Classification of Inborn Errors of Immunity (IEI) – IUIS 2024 Update

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Introduction

- - IEIs are genetic disorders affecting immune system development/function
- - Over 500 genes identified
- - Importance: Early diagnosis, targeted therapy, precision medicine

Overview of IEI Classification

- - Classified by IUIS into 10 major categories
- - Updated regularly to reflect new gene discoveries and clinical phenotypes

Category I – Immunodeficiencies affecting cellular and humoral immunity

- 1. T-B+ Severe Combined Immune Deficiency (SCID)
- 2. T-B- SCID
- 3. Combined Immunodeficiency (CID), Generally Less Profound than SCID

Category II – Combined immunodeficiencies with associated/syndromic features

- 1. Immunodeficiency with Congenital Thrombocytopenia
- 2. DNA Repair Defects Other Than Those Listed in Table 1

- Examples: Ataxia-telangiectasia , Nijmegen breakage syndrome, Bloom syndrome , …

- 3. Thymic Defects with Additional Congenital Anomalies
- 4. Immuno-osseous Dysplasia
- 5. Hyper IgE Syndromes (HIES)
- 6. Defects of Vitamin B12 and Folate Metabolism
- 7. Anhidrotic Ectodermodysplasia with Immunodeficiency (EDA-ID)
- 8. Calcium Channel Defects
- 9. Other Defects

Category III – Predominantly antibody deficiencies

- 1. Severe Reduction in All Serum Immunoglobulin Isotypes with Profoundly Decreased or Absent B Cells, Agammaglobulinemia
- 2. Severe Reduction in at Least 2 Serum Immunoglobulin Isotypes with Normal or Low Number of B Cells, CVID Phenotype
- 3. Severe Reduction in Serum IgG and IgA with Normal/Elevated IgM and Normal Numbers of B cells, Hyper IgM
- 4. Isotype, Light Chain, or Functional Deficiencies with Generally Normal Numbers of B Cells

Category IV – Diseases of immune dysregulation

- 1. Familial Hemophagocytic Lymphohistiocytosis (FHL syndromes)
- 2. FHL Syndromes with Hypopigmentation
- 3. Regulatory T Cell Defects
- 4. Autoimmunity with or without Lymphoproliferation
- 5. Immune Dysregulation with Colitis
- 6. Autoimmune Lymphoproliferative Syndrome (ALPS, Canale Smith syndrome)
- 7. Susceptibility to EBV and Lymphoproliferative Conditions

Category V – Congenital defects of phagocyte number, function, or both

- 1. Congenital Neutropenias
- 2. Defects of Motility
- 3.Defects of Respiratory Burst
- 4. Other Non-Lymphoid Defects

Category VI – Defects in intrinsic and innate immunity

- 1. Mendelian Susceptibility to mycobacterial disease (MSMD)
- 2. Epidermodysplasia verruciformis (HPV)
- 3. Predisposition to Severe Viral Infection
- 4. Herpes Simplex Encephalitis (HSE)
- 5. Predisposition to Invasive Fungal Diseases
- 6. Predisposition to Mucocutaneous Candidiasis
- 7. TLR Signaling Pathway Deficiency
- 8. Other Inborn Errors of Immunity Related to Non-Hematopoietic Tissues
- 9. Other Inborn Errors of Immunity Related to Leukocytes

Category VII – Autoinflammatory disorders

- 1. Type 1 Interferonopathies
- 2. Defects Affecting the Inflammasome
- 3. Non-Inflammasome Related Conditions

Category VIII – Complement deficiencies

- Complement Deficiencies

Category IX – Bone marrow failure syndromes

- 1. Bone Marrow Failure

Ex: - Fanconi anemia

-MIRAGE

(myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, enteropathy)

-Ataxia-Pancytopenia Syndrome

Category X – Phenocopies of IEI

- Associated with somatic mutations
- Associated with autoantibodies

Genetic and Diagnostic Advances

- - Gene sequencing (WES/WGS)
- - Functional testing
- - Impact on personalized medicine

Take Home Messages

- - Classification evolving with scientific advancements
- - Facilitates diagnosis, research, and therapy
- - Critical for global immunology and patient care