categorization should be reconsidered.

As a catalog of immunodeficiency disease, the current classification has become increasingly difficult and confusing, with historical clinical phenotypic description superimposed by more recent understandings of genotype and phenotype. Confusion or ambiguity arises as the heterogeneity of primary immunodeficiency becomes clear. Defects in the same gene can cause different clinical phenotypes, and defects in different genes can result in the same clinical phenotype. Defects in the recombination-activating gene (*RAG*) 1 and 2 serve as an example. Originally described in infants with nonradiosensitive T⁺B⁺ natural killer-positive severe combined immunodeficiency (SCID), hypomorphic mutations in the same *RAG1/2* genes were subsequently found in infants with Omenn syndrome. Omenn syndrome is categorized separately to T⁺B⁺ natural killer-positive SCID in the original and subsequent classifications, even though the clinical and immunologic phenotype overlaps with those found in patients with SCID and maternofetal engraftment caused by maternal T lymphocytes crossing the placenta *in utero*,⁶ although such patients are categorized within the grouping of SCID. To add to the confusion, other gene defects associated with classical SCID are now known to give rise to an Omenn syndrome phenotype, including defects in *DLCRE1C*, *IL2RG*, *IL7R*, and *ADA*.⁷ At least 2 other genetic defects giving rise to a specific combined immunodeficiency phenotype can also present as Omenn syndrome, namely defects in *LIG4*, and *RMRP*⁷ (found in patients with cartilage-hair hypoplasia), although both can also give rise to an SCID phenotype. Two further clinical phenotypes are described because of defects in *RAG1/2* genes, which give rise to a combined immunodeficiency, namely cytomegalovirus infection and an expansion of T-cell receptor $\gamma\delta$ T lymphocytes, which are associated with hypomorphic *RAG1* mutations, and combined immunodeficiency with cutaneous granulomatous lesions.⁸

Defects in the Wiskott-Aldrich syndrome protein gene (*WAS*) are inherited in an X-linked fashion, and 3 clinical phenotypes are described. X-linked thrombocytopenia and Wiskott-Aldrich syndrome are both caused by loss-of-function mutations, whereas X-linked severe congenital neutropenia is due to a gain-of-function mutation. Recently, autosomal dominant gain-of-function mutations in signal transducer and activator of transcription 1 (*STAT1*) were described in patients with chronic mucocutaneous candidiasis,⁹ although autosomal dominant loss-of-function mutations confer susceptibility to mycobacterial and salmonella infection and autosomal recessive loss-of-function mutations lead to severe viral or mycobacterial disease.¹⁰ These examples illustrate the wide heterogeneity increasingly found in

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clinical, immunologic, and genetic phenotypes of patients with primary immunodeficiencies.

Therefore although broad classification of T-lymphocyte deficiency, B-lymphocyte deficiency, and innate immune response deficiency, including phagocytic defects and complement deficiency, might have previously been adequate, as new clinical and genetic information is acquired, perhaps a new classification system is required. Diseases can change from one category to another as the molecular basis of disease is elucidated. Although the defect in CD40 ligand deficiency affects T lymphocytes, CD40 ligand interacts with CD40 on B lymphocytes, leading to failure of immunoglobulin isotype switching, increased IgM levels, and severely reduced or absent IgA and IgG levels. CD40 ligand deficiency was previously and continues to be described as a predominantly antibody deficiency and is also further categorized into the group of combined immunodeficiencies because patients experience opportunistic infection with *Pneumocystis jiroveci* and *Cryptosporidium*. More accurately, it is a T-lymphocyte deficiency, although sharing some immunoglobulin phenotypic similarities with autosomal recessive hyper-IgM syndromes, such as activation-induced cytidine deaminase and uracil DNA glycosylase deficiency. Other diseases appear in more than 1 category, such as DiGeorge syndrome and IKAROS deficiency. Dedicator of cytokinesis 8 deficiency is described as a combined immunodeficiency, as well as an autosomal recessive form of the hyper-IgE syndrome based on the information that initial descriptions of patients had high eosinophil numbers and increased IgE levels. Initially, many such patients were grouped as having hyper-IgE syndrome or Job syndrome based on this immunologic phenotype. As more patients were recognized, different clinical phenotypes and patterns of inheritance were recognized. Identification of genetic defects has confirmed the phenotypic differences.¹¹ However, now that a significant cohort of patients with dedicator of cytokinesis 8 deficiency has been identified, the clinical phenotype is more consistent with a combined immunodeficiency rather than a defect predominantly of cutaneous inflammatory responses, which has implications for the treatment of patients in the future.¹²

The most severe primary immunodeficiencies are SCIDs, so-called because of the absence of T lymphocytes with absence or lack of function of B lymphocytes, natural killer lymphocytes, or both. Initially classified in the lymphocyte phenotype on the basis of absent lymphocyte subsets, they can now be classified in a more complex system based on the effect of the gene defect on lymphocyte or lymphocyte receptor or signaling molecule development. Although the lymphocyte phenotype classification usefully enables a reasoned deduction concerning the underlying genetic defect, particular difficulties arise as different genetic diseases are arbitrarily grouped as specific entities. Profound immunodeficiencies, combined immunodeficiencies that are not so severe as SCID, illustrate the problem. Defining them is controversial, but many can have hypomorphic mutations in genes that are associated with SCID, and therefore the classification becomes semantic. The distinction between SCID, “atypical” SCID, “leaky” SCID, and profound combined immunodeficiency is hotly debated.^{13,14} Features, including lymphocyte count, reduction in thymic emigrants, increased IgE levels, immune dysregulation, and infection susceptibility, have been used to try and distinguish between phenotypes, but because many of these features are used to define the phenotypes, it is not surprising that phenotypic descriptions segregate into patterns that fit with

features used to define the pattern.¹³ Many of the genes implicated in classical SCID or combined immunodeficiency can also give rise to a clinical picture of “atypical,” “leaky,” or “profound” immunodeficiency if the mutation is hypomorphic, giving rise to a partially functional gene product. Furthermore, the clinical and immunologic phenotype might be dependent on other environmental and genetic modifying influences. SCID can evolve into Omenn syndrome given the appropriate antigenic trigger, and therefore a partial loss-of-function mutation might give rise to 2 separate phenotypes, even within a single kindred.

What purpose does the current classification serve? One purpose of trying to define the various clinical entities is to determine the best treatment strategy. A graduated approach from immunoglobulin substitution with or without prophylactic antimicrobial agents to stem cell therapy (as enzyme replacement, stem cell transplantation, or gene therapy) can be considered for severe common variable immunodeficiency, late-onset combined immunodeficiency, profound combined immunodeficiency, atypical severe combined immunodeficiency, and severe combined immunodeficiency.

Perhaps the most important questions relate to natural history and the most appropriate treatment, answers to which can only come from well-compiled longitudinal registries that accurately reflect outcome with or without different treatments. These registry datasets will become increasingly important, with the widespread introduction of neonatal screening programs,¹⁵ which detect the absence of early thymic emigrants. Early detection of these patients will only be useful if we are confident of the appropriate treatment to be offered. Furthermore, the increasing availability of new-generation and whole-exome sequencing will help us identify patients with novel defects in well-known genes, as well as aid in the discovery of new genetic diseases. Does it matter whether a defect in *RAG1* or *IL2RG* is phenotypically SCID, leaky SCID, atypical SCID, profound combined immunodeficiency, or late-onset combined immunodeficiency? It matters only if the treatment approach will differ. There is an urgent need for robust data and clinical consensus on the best and most appropriate treatments for each category of disease. Where those data are lacking, registry data should be collected and combined. Where there is controversy over treatment approaches, well-designed, multicenter clinical trials are required, so that patients can be confident of being offered the most appropriate treatment.

The current classification serves a purpose as an overarching reference catalog, and therefore newly presenting patients can be cross-referenced with well-recognized or previously described clinical and immunologic phenotypes-genotypes and should be retained as the comprehensive reference source. However, more user-friendly reference catalogs are now required and could be subcategorized according to primary function. A separate genetic catalog would group clinical and immunologic heterogeneity seen due to environmental or specific base changes within single genes to identify genotypic-phenotypic correlations for severity/outcome.

Furthermore, a treatment catalog is required so that similar genetic defects with differing phenotypes are managed appropriately and promptly referred for specialist treatment, such as stem cell transplantation, as appropriate. This is germane when considering whether a patient has SCID, profound combined immunodeficiency, or combined immunodeficiency, in which the likely outcome is severe infection and end-organ damage. Early intervention with stem cell transplantation will prevent sequelae and improve the likelihood of a successful outcome.

As increasing amounts of genetic and clinical information become available, now is the time to construct large international and intercontinental registries so that groups of patients with the same disorder can be collected and studied. Therefore over time, information can be collated on natural history and outcome after different treatment approaches to evolve the best treatment for each patient.¹⁶

Any catalog system in evolution will not be perfect, but the increasing demands on the classification system should be recognized to make it fit the needs of the 21st century.

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