2019 Update on Primary Immunodeficiency Disorders by the International Union of Immunological Societies

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International Union of Immunological Societies working group recently updated the human inborn errors of immunity. This classification includes 65 new disorders that have been added since the last classification in 2018. This article highlights the important aspects of new classification for the benefit of general pediatricians.

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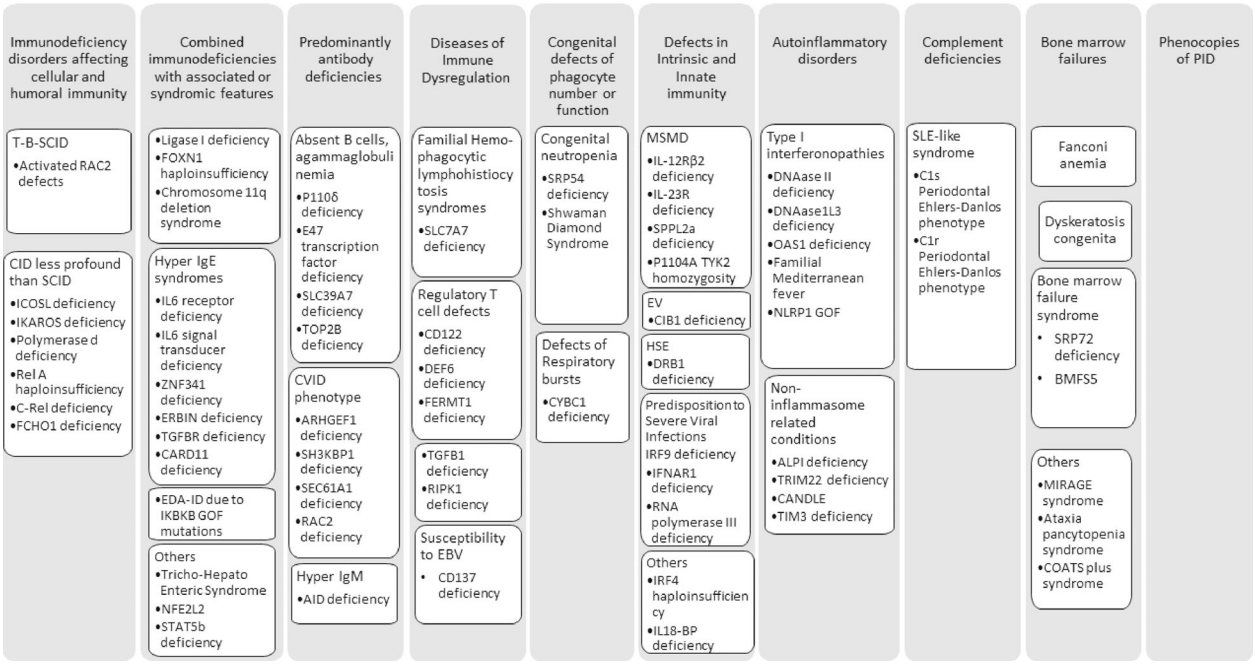
Primary immunodeficiency disorders, now known as Inborn errors of immunity, are a group of rare diseases affecting different arms of immune system. With the increased use of next generation sequencing, novel genes are being identified that have broadened our understanding of different clinical and immunological phenotypes. International Union of Immunological Societies have been updating the genetic causes for primary immunodeficiency disorders since 1970 [1]. Since 2013, the expert committee has started updating the phenotypic classification for the ease of practicing physicians [2]. In the last update, the inborn errors of immunity were classified in to nine categories, some of which were sub-classified in two categories based on severity of the disease [2]. The latest update has ten categories with a new category of bone marrow failures and 65 new disorders with total number of disorders reaching 430 (***Fig*.1**) [1,3]. Different modes of inheritance and distinct mechanisms like loss of function, gain of function, haploinsufficiency and dominant negative forms leading to different phenotypes are reported for 35 genes (***Fig*.2**).

In the category of Immunodeficiencies affecting cellular and humoral immunity, eight new genes are added. An autosomal dominant (AD) gain of function in *RAC2* gene causes recurrent bacterial and viral infections and may also be associated with neutropenia and lymphoproliferation. *ICOSL* deficiency patients have recurrent viral respiratory tract infections (RTI) with slowly progressive neutropenia and may have chronic diarrhea. *IKAROS* deficiency patients present with opportunistic infections like *P.jirovecii*, and agammaglobulinemia. These patients are at an increased risk to develop B cell ALL. Polymerase deficiency patients are of short stature and had recurrent respiratory tract and skin infections with molluscum contagiosum and viral warts. Rel A Haploinsufficiency patients have increased inflammatory cytokines signaling causing chronic mucocutaneous ulceration. c-Rel deficiency causes increased susceptibility to opportunistic organisms like Salmonella, Cryptobacterium, Cytomega-lovirus and Mycobacterium tuberculosis. FCHO1 deficient patients have failure to thrive, lympho-proliferation with predisposition to recurrent infections.

In Combined immunodeficiency with associated or syndromic features twelve new disorders have been added. LIG1 deficiency patients have growth retardation, increased sensitivity to radiation and sunlight with recurrent bacterial and viral infections. *FOXN1*-haploinsufficient patients also have recurrent bacterial and viral infections with eczema, dermatitis and nail dystrophy. Chromosome 11q23 deletion which causes Jacobsen syndrome have growth retardation, facial dysmorphism, warts and recurrent RTI. Seven disorders have been added with features like Hyper IgE syndrome due to mutations in *IL6R, IL6ST, ZNF341, ERBB2IP,TGFBR1,TGFBR2* and loss of function forms in *CARD11*. Recurrent bacterial, viral and fungal infections with ectodermal dysplasia is also seen due to gain of function mutations in *IKBKB*. Other syndromic defects are also listed (***Fig*. 1**). A dominant negative form of *STAT5b* deficiency with eczema and growth failure without immune defects like the autosomal recessive (AR) form is also added in this category.



Prepared from: SCID-Severe combined immunodeficiency disorder, CID-Combined immunodeficiency disorder, EDA ID-Anhidrotic ectodermodysplasia with immunodeficiency, CVID-Common variable immunodeficiency disorder, MSMD- Mendelian susceptibility to mycobacterial disease.

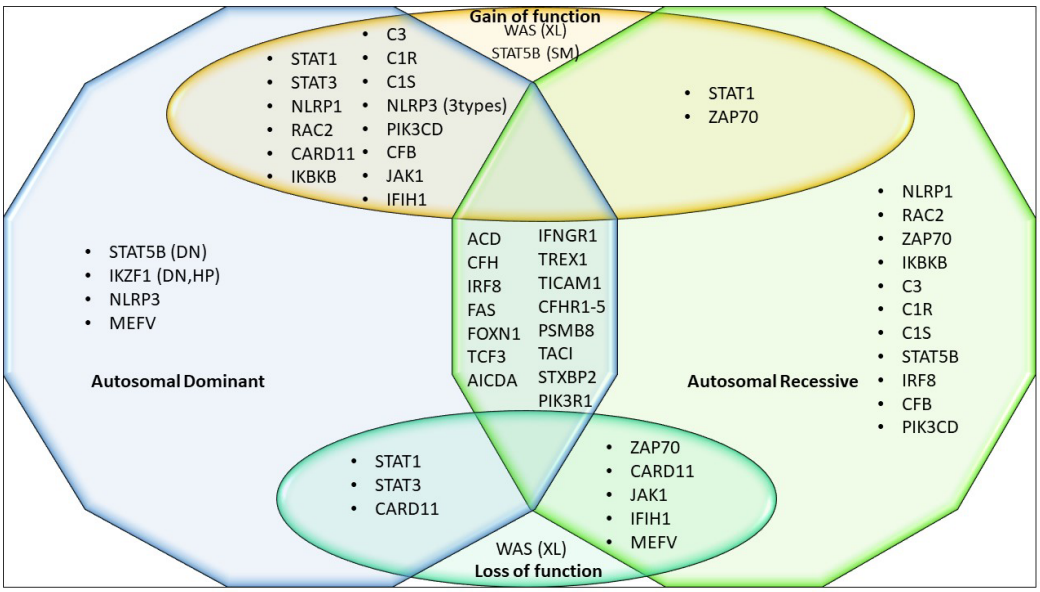
Fig. 1 *New disorders included in the 2019 update.*

In predominantly antibody deficiencies due to severe reduction in all serum immunoglobulin isotypes with profoundly decreased or absent B cells four disorders are added. p110δ deficient patient have severe bacterial infections and autoimmune complications like inflammatory bowel disease (IBD). AR forms of E47 transcription factor deficiency are more severe than the AD forms and present with recurrent bacterial infections and failure to thrive. *SLC39A7* (ZIP7) deficiency present at an early age with recurrent infections, blistering dermatosis and may have thrombocytopenia. Hoffman syndrome due to *TOP2B* deficiency present with recurrent infections with limb anomalies and facial dysmorphism. Four new disorders with Common variable immunodeficiency phenotype have been described (***Fig.* 1**). AD forms of *AID* deficiency causing Hyper IgM phenotype with lymphadenopathy and autoimmunity is also mentioned.

In diseases of immune dysregulation, one new disorder is added in familial hemophagocytic lymphohistiocytosis syndrome, *SLC7A7* defect leading to lysinuric protein intolerance which may be associated with pulmonary alveolar proteinosis and bleeding tendencies. Three new disorders with regulatory T cell (Treg) defects are CD122 deficiency with lymphoproliferation and autoimmunity, *DEF6* deficient patient had enteropathy, hepatosplenomegaly and cardiomyopathy and *FERMT1* deficient patients with severe dermatosis. *TGFB1* deficiency and *RPIK1* defects are new causes of immune dysregulation with colitis and CD137 deficiency a cause of increased susceptibility to Epstein-Barr virus and lymphoproliferation.

Two new disorders with congenital neutropenia are *SRP54* deficiency with exocrine pancreatic deficiency and neurodevelopmental delay and *ELF1* defect an additional cause for Shwachman-Diamond syndrome. A new form of functional phagocytic defect due to *CYBC1* deficiency causes inflammatory gastrointestinal symptoms with recurrent bacterial infections.

Mendelian susceptibility to mycobacterial disease involves three new genes namely *IL12RB2*, *IL23R* and *SPPL2A,* all of which predispose to mycobacterial and salmonella infections and a homozygous P1104A in *TYK2* gene which is associated with increased risk of tuberculosis. *CIB1* deficiency causes increased risk of epidermodysplasiaverruciformis (EV). *IRF9* deficient patients are at an increased risk of severe influenza infections. *IFNAR1* patients have severe disease after yellow fever and measles vaccination. Severe varicella



Prepared from: XL- X linked inheritance, SM- Somatic mutations, DN- Dominant negative, HP- Haploinsufficiency.

Fig. 2 *Genes with multiple modes of inheritance and mechanisms.*

zoster virus infections may be seen due to RNA polymerase III deficiency. *DBR1* deficiency can cause herpes simplex encephalitis (HSE) along with other viral infections of brain stem. *IRF4* haploinsufficiency is included under other inborn errors of immunity related to leukocytes presenting as Whipple disease.

Nine new disorders with Autoinflammatory phenotype are added in the update which include *DNASE2* deficiency with features likeAcardi-Goutieres Syndrome, *DNASE1L3* deficiency causing pediatric systemic lupus erythematosus, *OAS1* deficiency causing pulmonary alveolar proteinosis and skin rashes, an AD form of *MEFV* gene mostly M694del causing familial Mediterranean fever and *NLRP1* GOF variant causing juvenile onset recurrent respiratory papillomatosis, corneal scarring and palmoplantar carcinoma. Non-inflammasome related conditions included are *ALPI* and *TRIM22* deficiency causing IBD, mutations in *PSMG2* gene causing auto-immune hemolytic anemia, lipodystrophy and panniculitis with CANDLE like phenotype and T cell lymphoma subcutaneous panniculitis-like (*TIM3* deficiency).

In complement deficiency disorders GOF variants of *C1S* and *C1R* defects causing periodontal Ehlers-Danlos like phenotype causing hyperpigmentation and skin fragility are included in the new update.

To summarize, with frequent use of whole exome sequencing and whole genome sequencing the list of monogenic disorders will keep on increasing in times to come. With new genetic defects being identified,specific targeted therapies can be used increasingly like in patients with mutations in *JAK1, STAT1, STAT3, PIK3CD, DFE6, CTLA4, LRBA, IL12Râ2, IL23R AND IL18BP* genes [1].With clinical and immunophenotypic correlation of newer genes being identified, our understanding of immunology is bound to evolve.

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