Human Inborn Errors of Immunity: 2019 Update of the IUIS Phenotypical Classification

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Abstract
Since 2013, the International Union of Immunological Societies (IUIS) expert committee (EC) on Inborn Errors of Immunity (IEI) has published an updated phenotypic classification of IEI, which accompanies and complements their genotypic classification into ten tables. This phenotypic classification is user-friendly and serves as a resource for clinicians at the bedside. There are now 430 single-gene IEI underlying phenotypes as diverse as infection, malignancy, allergy, autoimmunity, and autoinflammation. We herein report the 2019 phenotypic classification, including the 65 new conditions. The diagnostic algorithms are based on clinical and laboratory phenotypes for each of the ten broad categories of IEI.

Keywords IUIS · primary immune deficiency · inborn errors of immunity · immune dysregulation · autoinflammatory disorders · classification

Introduction
Human inborn errors of immunity (IEI) are caused by monogenic germline mutations resulting in loss or gain of function of the encoded protein. They can be dominant or recessive, autosomal or X-linked, and with complete or incomplete penetrance. They manifest as increased susceptibility to a broad or narrow spectrum of infectious diseases, as well as a growing diversity of autoimmune, autoinflammatory, allergic, and/or malignant phenotypes. They now comprise 406 distinct disorders with 430 different gene defects listed in the 2019 International Union of Immunological Societies (IUIS) classical classification [1]. If most IEI are individually rare, they are collectively more common than generally thought [2].

The (IUIS) expert committee on IEI proposes every other year a genotypic classification of all these disorders [1], which facilitates both research on, and diagnosis of, these conditions worldwide. This classification is organized in ten tables, each of which groups IEI sharing a given pathogenesis. However, with the growing number of IEI included in this catalog, these tables are not always easy to use at the bedside. We thus reported from 2013 onward a more user-friendly classification adapted for the clinician, based on the clinical and laboratory features observed in these patients. This phenotypic classification proved to be as popular as the genotypic classification (15 k vs 12 k downloads on publisher site) [3] and has been adapted in a smartphone application [4].

Here, we present an update of the phenotypic classification of IEI, based on the 2019 IEI classical classification [1]. This tree-based decision-making process is aimed to physicians, regardless of their familiarity with IEI. It aims at helping them to reach a diagnosis based on simple clinical and biological phenotypes.

Methodology
We included in our figures all disorders indexed in the 2019 update of the IUIS IEI classification [1]. A phenotypic algorithm was assigned to each of the ten main groups of the classification and the same color was used for each group of similar conditions. Given the high
I. Immunodeficiencies affecting cellular and humoral immunity. (a) Severe combined immunodeficiencies SCID, defined by CD3 T cell lymphopenia.*

| CD19 NL: SCID T-B+ | CD19 ↓: SCID T-B- |
|---------------------|------------------|
| SCID T-B+NK-        | SCID T-B-NK-     |
| XL, CD 132 def      | ADA def. ADA     |
| γc deficiency       | Chondrosternal dysplasia, deafness, may have pulmonary alveolar proteinosis, cognitive defects |
| IL2RG               | Winged helix def*. FOXN1. |
| AR, CD 132+         | Severe infections; abnormal thymic epithelium; congenital alopecia, nail dystrophy, neural tube defect. Ig: decreased. Tc: Very low. |
| JAK-3 def           | Reticular dysgenesis. AK2 |
| JAK3                | Neutropenia, deafness. Some have anemia and thrombocytopenia. |

Results

Algorithms for the 2019 update of IUIS phenotypical classification are presented in Figs. 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10.

number of diseases, several categories have been split since last update [3] in two sub-figures to be more informative.

Disease names are presented in red and genes in bold italic. An asterisk is added to highlight extremely rare disorders (less than 10 reported cases to date). However, the reader should keep in mind that some genes have been very recently described and that true prevalence is unknown. A double asterisk is added when only one case or one kindred has been reported to date. In these cases, it is difficult to confirm than observed phenotype would be reproducible in other patients carrying the same defect, or if it is an exception.

Discussion

These algorithms are aimed to guide clinicians to diagnose patients presenting typical phenotype. However, readers should be aware of the limitations of such a work.

More and more reports show a spectrum of atypical presentations related to hypomorphic mutations of those genes. Omenn syndrome (OMIM #603554) is a good example of such an atypical presentation, as well as “leaky SCID” and RAG deficiency spectrum [5].

Moreover, readers should be extremely cautious with descriptions of disease when only one patient or kindred have been reported. We are aware that these reports may not reflect the typical phenotype of such defects, but the exception; however, we thought that it was needed to be mentioned in these classifications.
### I. Immunodeficiencies affecting cellular and humoral immunity

**b- Combined Immunodeficiencies Generally Less Profound than Severe Combined Immunodeficiency**

| Low CDA: MHCII Expression? | Low CDB: | Low Cbc: | Ig: often NL | Ig Low |
|----------------------------|---------|---------|-------------|--------|
| Absent                     | Present |         |             |        |

#### CD8 def*. CD8a
- Recurrent infections. Maybe asymptomatic CD8 Absent.

#### C-REL def**. RELA
- Recurrent infections with bacteria, mycobacteria, salmonella and opportunistic organisms. Defective innate immunity. Low Ig; Tc Decreased CDA, Poor proliferation.

#### ICOSIL def**. ICOSIL
- Recurrent respiratory tract viral infections. Hypermagnesemia, and Low Tc, Slowly progressive nephropathy.

#### IKAROS def**. (CD154), AD ON, IKZF1
- Opportunistic infections, including F-jewel, bacteria, viral and other fungal infections. Increased risk to T-ALL. Agammaglobulinemia, high recent thymic emigrants/Tc cells, low absent memory T-cells.

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#### DONK def**. DONKER
- Severe fever, Cutaneous viral and acanthocondral infections; severe atopy, cancer, diabetes, high IgF, Low IgM, Aspergillus. Absent IL2, IgG.

#### STX4 def**. STX4
- Recurrent viral, bacterial, fungal infections; diarrhea. Immune dysregulation and autoimmunity. Absent TCRβ except for a minor CD3-dim TCRβ population; poor proliferation.

#### IL21 def**. IL21
- Severe early infant colitis, Tc; IgF; low function. Hypogammaglobulinemia, poor specific antibody response; IgF.

#### NIK def**. MAP3K14
- Bacterial, viral and Cryptosporidium infections; IgF; IL6 levels & switched memory Bc. In Xg poor proliferation.

#### NEMO def**. NEMO
- Recurrent infections with bacteria, enteritis, neuropathy. IgF; over time, Tc defective migration, proliferation.

#### RhoK deficiency**. RELA, AGD
- Chronic mucocutaneous ulceration. Impaired NAD activation; reduced production of inflammatory cytokines.

#### IL21R def**. IL21R
- Recurrent infections; Pneumocystis, Cryptosporidium, liver disease. Tc: low cytokine production; poor antigen proliferation. Decreased memory and switched B cells. Poor specific antibody responses; increased IgG.

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#### Normal Ig but Poor Specific Antibody response

- MALT1 def*. MALT1: Bacterial, fungal and viral infections. Impaired Tc proliferation.

#### RelB def**. RELB
- Recurrent infections Tc: poor diversity, proliferation to mitogens; no response to Ag; BC: marked increase.

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### Fig. 1 (continued)
Fig. 2  a, b  CID with associated or syndromic features. Ab antibody, AD autosomal dominant transmission, ADN autosomal dominant transmission with dominant negative effect, ANA anti-nuclear antibodies, ANCA anti-neutrophil cytoplasm antibodies, AR autosomal recessive transmission, Bc B cells, BCG bacillus Calmette-Guerin, BCR B cell receptor, CD cluster of differentiation, CID combined immunodeficiency of T and B cells, CMV cytomegalovirus, CNS central nervous system, def deficiency, DNA deoxyribonucleic acid, EBV Epstein-Barr virus, EDA anhidrotic ectodermal dysplasia, GOF gain-of-function, HIES hyper IgE syndrome, FILS facial dysmorphism, immunodeficiency, livedo and short stature, IUGR intrauterine growth retardation, LOF loss-of-function, MCC mucocutaneous candidiasis, NL normal; response to PHA may be decreased. AD, Autosomal dominant; ADN, autosomal dominant with dominant-negative effect; AR, autosomal recessive; d, deficiency. Due to space limitations, some features are not listed.
### III. Predominantly Antibody Deficiencies

**a: Hypogammaglobulinemia**

- **IgG, IgA and/or IgM ↓↓**
- Exclude second causes: drugs [Hx], myeloma [bone marrow], lymphoma. Ig loss (not hypo-IgM) in urine, gastrointestinal or skin.

**→ B Lymphocyte (CD19+) enumeration (CMF)**

| Bc absent | Bc >1% |
|-----------|--------|
| **Severe bacterial infection.** All Ig isotypes decreased. | **Common Variable Immunodeficiency Phenotype** |
| **X-Linked Agammaglobulinemia.** BTK. | **CD200 deficiency**. Recurrent infections. Low IgG, Ni or elevated IgM and IgA. |
| Some patients have detectable Ig. ProBc: Ni | **CD20 deficiency**. Recurrent infections, may have glomerulonephritis. |
| **μ heavy chain Def.** IGHM | **CD81 deficiency**. Recurrent infections, may have glomerulonephritis. Phenocopy of CD20 deficiency. |
| lgs Def*, CD79A, Igl* Def*, CD79B, BLNK Def*, BLNK, A5 Def**, IGLL1, ProBc: Ni | **CD21 deficiency**. Recurrent infections. Low IgG, impaired anti-pneumococcal response. |
| **E47 transcription factor def*.** TCF3 | **TRNT1 deficiency.** TRNT1. Congenital sideroblastic anemia, deafness, developmental delay. B cell deficiency and hypogammagl. |
| Severe, failure to thrive. p85 def**, PIK3R1. Cytopenia, ProBc: ↓ | **NFKB1 deficiency.** NFKB1. AD. Recurrent sinopulmonary infections, COPD, EBV proliferation, autoimmune cytopenies, alopecia and autoimmune thyroiditis. Ig Nl or ↓, Bc ↓ or Nl, ↓ memory Bc. |
| p110δ def**, PIK3CD. Autoimmune complications | **NFKB2 deficiency.** NFKB2. AD. Recurrent sinopulmonary infections, alopecia and endocrinopathies (e.g., central adrenal insufficiency). Low Bc. |
| ZIPI7 def*. SL3C9A7. Early onset infections, blistering dermatosis, thrombocytopenia | **IKAROS haploinsufficiency.** IKZF1. AD. Recurrent sinopulmonary infections, increased risk of ALL, autoimmunity. Decreased pro-Bc, low or normal Bc reducing levels with age. |
| **AD** | **ATP6AP1 deficiency.** ATP6AP1. XL. Hepatopathy, leukopenia, low copper. Variable Ig findings. |
| **E47 transcription factor def*.** TCF3, Hoffman syndrome*. TOP2B. Facial dysmorphism, limb anomalies | **Mannosyl-oligosaccharide glucosidase deficiency (MOS1)**, **MOS5** (GOS5). Low bacterial and viral infections in comparison to the level of hypogammaglobulinemia, severe neurologic disease, also known as congenital disorder of glycosylation type Ib (CDG-Ib). |

Fig. 3 Predominantly antibody deficiencies. a Hypogammaglobulinemias. b Other antibody deficiencies. AD autosomal dominant transmission, AR autosomal recessive transmission, Bc B cells, BENTA B cell expansion with NF-xB and T cell anergy, CD cluster of differentiation, CMF flow cytometry, COPD chronic obstructive pulmonary disease, def deficiency, EBV Epstein-Barr virus, GOF gain-of-function, Hx patient history, Ig immunoglobulins, Ni normal, XL X-linked transmission.
### III. Predominantly Antibody deficiencies.

#### b: Other Antibody deficiencies

| Severe Reduction in Serum IgG and IgA with Normal or elevated IgM and Normal Numbers of Bc: | Isotype, Light Chain, or Functional Deficiencies with Generally Normal Numbers of Bc | High Bc numbers due to constitutive NF-κB activation |
|---|---|---|
| Hyper IgM Syndromes | Selective IgA deficiency. Unknown. May be asymptomatic. Bacterial infections, autoimmunity mildly increased. Very low to absent IgA with other isotypes normal, normal subclasses and specific antibodies. | CARD11 GOF. CARD11. AD. BENTA syndrome |
| AID deficiency. AICDA. AR or AD. Bacterial infections, enlarged lymph nodes and germinal centers. NI memory Bc, but lacking somatic hypermutation in AR form. | Transient hypogammaglobulinemia of infancy. Unknown. Usually not associated with significant infections, normal ability to produce antibodies to vaccine antigens. IgG and IgA decreased. | Splenomegaly, lymphadenopathy, poor vaccine responses. |
| UNG deficiency. UNG. Enlarged lymph nodes and germinal centers. | IgG subclass deficiency with IgA deficiency. Unknown. Recurrent bacterial infections. May be asymptomatic. Reduced IgA with decrease in one or more IgG subclass. | |
| INO80 def*. INO80*. Severe bacterial infections. | Isolated IgG subclass deficiency. Unknown. Usually asymptomatic, a minority may have poor antibody response to specific antigens and recurrent viral/bacterial infections. Reduction in one or more IgG subclass. | |
| MSH6*. MSH6*. Family or personal history of cancer. Variable IgG, defects, increased IgM in some, NI Bc, low switched memory Bc. | Specific antibody deficiency with normal Ig levels and normal B cells. Unknown. Reduced ability to produce antibodies to specific antigens. Ig: NI. | |
| | Ig heavy chain mutations and deletions. Mutation or chromosomal deletion at 14q32. May be asymptomatic. One or more IgG and/or IgA subclasses as well as IgE may be absent. | |
| | Kappa chain deficiency*. IGKC. Asymptomatic. All immunoglobulins have lambda light chain. | |
| | Selective IgM deficiency. Unknown. Pneumococcal / bacterial infections. Absent serum IgM. | |

Fig. 3 (continued)
### Diseases of immune dysregulation

| Hemophagocytic Lymphohistiocytosis (HLH) | Susceptibility to EBV |
|------------------------------------------|-----------------------|
| **Hypopigmentation:**                  |                        |
| Partial albinism, Decreased NK and CTL |                        |
| activities (cytotoxicity and/or degranulation), Bc and Tc: Nl |

| Chediak Higashi Sd, LYST               |                        |
|---------------------------------------|-----------------------|
| Recurrent infections, fever, HSM, bleeding |                        |
| tendency, progressive neurological |                        |
| dysfunction. Giant lysosomes (WBC), |                        |
| neutropenia, cytopenias, Specific hair |                        |
| shaft anomaly, Increased activated Tc. |                        |

| Griscelli Sd type 2, RAB27A.         |                        |
|--------------------------------------|-----------------------|
| Fever, HSM, cytopenias, Specific hair |                        |
| shaft anomaly                        |                        |

| Hermansky-Pudlak syndrome, type 10**, |                        |
|---------------------------------------|-----------------------|
| AP3D1.                                |                        |
| Oculocutaneous albinism, severe       |                        |
| neutropenia, recurrent infections, seizures, hearing loss and neurodevelopmental delay. | |

| Familial Hemophagocytic Lymphohistiocytosis Syndromes: | EBV associated HLH |
|-------------------------------------------------------|-------------------|
| Fever, HSM, cytopenias, NI Bc. Increased activated Tc. |                        |
| Decreased to absent NK and CTL activities (cytotoxicity or/and degranulation) |                        |

| Perforin deficiency (FHL2), PRF1. |                        |
|-----------------------------------|-----------------------|
| UNC13D / Munc13-4 deficiency (FHL3), UNCL3D. |                        |
| Syntaxin 11 deficiency (FHL4), STX11, STXB2 / Munc18-2 deficiency (FHL5) |                        |
| STXBP2. Enteropathy                |                        |

| FAAP24 deficiency**, FAAP24. |                        |
|-----------------------------|-----------------------|
| EBV-driven lymphoproliferative disease. |                        |
| Increased activated Tc. Failure to kill autologous EBV transformed Bc. |                        |
| NI NK cell function          |                        |

| SLCTA7 deficiency. SLCTA7. |                        |
|---------------------------|-----------------------|
| Lysinuric protein intolerance, bleeding tendency, alveolar proteinosis Hyper-inflammatory response of macrophages. |                        |
| NI Tc and NK cell function |                        |

| CD137 deficiency**, TNFRSF9. |                        |
|------------------------------|-----------------------|
| EBV lymphoproliferation, B cell lymphoma, chronic active EBV infection. Low IgA and IgG, poor response to antigens, decreased T cell proliferation |                        |

| RCPK deficiency**, PRKCD. |                        |
|--------------------------|-----------------------|
| Recurrent infections, EBV chronic infection, lymphoproliferation, SLE-like autoimmunity (nephrotic and antiphospholipid Sd). Low IgG, Low memory Bc high CD5 Bc and Tc. |                        |

| XL, XL2, XIAP. |                        |
|----------------|-----------------------|
| Splenomegaly, lymphoproliferation, Collitis, IBD, hepatitis. |                        |

| Hypogammaglobulinemia, Low INKT cells. |                        |
|----------------------------------------|-----------------------|
| Increased T cells susceptibility to apoptosis to CD95 and enhanced activation-induced cell death (AICD). Normal NK and CTL cytotoxic activity. XIAP def (FCM) |                        |

| XL, XL2, XIAP. |                        |
|----------------|-----------------------|
| Splenomegaly, lymphoproliferation, Collitis, IBD, hepatitis. |                        |

| AR, CD27 deficiency, CD27 (TNFRSF7). |                        |
|--------------------------------------|-----------------------|
| Features triggered by EBV infection, aplastic anemia, low INKT cells lymphoma. Low Ig |                        |

**Fig. 4** Diseases of immune dysregulation. a: Hemophagocytic lymphohistiocytosis. b: Other diseases of immune dysregulation. Ab antibody, AD autosomal dominant transmission, Ag antigen, AIHA autoimmune hemolytic anemia, ALPS autoimmune lymphoproliferative syndrome, APS autoimmune polyendocrinopathy syndrome, AR autosomal recessive transmission, Bc B cells, CD cluster of differentiation, CMF flow cytometry, CTL cytotoxicT lymphocytes, def deficiency, DNT double negative T cells, EBV Epstein-Barr virus, FHL familial hemophagocytic lymphohistiocytosis, GOF gain-of-function, HLH hemophagocytic lymphohistiocytosis, (H)SM (hepato)splenomegaly, IBD inflammatory bowel disease, Ig immunoglobulin, IL-10 interleukin-10, LOF loss-of-function, iNKT invariant NKT cells, NK natural killer cells, NI normal, sd syndrome, SLE systemic lupus erythematosus disease, Te T cells, TCR T cell receptor, XL X-linked transmission.
### IV. Diseases of immune dysregulation.

#### b: Syndromes with Autoimmunity and Others

**Syndromes with Autoimmunity**

| Increased CD4+ CD8+ TCR αβ+ (double negative (DN) T cells) | No : Regulatory T Cell Defects |
|-------------------------------------------------------------|-------------------------------|
| Yes: ALPS Autoimmune Lymphoproliferative Sd                 | No: |
| ALPS-FAS. TNFRSF6. AD or AR.                               |    |
| Autoimmune cytopenias, increased lymphoma risk, IgG and IgA Nl or increased, elevated serum FasL, IL-10, vitamin B12. | |
| ALPS-FASLG. TNFSF6.AR.                                      |    |
| Autoimmune cytopenias, SLE, soluble Fasl is not elevated   | |
| ALPS-Caspase10*. CASP10. AD.                                |    |
| ALPS-Caspase 8**. CASP8. AR.                                |    |
| Bacterial and viral infections, Hypogammaglobulinemia.      | |
| Defective lymphocyte activation. Slightly increased DNT cells. | |
| FADD deficiency. ** FADD. AR.                               | |
| Functional hypoplasenion, bacterial and viral infections, recurrent episodes of encephalopathy and liver dysfunction. | |

| No: ALPS Autoimmune Lymphoproliferative Sd                  | |
|-------------------------------------------------------------|    |
| Yes: ALPS Autoimmune Lymphoproliferative Sd                  | |
| Chronic adenopathy Splenomegaly, defective lymphocyte apoptosis. | |

**Immune Dysregulation with Colitis: IBD**

| IL-10 deficiency*. IL10. AR. Foliculitis, recurrent respiratory diseases, arthritis. No functional IL-10 secretion. |    |
|-----------------------------------------------------------------------------------------------------------------|---|
| IL-10R deficiency. AR. Foliculitis, recurrent respiratory diseases, arthritis, lymphoma.                         |    |
| IL10RA. Leukocytes unresponsive to IL-10.                                                                      |    |
| IL10RB. Leukocytes unresponsive to IL10, IL22, IL26, IL28A, IL28B, IL29.                                       |    |
| NFAT5 haploinsufficiency**. NFAT5. AD. Recurrent Sinopulmonary infections. Decreased memory Bc and plasmablasts. |    |
| TGFβ1 deficiency*. TGFBI. AR. Recurrent viral infections, microphosphyl, and encephalopathy. Decreased T cell proliferation in response to anti-CD3 |    |
| RIPK1 deficiency*. RIPK1. AR. Recurrent infections, progressive polyarthritis. Low Tc, low or nl Bc.           |    |

**Fig. 4 (continued)**
### V. Congenital defects of phagocyte number, function, or both. **a**: Neutropenia (without anti-PMN)

| Syndrome associated                                                                                                           | No syndrome associated                                                                                       |
|-----------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|
| Shwachman-Diamond Syndrome, DNAJC21. AR. EF1A*. AR. Pancytopenia, exocrine pancreatic insufficiency. SBDS. AR. rhodopsin dysplasia. | Elastase deficiency. (SCN1). ELANE. AD. Susceptibility to MDS/leukemia. Severe congenital neutropenia or cyclic neutropenia. (perform CBC twice weekly/ 4 weeks). |
| G6PC3 deficiency (SCN6). G6PC3. AR. Structural heart defects, unregional abnormalities, inner ear deafness, and venous angiectasias of trunks and limbs. Affected functions: Myeloid differentiation, chemotaxis, O2 production. | HAX1 deficiency (Kostmann Disease) (SCN3). HAX1. AR. Cognitive and neurological defects in patients with defects in both HAX1 isoforms, susceptibility to MDS/leukemia. |
| Glycogen storage disease type 1b. G6PT1. AR. Fasting hypoglycemia, lactic acidosis, hyperlipidemia, hepatomagaly.             | GP1F1 deficiency (SCN2)**. GP1F2. AD. B/T lymphopenia.                                                    |
| Cohen syndrome. COH1. AR. Osteomyelitis, mental retardation, obesity, deafness.                                              | X-linked neutropenia/ myelodysplasia WAS GOF. WAS. XL GOF.                                                |
| 3-Methylglutaconic aciduria. CLPB. AR. Neurocognitive developmental abberations, microcephaly, hypoglycemia, hypotonia, ataxia, seizures, cataracts, IUGR. | Myeloid maturation arrest, monocytopeania, variable lymphoid anomalies.                                    |
| Barth Syndrome (3-Methylglutaconic aciduria type II). TA2. XL. Cardiomyopathy, myopathy, growth retardation.               | G-CSF receptor deficiency*. CSF3R. AR. Stress granulopoiesis disturbed.                                      |
| Clericiotto syndrome (Poikiloderm with neutropenia). C16orf57 (USB1). AR. Extramedullary hematopoiesis, bone marrow fibrosis, nephromegaly. | Neutropenia with combined immune deficiency*. MX1L. AR.                                                     |
| VP454 deficiency (SCN5). VP454. AR. Extramedullary hematopoiesis, bone marrow fibrosis, nephromegaly.                     | Mild thomboptocyaemia. Lymphopenia.                                                                           |
| JAGN1 deficiency. JAGN1. AR. Osteopenia. Myeloid maturation arrest.                                                        | V. Congenital defects of phagocyte. **b**: Functional defects                                               |
| WDR1 deficiency. WDR1. AR. Poor wound healing, severe stomatitis, neutrophil nuclei herniate. Mild neutropenia.          |                                                                                                              |
| SMARCD2 deficiency*. SMARCD2. AR. Developmental abberations, bones defect, myelodysplasia                             |                                                                                                              |
| Specific granule deficiency*. CEBPE. AR. Neutrophils with bilobed nuclei. Chronic neutropenia.                           |                                                                                                              |
| HYOU1 deficiency**. HYOU1. AR. Hypoglycemia, inflammatory complications.                                                    |                                                                                                              |
| PI4/LAMTOR2 deficiency**. LAMTOR2. AR. Partial albinism, growth failure. Hypergammaglobulinemia, reduced CDB cytotoxicity. |                                                                                                              |

**Fig. 5** Congenital defects of phagocyte number, function, or both. **a**: Neutropenia. **b**: Functional defects of phagocytes. AD autosomal dominant transmission, AML acute myeloid leukemia, AR autosomal recessive transmission, BCG bacillus Calmette-Guerin, CD cluster of differentiation, CGD chronic granulomatous disease, CMF flow cytometry, CMML chronic myelomonocytic leukemia, def deficiency, DHR dihydrorhodamine-1,2,3, GM-CSF granulocytes/monocytes colony stimulation factor, GOF gain-of-function, IBD inflammatory bowel disease, IUGR intrauterine growth retardation, LAD leukocyte adhesion deficiency, MDS myelodysplasia, NBT nitroblue of tetrazolium, NK natural killer cells, WBC white blood cells, XL: X-linked transmission.
Fig. 6 Defects in intrinsic and innate immunity. a: Bacterial and parasitic infections. b: MSMD and viral infection. AD autosomal dominant transmission, AR autosomal recessive transmission, BCG bacillus Calmette-Guérin, CD cluster of differentiation, CMC chronic mucocutaneous candidiasis, EBV Epstein-Barr virus, GOF gain-of-function, IFNg interferon gamma, HHV6 human herpes virus type 6, HPV human papillomavirus, HSV herpes simplex virus, LOF loss-of-function, MSMD Mendelian susceptibility to mycobacterial disease, NK natural killer cells, RNA ribonucleic acid, sd syndrome, Tc T cells, TLR3 Toll-like receptor type 3, VZV varicella zoster virus, XL X-linked transmission
### VIIa. Auto-inflammatory disorders

| Recurrent inflammation         | Systemic inflammation with urticaria rash                                                                 | Others                                                                 |
|-------------------------------|----------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|
| **Familial Mediterranean Fever (FMF)** * | **Familial Cold Autoinflammatory Syndrome (CAPS) ** | **CANDLE**sd (chronic atypical neutrophilic dermatitis with lipodystrophy) |
| MEFV, AR or AD (Usually M694del variant) | NLRP3, NLRP12. AD GOF. DA: 24-48H | **PSMB8, AR and AD. Contractures, panniculitis, ICC, fevers.** |
| DA: 1–4 days FA : Variable. | Non-pruritic urticaria, arthritides, chills, fever and leukocytosis after cold exposure. | **PSMB9, AR. Panniculitis, lipodystrophy,** |
| Polyserositis, Abdominal pain, Arthritis | **Muckle Wells syndrome (CAPS) ** | **AIRA.** |
| Amyloidosis. Erysipelas-like erythema | NLRP3. AD GOF. | **OMERACT (variants in PSMB8, PSMB9, PSMB12, and PSMB14 have been proposed to cause a similar CANDLE phenotype in compound heterozygous monogenic, oligogenic and AD monogenic models).** |
| Predisposes to vasculitis and inflammatory bowel disease . | Continuous fever. Often worse in the evenings. Urticaria, Deafness (SNHL), Conjunctivitis, Amyloidosis. | **COPA defect. COPA. AD** |
| Colchicine-responsive ++. | Neonatal onset multisystem inflammatory disease (NOMID) or chronic infantile neurologic cutaneous and articular syndrome (CINCA) ** | **Autoimmune inflammatory arthritis and interstitial lung disease with TH17 dysregulation and autoantibody production** |
| **Mevalonate kinase del** * (Hyper IgD id). | Neonatal onset rash, with continuous fever and inflammation. Aseptic and chronic meningitis, chronic and articular syndrome. | **NLR4-MAS** (macrophage activating syndrome)** |
| MVK, AR | Sensorineural deafness. and Visual loss in some patients. | **AD GOF. Severe enterocolitis and macrophage activation syndrome (HLH).** |
| DA: 3–7 days FA : 1–2 monthly. | A20 holoinsufficiency ** | **Triggered by cold exposure.** |
| Cervical adenopathy. Oral aphthosis | TNFAIP3. AD GOF. | **NLRP1 GO. NLRP3. AD GOF.** |
| Diarrhea. Mevalonate aciduria during | Cervical adenopathy. Oral aphtosis. | **Palmoplantar carcinoma, corneal scarring; recurrent respiratory papillomatosis. Increased IL1β.** |
| attacks. Leukocytosis with high IgG levels. | Colchicine-responsive +++ | **ALPI deficiency** *: ALPI. AR. TRIM22 del **: TRIM22. AR** |
| **TNF receptor-associated periodic syndrome:** TRAPS. | | **Inflammatory bowel disease.** |
| TRIF. TRIF51. AD | | **T-cell lymphoma subcutaneous panniculitis-like (TMS deficiency). HAVC2. AR. Panniculitis, HLH, polyclonal cutaneous T cell infiltrates or T-cell lymphoma** |
| DA: 1–4 weeks FA : Variable | Prolonged fever. Serositis, rash, Periarticular edema and conjunctivitis. | | **Type 1 Interferonopathies** |
| Amyloidosis. Joint inflammation. | **Dyskeratosis, autoimmunity and arthritides.** | **Progressive encephalopathy, ICC. Cerebral atrophy, RSMG.** |
| **Mevalonate kinase del** * (Hyper IgD id). | | **Leukodystrophy, Thrombocytopenia, Elevated hepatic transaminases. Chronic cerebrospinal fluid (CSF) lymphocytosis.** |
| MVK, AR | | **Acardi-Goutieres Syndromes:** NLR1. TGRX1. AR-AD. (SLE, FCL). **RNASEH2A, RNASEH2B (SP).** |
| DA: 5 days FA : Fixed interval : 4 – 6 weeks | | **RNASEH2C, SA** |
| **Peygenc sterile arthritis, pyoderma gangrenosum, acne (PAPA) syndrome, hypereritrocitosis and hypercalciuric insufficiency. PSTPIP1** (C2BP1). AD | | **AP1S3 deficiency** *: AP1S3. AD GOF. **
| DA: 5 days FA : Fixed interval : 4 – 6 weeks | | **Recurrent respiratory papillomatosis.** |
| **Destructive arthritis, Pyoderma gangrenosum, inflammatory skin rash, Mxui. Acute-phase response during attacks.** | | **NLRP1 GOF.** |
| **Continuous inflammation.** | | **T-cell lymphoma subcutaneous panniculitis-like (TMS deficiency).** |
| **Urushi, Granulomatous synovitis, Campodactyly, Rash, Cranioophalangeal, 30% develop Crohn colitis. Sustained modest acute-phase response.** | | **HAVC2. AR. Panniculitis, HLH, polyclonal cutaneous T cell infiltrates or T-cell lymphoma** |
| **CAMSAP CARD14. AD:** | | **Inflammatory bowel disease.** |
| **Psoriasis.** | | **Streptomycin-induced dyslipidaemia with immune dysregulation (SPEND) syndrome.** |
| **DIFRA. (Deficiency of IL-36 receptor antagonist).** IL-36RN. AR | | **SPDO2** |
| **Life-threatening, multisystemic inflammatory disease characterized by episodic widespread, pustular piosis, malaise, and leukocytosis.** | | **SPONDI** |
| **ADAM17 deficiency** *: ADAM17. AR.** | | **NTRK1.** |
| **Early onset diarrhea and skin lesions. Severe bacteremia.** | | **C3 deficiency** |
| **Defective TNFα production.** | | **C3 deficiency** |
| **SLC29A3 mutation.** | | **NLRP1 GOF.** |
| **Scleroderma.** | | **T-cell lymphoma subcutaneous panniculitis-like (TMS deficiency).** |
| **Increased IL1β.** | | **Panniculitis, HLH, polyclonal cutaneous T cell infiltrates or T-cell lymphoma** |
| **TRIM22 del** *: TRIM22. AR | | **Panniculitis, HLH, polyclonal cutaneous T cell infiltrates or T-cell lymphoma** |
| **Neutrophilic dermatosis, childhood-onset, early-onset recurrent ischemic stroke and fever, Livedo racemosa, some patients develop hypogammaglobulinemia** | | **Inflammatory bowel disease.** |
| **NLRP1 GOF.** | | **Streptomycin-induced dyslipidaemia with immune dysregulation (SPEND) syndrome.** |
| **Increased IL6.** | | **SPDO2** |
| **Defective TNFα production.** | | **NLRP1 GOF.** |
| **Sclerodermatous erythroderma and systemic reticulosis syndrome.** | | **Spontaneous recurrent urticaria (SRU).** |
| **Morphea-like.** | | **Spontaneous recurrent urticaria (SRU).** |
| **Increased IL1β.** | | **Spontaneous recurrent urticaria (SRU).** |
| **Defective TNFα production.** | | **Spontaneous recurrent urticaria (SRU).** |

**Fig 7 a, b** Autoinflammatory disorders. AD autosomal dominant transmission, ANCA anti-neutrophilic cytoplasmic autoantibody, AR autosomal recessive transmission, BSNL bilateral striatal necrosis, CAPS cryopyrin-associated periodic syndrome, DA duration of acute inflammation episode, dsDNA double-stranded deoxyribonucleic acid, FA frequency of acute inflammation episode, FCL familial chilblain lupus, GOF gain-of-function, HLH hemophagocytic lymphohistiocytosis, HSM hepatosplenomegaly, ICC intracranial calcifications, IL interleukin, LOF loss-of-function, sC syndrome, SLE systemic lupus erythematosus, SMS Singleton-Merten syndrome, SNHL sensorineural hearing loss, SP spastic paraparesis, TORCH toxoplasmosis, other, rubella, cytomegalovirus, and herpes infections. 

### Vlb. Auto-inflammatory disorders

**Sterile Inflammation (skin / bone / joints)**

- **Predominant on the bone / joints**
  - **Peygenc sterile arthritis, pyoderma gangrenosum, acne (PAPA) syndrome, hypereritrocitosis and hypercalciuric insufficiency.**
    - PSTPIP1 (C2BP1). AD
    - DA: 5 days FA: Fixed interval: 4-6 weeks

- **Predominant on the skin**
  - **Blau syndrome. NOD2 (CARD15). AD:**
    - Continuous inflammation.
  - **Uveitis, Granulomatous synovitis, Campodactyly, Rash, Cranioophalangeal, 30% develop Crohn colitis. Sustained modest acute-phase response.**

**Type 1 Interferonopathies**

- **Progressive encephalopathy, ICC. Cerebral atrophy, RSMG.**
- **Leukodystrophy. Thrombocytopenia, Elevated hepatic transaminases. Chronic cerebrospinal fluid (CSF) lymphocytosis.**
- **Acardi-Goutieres Syndromes:**
  - NLR1. TGRX1. AR-AD.
  - (SLE, FCL).
  - RNASEH2A, RNASEH2B (SP).
  - RNASEH2C, SA (FCL)
  - ADAR1 (HBN, SP).
- **RNaseH2 (FCL, AD):**
  - SLE.
  - SP.
  - RNaseH2A, RNaseH2B.
- **Aicardi-Gouries Syndromes:**
  - Transaminases.
  - Chronic cerebrospinal fluid (CSF) lymphocytosis.
  - Leukodystrophy.
  - Thrombocytopenia.
  - Elevated hepatic transaminases.
- **DNASE2:**
  - RHD.
  - RNaseH2A, RNaseH2B.
- **RNaseH2A, RNaseH2B:**
  - Aicardi-Gouries Syndromes.
- **Others**
  - **Sporadic urticaria rash:**
    - Painless urticaria rash, arthralgia, chills, fever and malaise.
  - **Dyskeratosis, autoimmunity and arthritides.**
  - **Panniculitis, HLH, polyclonal cutaneous T cell infiltrates or T-cell lymphoma**
## VIII. Complement deficiencies

### Susceptibility to infections

| High | Recurrent pyogenic infections | Low | SLE-like syndrome. Infections with encapsulated organisms | Atypical Hemolytic Uremic Syndrome | Others |
|------|-------------------------------|-----|--------------------------------------------------------|---------------------------------|--------|
| Disseminated Neisserial infections | C3 LOF. C3. AR. Absent CH50 and AH50 hemolytic activity. Defective bactericidal activity. | C3 GOF. C3. AD. Glomerulonephritis. Increased activation of complement | C1q def. C1QA, C1QB, C1QC. | Factor B GOF. CFB. AD. Increased spontaneous AH50 | C1 inhibitor. SERPING1. AD, Hereditary angioedema. Spontaneous activation of the complement pathway with consumption of C4/C2 |
| | Properdin def. FCN3. AR. Infections mainly in the lungs; abscesses, necrotizing enterocolitis in infancy; selective antibody defect to Pneumococcal polysaccharides. Absence of complement activation by the Ficolin 3 pathway | C1r def. C1R. Ehlers Danlos phenotype | C1s def. C1S. Multiple autoimmune diseases; Ehlers Danlos phenotype | Factor H def. CFH. AR or AD. Infections, disseminated neisserial infections, preeclampsia. Spontaneous activation of the alternative complement pathway with consumption of C3 | Membrane Attack Complex Inhibitor deficiency. CD59. Hemolytic anemia. Polyneuropathy. |
| | Factor D def. CFD. AR. | C2 def. C2. Vasculitis, Polyangiitis, atherosclerosis | Complete C4 def. | Factor I deficiency. AR. Infections, disseminated neisserial infections, preeclampsia. Spontaneous activation of the alternative complement pathway with consumption of C3 | CD55 deficiency (CHAPLE disease). CD55. AR. Protein losing enteropathy, thrombosis |
| | C9 def. C9. Mild susceptibility. | | | | Periodontal Ehlers Danlos. C1R/C1S. AD GOF. Hyperpigmentation skin fragility. Normal CH50. |

| Normal CH50. Absent AH50 hemolytic activity. | Normal CH50. Absent AH50 hemolytic activity. |
|-------------------------------------------------|-------------------------------------------------|
| C5 def. C5 | C6 def. C6 |
| C6 def. C6 | C7 def . C7. + Vasculitis |
| C8 def. | C8A, C8B, C8G |
| C9 def. C9. | C9 def. C9. |

Fig. 8 Complement deficiencies. AD autosomal dominant transmission, AH50 alternate pathway hemolytic activity, AR autosomal recessive transmission, CH50 complement hemolytic activity, def deficiency, GOF gain-of-function, LOF loss-of-function, sd syndrome, SLE systemic lupus erythematosus, XL X-linked transmission
### IX. Bone marrow failure

| Fanconi anemia | Dyskeratosis congenita (DKC) | Bone marrow failure sd (BMFS) | Others |
|---------------|-----------------------------|-------------------------------|--------|
| CNS, skeletal, skin, cardiac, GI, urogenital anomalies. Increased chromosomal breakage, pancytopenia. | Dyskeratosis congenita: IUGR, microcephaly, pulmonary and hepatic fibrosis, nail dystrophy, sparse scalp hair and eyelashes; reticulate skin pigmentation; palmar hyperkeratosis; premalignant oral leukoplakia; pancytopenia; +/- recurrent infections. DKC1: XL, Bc and Tc: Progressive decrease. NOLA2 (NHP2), NOLA3 (NOP10): AR, Tc: Decreased. RET1: AD, Tc: Decreased. TERC, TINF2, ACD: AD, Tc: variable. DCLRE1B/SN411/APOLLO, WRAP53*: AR, Tc: variable. Hoyeraal-Hreidarsson Syndrome (HHS) Severe phenotype with developmental delay and cerebellar hypoplasia. AR, RET1, PARN, ACD | SRP72- deficiency**. SRP72, AD Bone marrow failure and congenital nerve deafness BMF55* TPS3, AD Erythroid hypoplasia, B-cell deficiency | MIRAGE sd, AD. SAMD9 (GOF): IUGR with gonadal abnormalities, adrenal failure, MDS with chromosome 7 aberrations, predisposition to infections, enteropathy, absent spleen Ataxia pancytopenia sd, AD. SAMD9L (GOF): Cytopenia, predisposition to MDS with chromosome 7 aberrations and progressive cerebellar dysfunction COATS plus Sd: Intracranial calcification, abnormal telomeres, IUGR, gastrointestinal hemorrhage due to vascular ectasia, hypocellular bone marrow, pancytopenia STN1: premature aging, CTC1: sparse graying hair, dystrophic nails, osteopenia, retinal telangiectasia, |

**Fig. 9** Bone marrow failure disorders. AD autosomal dominant transmission, AR autosomal recessive transmission, Bc B cells, BMFS bone marrow failure syndrome, CNS central nervous system, DKC dyskeratosis congenita, GI gastrointestinal, GOF gain-of-function, IUGR intrauterine growth retardation, MDS myelodysplasia, sd syndrome, Tc T cells, XL X-linked transmission
This phenotypic classification of IEI forms a diagnostic resource, aimed to complement the 2019 IUIS genotypic classification. These figures serve as diagnostic orientation tools for patients with any of the typical phenotypic presentations of IEI, whether clinical or biological. They were designed for, and will hopefully be useful to physicians and biologists who are not experts in the field of IEI. We hope that these figures can help them reach a diagnosis of IEI when encountering patients whose clinical or biological phenotypes are evocative of IEI.

Compliance with Ethical Standards

Conflict of Interest  The authors declare that they have no conflict of interest.

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Conclusion

This phenotypic classification of IEI forms a diagnostic resource, aimed to complement the 2019 IUIS genotypic classification. These figures serve as diagnostic orientation tools for patients with any of the typical phenotypic presentations of IEI, whether clinical or biological. They were designed for, and will hopefully be useful to physicians and biologists who are not experts in the field of IEI. We hope that these figures can help them reach a diagnosis of IEI when encountering patients whose clinical or biological phenotypes are evocative of IEI.

X. Phenocopies of PID

| Associated with Somatic Mutations | Associated with Auto-Antibodies |
|---------------------------------|--------------------------------|
| **Splenomegaly, lymphadenopathy, autoimmune cytopenias. Defective lymphocyte apoptosis.** | **Chronic mucocutaneous candidiasis (isolated or with APECED syndrome) AutoAb to IL-17 and/or IL-22.** |
| **ALPS-SFAS** *(somatic mutations in TNFRSF6)*/ ALPS-FAS *(ALPS type lm)* | **Endocrinopathy, chronic mucocutaneous candidiasis /CMC. Germline mutation in AIRE** |
| **RALD. RAS-associated autoimmune leukoproliferative disease.** *(ALPS Like)*; **N-RAS GOF, K-RAS GOF** | **Adult-onset immunodeficiency with susceptibility to mycobacteria. Auto-Ab to IFNg**. |
| Sporadic; granulocytosis, monocytosis/ALPS-like | Mycobacterial, fungal, salmonella, VZV infections /MSMD or CID. |
| **Cryopyrinopathy, (Muckle-Wells /CINCA/NOMID-like syndrome).** NLRP3. | **Recurrent skin infection. AutoAb to IL-6.** |
| Urticaria-like rash, arthropathy, neurological symptoms | Staphylococcal infections / STAT3 deficiency |
| **Hyperesinophilic syndrome due to somatic mutations in STAT5b. STAT5b. GOF.** | **Pulmonary alveolar proteinosis. AutoAb to GM-CSF.** |
| Atopic dermatitis, urticarial rash, diarrhea. Eosinophilia. | Pulmonary alveolar proteinosis, cryptococcal meningitis, disseminated nocardiosis/GSF2RA deficiency |

Fig. 10 Phenocopies of PID. ALPS autoimmune lymphoproliferative syndrome, AutoAb autoantibodies, CID combined immunodeficiency, CMC chronic mucocutaneous candidiasis, GOF gain-of-function, MSMD Mendelian susceptibility to mycobacterial disease, PRCA pure red cell aplasia

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