

# What's new in the 2013 Update on the Classification of Primary Immunodeficiency Diseases?

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The International Union of Immunological Societies Expert Committee on Primary Immunodeficiency Diseases (PIDs) meets biennially to update the classification schema for PIDs. The committee met in April 2013 for its most recent update. After this meeting, the committee has reported the updated classification in 2014 in *Frontiers in Immunology*. Primary immunodeficiency diseases have been classified into broad categories according to the major immunological defect as in the previously reported classifications.

## Major differences from the previous classification update in 2011

Table 1 in the present update enlists combined immunodeficiencies which do not have any associated non-immunologic phenotypic features. Combined immunodeficiencies with associated non-immunologic defects are now in Table 2, which has been renamed as 'Combined immunodeficiencies with associated or syndromic features' in lieu of the title "Well defined syndromes with immunodeficiency" in the previous report. The titles and classification in Tables 3 to 8 represent the same broad categories as in the previous classification.

The other major change from the previous classification is the inclusion of a new category in the present report appended as Table 9 and titled 'Phenocopies of PID'. The disorders included in this category are not due to germline mutations in genes involved in immune mechanisms. Instead, the defects included in this group include disorders with somatic mutations in a specific immune cell population and also disorders with autoantibodies against specific cytokines or other immunologic factors.

The disorders listed in this new category in the present report include:

- I. *Disorders associated with somatic mutations.* Included in this subcategory are disorders with:
  - i. Somatic mutations in the TNFRSF6 gene resulting in an autoimmune lymphoproliferative syndrome (ALPS) phenotype
  - ii. Gain of function somatic mutations in the K-RAS and N-RAS gene resulting in an autoimmune leucoproliferative disease
- II. *Disorders with autoantibodies to cytokines and immunologic factors.* Defects in this subcategory include:
  - i. Autoantibodies to IL-17 and/or IL-22 resulting in chronic mucocutaneous candidiasis
  - ii. Autoantibodies to GM-CSF resulting in pulmonary alveolar proteinosis
  - iii. Acquired angioedema due to autoantibodies to C1 inhibitor
  - iv. Autoantibodies to IL-6 resulting in recurrent skin infections due to staphylococci.
  - v. Autoantibodies to IFN- $\gamma$  leading to an adult onset immunodeficiency with exquisite predisposition to mycobacterial, fungal, Salmonella and Varicella zoster with features reminiscent of Mendelian susceptibility to mycobacterial disease (MSMD)

It is expected the list of disorder in the category 'Phenocopies of primary immunodeficiency' would expand in the future as more of such disorders would be identified with each passing year.

Apart from these changes, 30 new monogenic defects have been added in this classification, these disorders are represented in all the major groups of PID enlisted in this new update.