The 2017 IUIS Phenotypic Classification for Primary Immunodeficiencies

Aziz Bousfiha 1 • Leïla Jeddane 1,2 • Capucine Picard 3,4 • Fatima Ailal 1 • H. Bobby Gaspar 5 • Waleed Al-Herz 6 • Talal Chatila 7 • Yanick J. Crow 8,9 • Charlotte Cunningham-Rundles 10 • Amos Etzioni 11 • Jose Luis Franco 12 • Steven M. Holland 13 • Christoph Klein 14 • Tomohiro Morio 15 • Hans D. Ochs 16 • Eric Oksenhendler 17 • Jennifer Puck 18 • Mimi L. K. Tang 19,20,21 • Stuart G. Tangye 22,23 • Troy R. Torgerson 16 • Jean-Laurent Casanova 24,25,26,27 • Kathleen E. Sullivan 28

Received: 26 July 2017 / Accepted: 31 October 2017 / Published online: 11 December 2017
© The Author(s) 2017. This article is an open access publication

Abstract Since the 1990s, the International Union of Immunological Societies (IUIS) PID expert committee (EC), now called Inborn Errors of Immunity Committee, has published every other year a classification of the inborn errors of immunity. This complete catalog serves as a reference for immunologists and researchers worldwide. However, it was unadapted for clinicians at the bedside. For those, the IUIS PID EC is now publishing a phenotypical classification since 2013,
which proved to be more user-friendly. There are now 320 single-gene inborn errors of immunity underlying phenotypes as diverse as infection, malignancy, allergy, auto-immunity, and auto-inflammation. We herein propose the revised 2017 phenotypic classification, based on the accompanying 2017 IUIS Inborn Errors of Immunity Committee classification.

**Keywords** Primary immunodeficiencies · Classification · Phenotypic · IUIS · Inborn errors of immunity

Human primary immunodeficiency diseases (PID) comprise 330 distinct disorders with 320 different gene defects listed [1]. Long considered as rare diseases, recent studies tend to show that they are more common than generally thought, if only by their rapidly increasing number [2, 3]. The International Union of Immunological Societies (IUIS) PID expert committee proposed a PID classification since 1999 [1], which facilitates clinical research and comparative studies worldwide; it is updated every other year to include new disorders or disease-causing genes. This classification is organized in tables, each of which groups PIDs that share a given pathogenesis. As this catalog is not adapted for use by the clinician at the bedside, the now called Inborn Errors of Immunity Committee proposed since 2013 a phenotypic complement to its classification [4]. Moreover, a smartphone application has been published, based on the 2015 phenotypic classification [5]. As the number of inborn errors of immunity is quickly increasing, and at an even faster pace since the advent of next-generation sequencing, this phenotypic classification requires revision at the same pace as the classical IUIS classification.

Here, we present an update of these figures (Figs. 1, 2, 3, 4, 5, 6, 7, 8, and 9), based on the accompanying 2017 report in inborn errors of immunity. We included all diseases included in the 2017 update of the IUIS classification [1] and split some categories in two parts to ease the lecture. An algorithm was assigned to each of the nine main groups of the classification and the same color was used for each group of similar conditions. Disease names are presented in red and genes in bold and italics. Mode of inheritance is expressed when adequate; if not expressed, the default mode of transmission is autosomal recessive. Clinical features that point to several diseases are presented in italics before the disease names.

---

24 St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, The Rockefeller University, New York, NY, USA

25 Howard Hughes Medical Institute, New York, NY, USA

26 Laboratory of Human Genetics of Infectious Diseases, Necker Branch, INSERM UMR1163, Imagine Institute, Necker Hospital for Sick Children, University Paris Descartes, Paris, France

27 Pediatric Hematology-Immunology Unit, Necker Hospital for Sick Children APHP, Paris, France

28 Division of Allergy Immunology, Department of Pediatrics, The Children’s Hospital of Philadelphia, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA
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-        |                   |
| XL, CD 132-yc deficiency. IL2RG |
|                   |                   |
| SCID T-B+NK+        |                   |
| IL7RA, IL7R         |
| No γ/δ T cells: CD3δ, CD3ε, CD3ζ. |
|                   |                   |
| SCID T-B-NK-        |                   |
| ADA def : ADA       |
| Chondrosteal dysplasia, deafness, may have pulmonary alveolar proteinosis, cognitive defects |
|                   |                   |
| SCID T-B-NK+        |                   |
| Microcephaly ?      |

- With facial dysmorphism:
  - DNA ligase IV def. LIG4
  - CERNUNNOS/XLF def. NHEJ1
  - Radiation sensitive

- Without facial dysmorphism:
  - DNA Pks def. PRKDC

I. Immunodeficiencies affecting cellular and humoral immunity

(b) Combined Immunodeficiencies Generally Less Profound than Severe Combined Immunodeficiency

| Low CD4: MHCII Expression | Low CD8 | Low Bl: | Ig : often NL | Ig Low | Normal Ig but Poor Specific Antibody response |
|---------------------------|---------|--------|--------------|--------|---------------------------------------------|
| CD8 def: CD8A            | CD8B    | Absent | DOCK8 def: DOCK8. Severe Eczema. Cutaneous viral and staphylococcal infections; severe atopy; cancer; alopecia. High IgE, Low IgM, eosinophilia. Low NE with poor function. Low CD7+ memory Bi Poor peripheral Tc tolerance. |
| Absent: MHCII def.       |         |        |              |        | IL22R def : IL22R. Recurrent infections; Pneumocystis, Cryptococcus. Tc: low cytokine production; poor antigen proliferation. |
| RYKAM,CIT2, RYK, RFAP   |         |        |              |        | MALT1 def : MALT1. Bacterial, fungal and viral infections. Impaired Tc proliferation and antibody response. |
| Diarrhea, respiratory infections, liver/biliary tract disease |
| Absent: MHC I on lymphocytes. |
| CD8 def: CD8A            | CD8B    | Absent | DOCK8 def: DOCK8. Severe Eczema. Cutaneous viral and staphylococcal infections; severe atopy; cancer; alopecia. High IgE, Low IgM, eosinophilia. Low NE with poor function. Low CD7+ memory Bi Poor peripheral Tc tolerance. |
| Absent: MHCII def.       |         |        |              |        | IL22R def : IL22R. Recurrent infections; Pneumocystis, Cryptococcus. Tc: low cytokine production; poor antigen proliferation. |
| RYKAM,CIT2, RYK, RFAP   |         |        |              |        | MALT1 def : MALT1. Bacterial, fungal and viral infections. Impaired Tc proliferation and antibody response. |
| CD19 ↓ : SCID T-B-       |         |        |              |        | IL22R def : IL22R. Recurrent infections; Pneumocystis, Cryptococcus. Tc: low cytokine production; poor antigen proliferation. |

NC MNC on lymphocytes.
ZAP-70 def: ZAP70 may have immune dysregulation, autoimmunity. Mlg. CD4: Low function.
Absence MHC I on lymphocytes.
MHC-I def .
TAP2, TAP3 or TAPBP
Vasculitis, periorbital gangrene.
Mlg. IBM
Sesquidulatory infections, cutaneous granulomas.
Mlg. Hypoproteinemia. Absent IBM associated proteins MHC I, CD5a, CD5b, CD1v.
### DNA Repair Defects other than those listed in Table 1: Karyotype

| DNA Repair Defect | Karyotype |
|-------------------|-----------|
| XRCC6/ERCC4       | YR115.2 deletion |
| HMMR              | 1p36.3 deletion |
| MUTLh             | 3q26 deletion |
| XRCC6/ERCC4       | 1p36.3 deletion |
| HMMR              | 1p36.3 deletion |
| MUTLh             | 3q26 deletion |

### Immuno-osseous dysplasias

| Immuno-osseous dysplasia | Description |
|--------------------------|-------------|
| Aplastic anemia           | Immune dysfunction |
| Anemia                   | Immune dysfunction |
| Aplastic anemia           | Immune dysfunction |
| Anemia                   | Immune dysfunction |

### Thymic Defects with Additional Congenital Anomalies

| Thymic Defect | Additional Congenital Anomalies |
|---------------|---------------------------------|
| MOPD1         | Immunodeficiency, livedo and short stature |
| MOPD1         | Immunodeficiency, livedo and short stature |
| MOPD1         | Immunodeficiency, livedo and short stature |
| MOPD1         | Immunodeficiency, livedo and short stature |

---

**Fig. 2 a, b CID with associated or syndromic features.**

- **Ab:** antibody
- **AD:** autosomal dominant transmission
- **ANCA:** anti-neutrophil cytoplasm antibodies
- **AR:** autosomal recessive transmission
- **Bc:** B cells
- **BCG:** Bacillus Calmette-Guérin
- **BRC:** B cell receptor
- **CD:** cluster of differentiation
- **CMV:** cytomegalovirus
- **CNS:** central nervous system
- **def:** deficiency
- **DNA:** desoxyribonucleic acid
- **DKC:** dyskeratosis congenita
- **EDA:** anhidrotic ectodermal dysplasia
- **GOF:** gain-of-function
- **HIES:** hyper IgE syndrome
- **FILS:** facial dysmorphism, immunodeficiency, livedo and short stature
- **ID:** immunodeficiency
- **IgM:** immunoglobulin M
- **IUGR:** intrauterine growth retardation
- **LOF:** loss-of-function
- **MDS:** myelodysplasia
- **NK:** natural killer
- **PHA:** phytohemagglutinin
- **PPS:** polysaccharides
- **SCID:** severe combined immunodeficiency
- **SD:** syndrome
- **Tc:** T cell receptor
- **TREC:** T cell receptor excision circle
- **XL:** X-linked
**ibl. CID with associated or syndromic features**

### Hyper-IgE syndromes (HIES)

**AD-HIES (Job syndrome)**: STAT3, UOF. Distinctive facial features (broad nasal bridge); bacterial infections (boils and pulmonary abscesses, pneumatoceles) due to S. aureus, Aspergillus, Pneumocystis jiroveci; eczema; mucocutaneous candidiasis; hypereosinophilic joint, osteoporosis and bone fractures, scoliosis, retention of primary teeth; anorexia and failure to thrive; lymphadenopathy. Increase in IgE; specific antibody production decreased. 

**Comel Netherton syndrome (SPINK5)**: hyper-IgE may be decreased. Hypomelanosis, infections; cognitive impairment; abscesses, bacterial and viral pneumonia, recurrent skin atopy; autoimmunity; immune dysregulation.

**PGM3 deficiency**: Switched and non-switched Bc. Elevated IgE and hair; atopic diathesis; increased risk of Bacterial infections. Elevated IgE and IgA; Other Ig: variably decreased.

### Dyskeratosis congenita (DKC)

**Myelodysplasia, defective telomere maintenance**

Exclude other causes: Fanconi anemia, Blackfan-Diamond

**Dyskeratosis congenita (DKC)**: 

| Defects of Vitamin B12 and Folate Metabolism: | Anhidrotic Ectodermodyplasia with ID | Others |
|-----------------------------------------------|--------------------------------------|--------|
| Megaloblastic anemia, IgG decreased. Transcobalamin 2 deficiency. TCN2. pancytopenia; untreated for prolonged periods results in intellectual disability. Deficiency causing hereditary folate malabsorption. SC46A2. If untreated for prolonged periods results in intellectual disability. | Anhidrotic ectodermal dysplasia, various infections (bacterial, mycobacterial, viruses and fungi), colitis, variable defects of skin and hair. | ID with multiple intestinal atresias. TCTA. Bacterial (sepsis), fungal, viral infections, multiple intestinal atresias, often with intravascular polythrombosis and early demise, some with SCID phenotype. Markedly decreased IgG, IgA, IgM. Low Tc: Variable, severe Bc. |

**POMT1 deficiency**: Reduced. 

**RTEL1**: Developmental delay and cerebellar hypoplasia

**SAMD9**: Decreased. 

**TINF2**: AD.

**TERT, TPP1**: Decreased. 

**TERC**: Normal, Tc: Increased.

### Vici syndrome

**EPG5**: Agnathia of the corpus callosum, cataracts, cardiomyopathy, skin hypopigmentation, intellectual disability. IgG: Decreased. IgG2, IgA: Defective. Profound depletion of CD4+ cells.

### Calcium Channel Defects

**Autoimmunity, ADA, non-progressive myopathy. Ig and Bc: Decreased.** 

**Hepatic veno-occlusive disease with immunodeficiency (VODI), SPEI**.

**Hepatic veno-occlusive disease, Pneumocystis jiroveci pneumonia, CMV, candida, thrombocytopenia, hepatosplenomegaly, cerebrospinal hypoalbuminemia.** Decreased IgG, IgA, IgM, absent germinal centers and tissue plasma cells. Decreased memory Bc. Decreased memory Tc.

**Histiocytic lymphomyeloproliferative syndrome** (HLMP): Variable.

**Leukocyte adhesion deficiency (LAD)**: Normal. 

**SIDC**: Cytopenia, absent germinal centers.

**SCID**: Normal. 

### Others

**Hermansky-Pudlak syndrome (HPS)**: Neurodegeneration, mucocutaneous bleeding, ophthalmologic defects, pigmentary retinopathy, albinism, cutaneous atrophy. 

**HALLID**: Common variable immunodeficiency (CVI), X-linked severe combined immunodeficiency (X-SCID), early-onset CID with associated or syndromic features. 

**Familial hypercholesterolemia (FH)**: Familial hypertriglyceridemia (FH-TG), familial combined hyperlipidemia (FH-C), familial hypertriglyceridemia (FH-HI).

**LMO2, TSC1, TSC2**: Lhermitte-Duclos disease. Constitutional telomere dysfunction.

**PIK3CA**: Bacterial infections, autoinflammation, amyloidosis. Bc: Decreased memory Bc.

**PDZL1 deficiency**: Deficiency. Bc: Decreased, low Tc.

**PLOD2 deficiency**: Deficiency. 

**PYCARD deficiency**: Deficiency. 

**RAG2 deficiency**: Deficiency. 

**SCLC1 deficiency**: Deficiency.

**SHP2 deficiency**: Deficiency. 

**TGFbeta receptor deficiency**: Deficiency. 

**TRA1 deficiency**: Deficiency.

**VPS13A deficiency**: Deficiency.

**WASP deficiency**: Deficiency. 

**X-linked agammaglobulinemia (XLA)**: Deficiency.

**X-linked lymphoproliferative syndrome** (XLP): Deficiency.

**X-linked immunodeficiency with hypogammaglobulinemia E (XHIE)**: Deficiency.

**X-linked agammaglobulinemia (XLA)**: Deficiency.

**X-linked lymphoproliferative syndrome** (XLP): Deficiency.

**X-linked lymphoproliferative syndrome** (XLP): Deficiency.
### III. Predominantly Antibody deficiencies, a: Hypogammaglobulinemia

#### Serum Immunoglobulin Assays: IgG, IgA, IgM, IgE

| IgG, IgA and/or IgM ↓ | B > 1 % |
|----------------------|---------|
| CD81 deficiency. CD81. Recurrent infections, may have glomerulonephritis. |         |
| TACI deficiency. TNFRSF13B (TAC). AD or AR. Variable clinical expression |         |
| BAFF receptor deficiency. TNFRSF13C (BAFF-R). Variable clinical expression. Low IgG and IgM. |         |
| TWEAK deficiency. TWEAK (TNFSF12). AD. Pneumonia, bacterial infections, warts, thrombocytopenia. Neutropenia. Low IgM and A, lack of anti-pneumococcal antibody. |         |
| Mannosyl-oligosaccharide glucosidase deficiency (MOGS). MOGS (GCS1). Bacterial and viral infections, severe neurologic disease, also known as congenital disorder of glycosylation type IIb (CDG-IIb). Severe hypogammagl. |         |
| TTC37 deficiency. TTC37. Recurrent bacterial and viral infections. Abnormal hair findings: trichorrhexis nodosa. Poor antibody response to pneumococcal vaccine. |         |
| IRF2BP2 deficiency. IRF2BP2. Recurrent infections, possible autoimmunity and inflammatory disease. Hypogammaglobulinemia, absent IgA. |         |

### III. Predominantly Antibody deficiencies, b: Other Antibody deficiencies

#### Serum Immunoglobulin Assays: IgG, IgA, IgM, IgE

| Isotype, Light Chain, or Functional Deficiencies with Generally Nil Numbers of Bc | High Bc numbers due to constitutive NF-κB activation |
|--------------------------------------------------------------------------------|--------------------------------------------------|
| Selective IgA deficiency. Unknown. | CARD11 GOF. |
| Bacterial infections, autoimmunity mildly increased. Very low to absent IgA with other isotypes normal, normal subclasses and specific antibodies. | CARD11. AD. BENTA syndrome |
| Transient hypogammaglobulinemia of infancy. Unknown. | Splenomegaly, lymphadenopathy, poor vaccine responses. |
| Usually not associated with significant infections, normal ability to produce antibodies to vaccine antigens. IgG and IgA decreased. | |
| IgG subclass deficiency with IgA deficiency. Unknown. | |
| Recurrent bacterial infections. Reduced IgA with decrease in one or more IgG subclass. | |
| 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. | |
| 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. IGK. | |
| Asymptomatic. All immunoglobulins have lambda light chain. | |
| Selective IgM deficiency. Unknown. Pneumococcal / bacterial infections. Absent serum IgM. | |
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 globulins; Nl: normal; XL: X-linked transmission

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

Compliance with Ethical Standards

IV. Diseases of immune dysregulation.

a : Hemophagocytic Lymphohistiocytosis (HLH) & EBV susceptibility

| Hyopigmentation: Partial albinism. Decreased NK and CTL activity/cytotoxicity and/or degranulation. Bc and Tc: Nl. |
|---|
| Chediak Higashi sd. LYST |
| Recurrent infections, fever, (H)SM, bleeding tendency, progressive neurological dysfunction. Giant lysosomes (WBC), neutropenia, cytopenias. Specific hair shaft anomaly. |
| Griscelli sd type 2. RA827a. |
| Fever, (H)SM, cytopenias. Specific hair shaft anomaly. |
| Hermansky-Pudlak sd type 2. AP3B1. |
| Recurrent infections, pulmonary fibrosis, increased bleeding, neutropenia. Specific hair shaft anomaly. |
| Hermansky-Pudlak sd, type 10. AP3D1. |
| Oculocutaneous albinism, severe neutropenia, recurrent infections, seizures, hearing loss and neurodevelopmental delay. |
| Familial Hemophagocytic Lymphohistiocytosis Syndromes: Fever, (H)SM, cytopenias, Nl Bc. Increased activated Tc. Decreased to absent NK and CTL activities cytotoxicity. |
| Perforin deficiency (HLH2). PRF1. |
| UNC13D / Munc13-4 deficiency (HLH3). UNC13D. |
| Syntaex 11 deficiency (HLH4). STX11. |
| STXB P / Munc18-2 deficiency (HLH5). STXB P2. |
| Interopathy |
| RASGRP1 deficiency. RASG R P1. |
| Recurrent pneumonia, herpes virus infections, EBV associated lymphoma. Increased IgA, Bc and Tc. Poor activation, proliferation, motility. |
| CD70 deficiency. CD70 (TNFSF7). |
| Hodgkin’s lymphoma. Reduced IgM, IgG, IgA (75%) and reduced Ag-specific Ab responses (50%). Bc/poor antibody and memory responses. Tc:low Treg, poor activation and function. |
| CTP51 deficiency. CTP51. |
| Recurrent/chronic bacterial and viral infections (EBV, VZV), EBV lymphoproliferation, Bc non-Hodgkin lymphoma. Tc: poor proliferation to Ag |
| RBITC (CARMIL2) deficiency. RBITC. |
| Recurrent bacterial, fungal and mycobacterial infections, viral warts, molluscum and EBV lymphoproliferative and other malignancy, atopy. Ig Nl to low, poor T dependent antibody response. Nl Bc. Tc: low Treg, high CD4, poor function. |
| ITK deficiency. ITK. |
| EBV associated Bc lymphoproliferation, lymphoma, Nl or low IgG. Tc: Progressive decrease |
| MAGT1 deficiency (XMEN). MAGT1. |
| EBV infection, lymphoma, viral infections, respiratory and GI infections. Low CD4. Low recent thymic emigrant cells, poor proliferation to CD3 |
| PRKCD deficiency. PRKCD. |
| Recurrent infections, EBV chronic infection, lymphoproliferation, SLE-like autoimmunity (nephrotic and antiphospholipid Sd). Low IgG. Low memory Bc high CD5 Bc |
| XL, XLIP1, SH2D1A. |
| Clinical and immunologic features triggered by EBV infection: lymphoproliferation, Lymphoma. Hypogamma globulinemia, Absent NK T cells. Impaired NK cell and CTL cytotoxic activity. Reduced Memory B cells. SAP deficiency (CMF). |
| XL, XLIP2. XIA P. |
| Splenomegaly, lymphoproliferation, Coiffs, IBD. Hypogamma globulinemia, 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 (CMF). |
| AR, CD27 deficiency. CD27 (TNFRSF7). |
| Features triggered by EBV infection, aplastic anemia, low INKTc lymphoma. Low Ig |
| FAAP24 deficiency. FAAP24. |
| EBV-driven lymphoproliferative disease. Failure to kill autologous EBV transformed Bc. |
### IV. Diseases of immune dysregulation. b: Sd with Autoimmunity and Others

#### Syndromes with Autoimmunity

| Yes | Occasionally | No | No: Regulatory T Cell Defects? |
|-----|--------------|----|--------------------------------|
| ALPS Autoimmune Lymphoproliferative Sd | | | |
| Chronic adenopathy Spleenomegaly, defective lymphocyte apoptosis. | | | |
| ALPS-FAS. TNFRSF6. AD or AR. Autoimmune cytopenias, increased lymphoma risk, IgG and IgA Ni or increased, elevated serum Fas, IL-10, vitamin B12. | | | |
| ALPS-FASLG. TNFSF6 AR. autoimmune cytopenias, SLE, soluble Fas 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 hypoplasenism, bacterial and viral infections, recurrent episodes of encephalopathy and liver dysfunction. | | | |

#### Immune Dysregulation with Colitis: IBD, NI Tc & Bc

- **IL-10 deficiency. IL10: AR.**
  - Folliculitis, recurrent respiratory diseases, arthritis. No functional IL-10 secretion.

- **IL-10Ra deficiency. IL10RA AR.**
  - Folliculitis, recurrent respiratory diseases, arthritis, lymphoma.
  - Leukocytes unresponsive to IL-10.

- **IL-10Rb deficiency. IL10RB AR.**
  - Folliculitis, recurrent respiratory diseases, arthritis, lymphoma.
  - Leukocytes unresponsive to IL10, IL22, IL26, IL28A, IL28B, IL29

- **NFAT5 haploinsufficiency. NFAT5. AR.**
  - Recurrent Sinopulmonary infections. Decreased memory Bc and plasmablasts.

---

**Fig. 4 (continued)**

**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; CFM: flow cytometry; CMMI: chronic myelomonocytic leukemia; def: deficiency; DHR: dihydorhodamine-1,2,3; GOF: gain-of-function; IUGR: intrauterine growth retardation; MDS: myelodysplasia; NBT: nitroblue of tetrazolium; NK: natural killer cells; WBC: white blood cells; XL: X-linked transmission
**V. Congenital defects of phagocyte number, function, or both. a : Neutropenia**

| Syndrome associated | No syndrome associated |
|---------------------|------------------------|
| Shwachman-Diamond syndrome. SBDS. AR.  | Elastase deficiency (SCN1). ELANE. AD.  |
| Pancytopenia, exocrine pancreatic insufficiency, chondrodyplasia | Susceptibility to MDS/leukemia. Severe congenital neutropenia or cyclic neutropenia (perform CBC twice weekly/ 4 weeks). |
| G6PC3 deficiency (SCN4). G6PC3. AR. Structural heart defects, urogenital abnormalities, inner ear deafness, and venous angiectasias of trunks and limbs. Affected functions: Myeloid differentiation, chemotaxis, O2 \(_2\) 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, hepatomegaly. | GFI 1 deficiency (SCN2). GFI1. AD. B/T lymphopenia |
| Cohen syndrome. COH1. AR. Dysmorphism, mental retardation, obesity, deafness. | X-linked neutropenia/ myelodysplasia WAS GOF. WAS. Myeloid maturation arrest, monocytopenia, variable lymphoid anomalies . |
| Barth Syndrome (3-Methylglutaconic aciduria type II). TA2. XL. |  |
| Cardiomyopathy, myopathy, growth retardation. | G-CSF receptor deficiency. CSF3R. AR.  |
| Clericiuio syndrome (Poikiloderma with neutropenia). C16ORF57 (USB1). AR. | Stress granulopoiesis disturbed |
| Poor wound healing, severe stomatitis, neutrophil nuclei herniate. Mild neutropenia. | Neutropenia with combined immune deficiency. MKL1. AR.  |
| HYOU1 deficiency. HYOU1. AR. Hypoglycemia, inflammatory complications. | Mild thrombocytopenia. Lymphopenia. |

**Syndrome associated**

| Normal | Abnormal |
|--------|---------|
| GATA2 def (MonoMac sd) . GATA2, AD. | CCG. Early onset of severe and recurrent infections affecting initially the natural barriers of the organism ( lungs, lymph nodes, skin), and eventually inner structures (liver, spleen, bones, brain, and +++ hepatic abscess). Autoinflammatory phenotype, IBD. |
| Susceptibility to Mycobacteria, Papilloma Viruses, Histoplasmosis, Lymphedema. Pulmonary alveolar proteinosis, myelodysplasia/AML/ CMLL. Monocytopenia. Low NK. | Granulomas obstructing respiratory, urinary or gastrointestinal tracts. Inflammatory bowel disease (Crohn’s like disease) and perianal disease : up to 30 %.  |
| Pulmonary alveolar proteinosis. CSF2RA, AR. Bilobed nuclei | Pathogens : typically catalase positive bacteria ( S. aureus and gram-negative bacilli, Aspergillus, Candida); other: Burkholderia cepacia, Chromobacterium violaceum, Nocardia, and invasive Serratia marcescens. In developing countries, BCG : adverse effects in 150,000 with 60–85 % neutrophils) deficiency in CD18. (WBC 20,000– 150,000 with 60–85 % neutrophils) severity of the disease correlates with the degree of deficiency in CD18. (WBC 20,000– 150,000 with 60–85 % neutrophils) Early onset of severe and childhood infections. Severe cerebral infection and severe intellectual deficit. Facial dysmorphism ( depressed nasal bridge). Severe periodontitis later in life. Bombay blood group. Infections: rarely life threatening. Patients may live to adulthood. |
| Specific granule deficiency. C/EBPε. | Pulmonary alveolar proteinosis. CSF2RA, AR. Bilobed nuclei |
| C/EBPε. Bilobed nuclei | Specific granule deficiency. C/EBPε. Bilobed nuclei |
| Leukocyte adhesion deficiency. Skin infections evolve to large ulcers. Leukocytosis with neutrophilia (WBC > 25000) | Specific granule deficiency. C/EBPε. Bilobed nuclei |
| LAD I. ITGB2 Delayed cord separation with omphalitis++, no pus formation. Lack of inflammation is observed in infection area. Periodontitis leads to early loss of teeth. . CD18 def (CMF) severity of the disease correlates with the degree of deficiency in CD18. (WBC 20,000– 150,000 with 60–85 % neutrophils) | Specific granule deficiency. C/EBPε. Bilobed nuclei |
| Localized juvenile periodontitis . FPR1. Periodontitis only | Specific granule deficiency. C/EBPε. Bilobed nuclei |
| β-Actin . ACTB Mental retardation. | Specific granule deficiency. C/EBPε. Bilobed nuclei |
| Papillon-Lefèvre . CTSC. Periodontitis, palmoplantar hyperkeratosis | Specific granule deficiency. C/EBPε. Bilobed nuclei |
| LAD II. SLC35C1 Extremely rare. Recurrent infections. Severe growth delay and severe intellectual deficit. Facial dysmorphism ( depressed nasal bridge). Severe periodontitis later in life. Bombay blood group. Infections: rarely life threatening. Patients may live to adulthood. | Specific granule deficiency. C/EBPε. Bilobed nuclei |
| LAD III. FERMT3 Severe bacterial infections and severe bleeding disorder; osteoporosis (severe cases). Platelet aggregation assay. | Specific granule deficiency. C/EBPε. Bilobed nuclei |

**V. Congenital defects of phagocyte. b : Functional defects**

| Syndrome associated | No Syndrome associated: DHR assa (or NBT test)? |
|---------------------|---------------------------------------------|
| Cystic fibrosis. CFTR. AR. Pancreatic insufficiency. Respiratory infections, elevated sweat chloride | Normal |
| Papillon-Lefèvre . CTSC. Periodontitis, palmoplantar hyperkeratosis | Abnormal |
| Localized juvenile periodontitis . FPR1. Periodontitis only | CCG. Early onset of severe and recurrent infections affecting initially the natural barriers of the organism ( lungs, lymph nodes, skin), and eventually inner structures (liver, spleen, bones, brain, and +++ hepatic abscess). Autoinflammatory phenotype, IBD. |
| β-Actin . ACTB Mental retardation. | Granulomas obstructing respiratory, urinary or gastrointestinal tracts. Inflammatory bowel disease (Crohn’s like disease) and perianal disease : up to 30 %.  |
| Leukocyte adhesion deficiency. Skin infections evolve to large ulcers. Leukocytosis with neutrophilia (WBC > 25000) | Pathogens : typically catalase positive bacteria ( S. aureus and gram-negative bacilli, Aspergillus, Candida); other: Burkholderia cepacia, Chromobacterium violaceum, Nocardia, and invasive Serratia marcescens. In developing countries, BCG : adverse effects in 150,000 with 60–85 % neutrophils) deficiency in CD18. (WBC 20,000– 150,000 with 60–85 % neutrophils) Early onset of severe and childhood infections. Severe cerebral infection and severe intellectual deficit. Facial dysmorphism ( depressed nasal bridge). Severe periodontitis later in life. Bombay blood group. Infections: rarely life threatening. Patients may live to adulthood. |
| LAD I. ITGB2 Delayed cord separation with omphalitis++, no pus formation. Lack of inflammation is observed in infection area. Periodontitis leads to early loss of teeth. . CD18 def (CMF) severity of the disease correlates with the degree of deficiency in CD18. (WBC 20,000– 150,000 with 60–85 % neutrophils) | Pulmonary alveolar proteinosis. CSF2RA, AR. Bilobed nuclei |
| Localized juvenile periodontitis . FPR1. Periodontitis only | Pulmonary alveolar proteinosis. CSF2RA, AR. Bilobed nuclei |
| β-Actin . ACTB Mental retardation. | Pulmonary alveolar proteinosis. CSF2RA, AR. Bilobed nuclei |
| Papillon-Lefèvre . CTSC. Periodontitis, palmoplantar hyperkeratosis | Pulmonary alveolar proteinosis. CSF2RA, AR. Bilobed nuclei |
| Localized juvenile periodontitis . FPR1. Periodontitis only | Pulmonary alveolar proteinosis. CSF2RA, AR. Bilobed nuclei |
| β-Actin . ACTB Mental retardation. | Pulmonary alveolar proteinosis. CSF2RA, AR. Bilobed nuclei |
| Leukocyte adhesion deficiency. Skin infections evolve to large ulcers. Leukocytosis with neutrophilia (WBC > 25000) | Pulmonary alveolar proteinosis. CSF2RA, AR. Bilobed nuclei |
| LAD I. ITGB2 Delayed cord separation with omphalitis++, no pus formation. Lack of inflammation is observed in infection area. Periodontitis leads to early loss of teeth. . CD18 def (CMF) severity of the disease correlates with the degree of deficiency in CD18. (WBC 20,000– 150,000 with 60–85 % neutrophils) | Pulmonary alveolar proteinosis. CSF2RA, AR. Bilobed nuclei |
| Localized juvenile periodontitis . FPR1. Periodontitis only | Pulmonary alveolar proteinosis. CSF2RA, AR. Bilobed nuclei |
| β-Actin . ACTB Mental retardation. | Pulmonary alveolar proteinosis. CSF2RA, AR. Bilobed nuclei |
| Papillon-Lefèvre . CTSC. Periodontitis, palmoplantar hyperkeratosis | Pulmonary alveolar proteinosis. CSF2RA, AR. Bilobed nuclei |
| Localized juvenile periodontitis . FPR1. Periodontitis only | Pulmonary alveolar proteinosis. CSF2RA, AR. Bilobed nuclei |
| β-Actin . ACTB Mental retardation. | Pulmonary alveolar proteinosis. CSF2RA, AR. Bilobed nuclei |
### VI. Defects in Intrinsic and Innate immunity.

**a : Bacterial and Parasitic Infections**

| Predisposition to Invasive Bacterial infections (pyogens): | Predisposition to Parasitic and Fungal infections |
|------------------------------------------------------------|--------------------------------------------------|
| meningitis, sepsis, arthritis, osteomyelitis and abscesses, often in the absence of fever. | Predisposition to Mucocutaneous Candidiasis (CMC) |
| Predominant pathogens (S. pneumoniae, S. aureus and Pseudomonas aeruginosa). Non-invasive bacterial infections (skin infections and upper respiratory tract infections). Improve with age. | Chronic Mucocutaneous Candidiasis without ectodermal dysplasia |
| Routine Usual screening tests are normal. Specific screening tests (lack of proinflammatory cytokine production and CD62L shedding): available only in specialized clinical immunology laboratories. | STAT1 GOF. STAT1, AD |
| IRAK4 def. IRAK4, AR | IL-17F deficiency. IL17F, AD. Folliculitis. |
| IRAK4 def. IRAK4, AR | IL-17RA deficiency. IL17RA, AR |
| IRAK-1 def. IRAK1, XL | IL-17RC deficiency. IL17RC, AR |
| TIRAP def. TIRAP, AR | ACT1 deficiency. ACT1, AR |
| Staphylococcal disease during childhood. |CARD9 def. CARD9, AR. |
| Isolated congenital asplenia. Bacteremia (encapsulated bacteria). No spleen. | Invasives Fungal Diseases. |
| RPSA, AD | Invasive candidiasis infection, deep dermatophytoses, other invasive fungal infections. |
| HMGS, AR. Hemolysis, nephritis, inflammation | Trypanosomiasis. APOL1, AD |
| | Inborn Errors of Immunity Related to Non-Hematopoietic Tissues |

**b : MSMD and viral infection.**

| Osteopetrosis. TNSF11A, PLEKHM1 AR. |
| TCIRG1, AR. + hypocalcemia |
| CLCN7, OSTM1, AR. + hypocalcemia, neurologic features |
| SNX10, AR. + visual impairment |
| TNFSF11, AR. + severe growth retardation |
| Hydadenitis suppurativa. PSENEN, AD. |
| Acute liver failure due to NBAS def. NBAS, AR. |
| Fever induces liver failure |
| Acute necrotizing encephalopathy. RANBP2, AD. |
| Fever induces acute encephalopathy |

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-Guerin; CD: cluster of differentiation; CMC: chronic mucocutaneous candidiasis; GOF: gain-of-function; IFNg: interferon-gamma; HHV6: human herpes virus type 6; HPV: human papilloma virus; 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.
VI. Defects in Intrinsic and Innate immunity.  b : MSMD and Viral infection

| Mendelian Susceptibility to mycobacterial disease (MSMD) | Predominant susceptibility to viral infection |
|--------------------------------------------------------|--------------------------------------------|
| **Severe phenotypes.** | **Predisposition to Severe Viral Infection** |
| Complete IFNGR1 Def and IFNGR2 Def. IFNGR1, IFNGR2. AR. | | STAT1 Def (AR LOF). STAT1. (+ Mycobacteria) |
| Serious disseminated BCG and environmental mycobacterial infections (soft tissue, bone marrow, lungs, skin, bones and lymph nodes), Salmonella spp., Listeria monocytogenes and viruses | | STAT2 deficiency. STAT2. AR. Disseminated vaccine-strain measles |
| With Susceptibility to Salmonella IL-12 and IL-23 receptor b1 chain deficiency. IL12RB1 .AR. IL-12p40 (IL-12 and IL-23) def. IL12B .AR. | | IRF7 deficiency. IRF7. AR. Severe influenza disease. Defect of IFN-α,β and γ production and IFN-λ production |
| STAT1 LOF. STAT1(AD) | | IFNAR2 deficiency. IFNAR2 AR. Disseminated vaccine-strain measles, HHV6. No response to IFN-α. |
| Partial IFNγR1. IFNγR1. AR. Partial IFNγR2. IFNγR2 AR. | | CD16 deficiency. FCGR3A. AR. Severe herpes viral infections, particularly VZV, Epstein Barr virus (EBV), and HPV. |
| AD IFNγR1. IFNγR1. AD. Mycobacterial osteomyelitis Tyk2 deficiency. TYK2. AR. Susceptibility to viruses, γ/γ-elevated IgE. Multiple cytokine signaling defect. | | MDA5 deficiency (LOF). IRF7. AR. Rhinovirus and other RNA viruses |
| ISG15 Def. ISG15. AR. Brain calcification. IFNg production defect. Macrophase gp91 phox deficiency. CYBB, XL IRF8 deficiency. IRF8 AD | | | |
| IRF8 deficiency. IRF8 AR Multiple other infectious agents. Myeloproliferation RORc deficiency. RORc AR. Susceptibility to Candida. IFNg production defect, complete absence of IL-17A/F-producing Tc | | | |
| JAK1 (LOF). JAK1. AR. Susceptibility to viruses, urothelial carcinoma. IFNg production. | | | |
| | | | |

**Fig. 6 (continued)**

Dominant clinical phenotype is Herpes simplex encephalitis (HSE) during primary infection with herpes simplex virus type 1 (HSV1), usually between 3 months and 6 years of age. Incomplete clinical penetrance for all etiologies listed here.

Routine screening tests are normal.

Specific tests examining the TLR3 pathway: marked decrease in the ability of patient’s fibroblasts to produce IFN-α and β in response to HSV1 infection.

TLR3 (AD,AR), UNC93B1 (AR), TRAF3 (AD), TICAM1 (TRIF) (AR,AD), TBK1 (AD), IRF3 (AD).
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 | *NLRP3, NLRP12*. AD GOF DA: 24-48H | *PSMB8*. AR and AD. (Variants in PSMB4, PSMB9, PSMA3, and POMP) Contractures, panniculitis, ICC, fevers. |
| DA: 1–4 days FA: Variable | Non-pruritic urticaria, arthritis, chills, fever and leukocytosis after cold exposure. | **COPA defect**. COPA. AD. Autimmune inflammatory arthritis and interstitial lung disease with Th17 dysregulation and autoantibody production. |
| Polyserositis, Abdominal pain, Arthritis, Amyloidosis. Erysipelas-like erythema. Predisoposes to vasculitis and inflammatory bowel disease | **Muckle Wells syndrome (CAPS)** *. NLRP3*. AD GOF. | **NLRC4-MAS** (macrophage activating syndrome)*. **NLRC4**. |
| Colchicine-responsive +++ | Ethnic group: North European | AD GOF. |
| Continuous fever. Often worse in the evenings. Deafness (SNHL), Conjunctivitis, Amyloidosis. | **Neonatal onset multisystem inflammatory disease (NOMID) or chronic infantile neurologic cutaneous and articular syndrome (CINCA)** *. NLRP3*. AD GOF. | Severe enterocolitis and macrophage activation syndrome (HLH). Triggered by cold exposure. |
| | Neonatal onset rash, with continuous fever and inflammation. Aseptic and chronic meningitis, Deforming arthropathy, Mental retardation. Sensorineural deafness. Visual loss. | **PLAID (PLCg2 associated antibody deficiency and immune dysregulation), or APLAID***. PLC2G*. AD GOF. |
| | | Cold Urticaria. Autoimmunity. Blistering skin lesion, pulmonary and bowel disease. Hypogammaglobulinemia, autoimmnflammatin. |
| **Mevalonate kinase def*** (Hyper IgD sd). **MVK**. AR | **NLRP1 deficiency***. **NLRP1**. AR. | **A20 haploinsufficiency**. **TNFAIP3**. AD LOF. Early onset systemic inflammation, Arthralgia/arthritis, oral/genital ulcers, ocular inflammation. |
| DA: 3–7 days FA: 1–2 monthly. Cervical adenopathy. Oral aphirosis. Diarrhea. Mevalonate aciduria during attacks. Leukocytosis with high IgD levels. | Dyskeratosis, autoimmunity and arthritis. | **HSM**: hepatosplenomegaly; ICC: intracranial calcifications; IL: interleukin; LOF: loss-of-function; sd: syndrome; SLE: systemic lupus erythematosus; SMS: Singleton-Merten syndrome; SNHL: sensorineural hearing loss; SP: spastic paraparesis; TORCH: toxoplasmosis, other, rubella, cytomegalovirus, and herpes infections. |

---

**Fig. 7 a, b** Autoinflammatory disorders. *Diseases affecting the inflammasome. AD: autosomal dominant transmission; AR: autosomal recessive transmission; BSN: bilateral striatal necrosis; CAPS: cryopyrin-associated periodic syndrome; DA: duration of inflammation episode; FA: frequency of inflammation episode; FCL: familial chilblain lupus; GOF: gain-of-function; HLH: hemophagocytic lymphohistiocytosis; HSM: hepatosplenomegaly; ICC: intracranial calcifications; IL: interleukin; LOF: loss-of-function; sd: syndrome; SLE: systemic lupus erythematosus; SMS: Singleton-Merten syndrome; SNHL: sensorineural hearing loss; SP: spastic paraparesis; TORCH: toxoplasmosis, other, rubella, cytomegalovirus, and herpes infections.**
VIIb. Auto-inflammatory disorders

### Sterile inflammation (skin/bone/joints)

| Predominant on the bone/joints | Predominant on the skin |
|---------------------------------|-------------------------|
| **Pyogenic sterile arthritis, pyoderma gangrenosum, acne (PAPA) syndrome, hyperzincemia and hypercalprotectinemia.** PSTPIP1 (C2BP1). AD |
| DA: 5 days FA: Fixed interval: 4-6 weeks |
| Sterile pyogenic arthritis, Pyoderma gangrenosum, inflammatory skin rash, Myositis. Acute-phase response during attacks |
| **Chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anemia (Majeed syndrome).** LPIN2. AR |
| DA: Few days FA: 1-3/month |
| Chronic recurrent multifocal osteomyelitis, severe pain, tender soft tissue swelling, Transfusion-dependent anemia, cutaneous inflammatory disorders |
| **DIAPA (Deficiency of the Interleukin 1 Receptor Antagonist).** IL1RN. AR |
| Continuous inflammation. Neonatal onset of sterile multifocal osteomyelitis, periostitis and pustulosis. |
| **Cherubism.** SH3BP2. AR. Bone degeneration in jaws |

| **Blau syndrome. NOD2 (CARD15). AD.** |
| Continuous inflammation. |
| Uveitis, Granulomatous synovitis, Camptodactyly, Rash, Cranial neuropathies, 30% develop Crohn colitis. Sustained modest acute-phase response. |
| **CAMPS. CARD14. AD. Psoriasis.** |
| **DITRA. (Deficiency of IL-36 receptor antagonist). IL-36RN. AR.** |
| Life-threatening, multisystemic inflammatory disease characterized by episodic widespread, pustular psoriasis, malaise, and leukocytosis. |
| **ADAM17 deficiency. ADAM17. AR.** |
| Early-onset pustular dermatitis, short and broken hair, paronychia, frequent cutaneous bacterial infections, and Early onset diarrhea, high IL-1 and IL-6 production. Lack of TNF-α was considered partly responsible for their increased susceptibility to infection and development of cardiomyopathy. |
| **SLC29A3 mutation. SLC29A3. AR.** |
| Hyperpigmentation hypertrichosis, Rosai-Dorfman like histiocytosis-lymphadenopathy plus H syndrome |
| **Otulipenia/ORAS. OTULIN. AR.** |
| Arthralgia, Fever, diarrhea, dermatitis. Lipodystrophy, myalgia, Neutrophilia |
| **AP1S3 deficiency. AP1S3. AR.** |
| Pustular psoriasis |

**Type 1 Interferonopathies**

| **Progressive encephalopathy, ICC, Cerebral atrophy, HSM, leukodystrophy, Thrombocytopenia, Elevated hepatic transaminases. Chronic cerebrospinal fluid (CSF) lymphocytosis.** |
| **Aicardi-Goutieres syndrome.** |
| **TREX1. AR-AD (+SLE, FCL), RNASEH2A, RNASEH2B (+SP), RNASEH2C, SAMHD1 (+ Skin vascularitis, mouth ulcers, arthropathy, FCL), ADAR1 (+BSN, SP), IFIH1 GOF AD (+SLE, SP, SMS).** |
| **Type 1 Interferonopathies.** |
| **Spondyloenchondro-dysplasia with immune dysregulation (SPEND). ACP5.** |
| Possibly recurrent bacterial and viral infections, SLE-like auto-immunity (Sjögren’s syndrome, hypothyroidism, inflammatory myositis, Raynaud’s disease and vitiligo), hemolytic anemia, thrombocytopenia, skeletal dysplasia, short stature, SP, ICC. |
| **STING-associated vasculopathy, infantile-onset. TMEM173.** Early-onset inflammatory disease, Skin vasculopathy, inflammatory lung disease, systemic autoinflammation and ICC, FCL. |
| **ADA2 deficiency.** CECR1. Polyarteritis nodosa, childhood-onset, early-onset recurrent ischemic stroke and fever, Livedo racemosa, low IgM, Hypogammagl, Lymphopenia |
| **XL reticulate pigmentary disorder. POLA1.** Hyper-pigmentation, reticulate pattern. Inflammatory lung and Gastroenteritis or colitis. Corneal scarring, characteristic facies |
| **USP18 def. USP18.** TORCH like syndrome. |
VIII. Complement deficiencies

| Susceptibility to infections | High | Low |
|------------------------------|------|-----|
| **Disseminated Neisserial infections** | **Recurrent pyogenic infections** | **SLE-like syndrome**. Infections with encapsulated organisms |
| Absent CH50 and AH50 hemolytic activity. Defective bactericidal activity. | C6 LOF. C7 AR. Absent CH50 and AH50 hemolytic activity, defective opsonization and humoral response | Absent CH50 hemolytic activity |
| C5 def. C5 | C3 LOF. C3 AR. | C1q def. C1QA, C1QB, C1QC. |
| Properdin def. PFC. XL | C1r def. C1R. Ehlers Danlos phenotype | Factor B GOF. CFB. AD. Increased spontaneous AH50 |
| C6 def. C6 | Factor D def. CFD. AR. | Factor H def. CFH. AR or AD. |
| C7 def. C7. > Vascularitis | MasP2 def. MasP2. AR. Inflammatory lung disease, autoimmune | Infections, disseminated neisserial infections, preeclampsia. Spontaneous activation of the alternative complement pathway with consumption of C3 |
| C8 def. C8A, C8B, C8G | Factor B. CFB LOF. AR. Infections with encapsulated organisms. Deficient activation of the alternative pathway | Factor H-related protein deficiencies. CFHR1-5. AR or AD. |
| C9 def. C9. Mild susceptibility. | Factor C. C2. | Factor I deficiency. AR, infections, disseminated neisserial infections, preeclampsia. Spontaneous activation of the alternative complement pathway with consumption of C3 |

C1 inhibitor. SERPING1. AD. Hereditary angioedema. |
| Membrane Attack Complex Inhibitor deficiency, CD59. Hemolytic anemia, Polynuropathy. |
| CDSS deficiency (CHAPLE disease). CD55. AR. Protein losing enteropathy, thrombosis. |

LOF: loss-of-function; sd: syndrome; SLE: systemic lupus erythematosus; XL: X-linked transmission

IX. Phenocopies of PID

**Associated with Somatic Mutations**

- Spinalomegalgy, lymphadenopathy, autoimmune cytopenias. Defective lymphocyte apoptosis.
- ALPS-SFAS.
- (Somatic mutations in TNFRSF6J) ALPS-FAS (ALPS type Im)
- RALD. TAS-associated autoimmune leukoproliferative disease. (ALPS Like). N-RAS GOF, K-RAS GOF
- Sporadic; granulocytosis, monosomy/ALPS-like
- Cryopyrinopathy, (Muckle-Wells/CINCA/NOMID-like syndrome). NLRP3
- Urticaria-like rash, arthropathy, neurological symptoms
- Hypersesinophilic syndrome due to somatic mutations in STAT5b. STAT5b. GOF.
- Atopic dermatitis, urticarial rash, diarrhea. Eosinophilia.

**Associated with Auto-Antibodies**

- Chronic mucocutaneous candidiasis (isolated or with APECED syndrome). AutoAb to IL-17 and/or IL-22.
- Endocrinopathy, chronic mucocutaneous candidiasis /CMC. Germline mutation in AIRE
- Adult-onset immunodeficiency with susceptibility to mycobacteria. Auto-Ab to IFNg.
- Mycobacterial, fungal, salmonella, VZV infections / MSMD or CID.

- Recurrent skin infection. AutoAb to IL-6.
- Staphylococcal infections / STAT3 deficiency

- Pulmonary alveolar proteinosis. AutoAb to GM-CSF.
- Pulmonary alveolar proteinosis, cryptozcal meningitis, disseminated nocardiosis/CSF2RA deficiency

- Acquired angioedema. AutoAb to C1 inhibitor.
- Angioedema /C1 inhibitor deficiency

- Atypical Hemolytic Uremic Syndrome. AutoAb to Factor H.
- Spontaneous activation of the alternative complement pathway

- Thrombosis with hypogammaglobulinemia (Good syndrome).
- AutoAb to various cytokines. Invasive bacterial, viral or opportunistic infections, autoimmunity, PRCA, lichen planus, cytopenia, colitis, chronic diarrhea. No B cells.

Fig. 8 Complement deficiencies. AD: autosomal dominant transmission; AH50: alternate pathway hemolytic activity; AR: autosomal recessive transmission; CH50: complement hemolytic activity; def: deficiency; LOF: loss-of-function; sd: syndrome; SLE: systemic lupus erythematosus; XL: X-linked transmission

Fig. 9 Phenocopies of PID.
- ALPS: autoimmune lymphoproliferative syndrome; AutoAb: auto-antibodies; CID: combined immunodeficiency; CMC: chronic mucocutaneous candidiasis; GOF: gain-of-function; MSMD: Mendelian susceptibility to mycobacterial disease; PRCA: pure red cell aplasia
The authors declare that they have no conflict of interest.

This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

References

1. Picard C, Gaspar HB, Al-Herz W, Bousfiha A, Chatila T, Crow YJ, et al. International Union of Immunological Societies: 2017 Primary Immunodeficiency Diseases Committee report on inborn errors of immunity. J Clin Immunol 2017(in Press).

2. Bousfiha AA, Jeddane L, Ailal F, Benhsaïen I, Mahlaoui N, Casanova JL, et al. Primary immunodeficiency diseases worldwide: more common than generally thought. J Clin Immunol. 2013;33(1):1–7.

3. Kobrynski L, Powell RW, Bowen S. Prevalence and morbidity of primary immunodeficiency diseases, United States 2001-2007. J Clin Immunol. 2014;34(8):954–61.

4. Bousfiha AA, Jeddane L, Ailal F, Al Herz W, Conley ME, Cunningham-Rundles C, et al. A phenotypic approach for IUIS PID classification and diagnosis: guidelines for clinicians at the bedside. J Clin Immunol. 2013;33(6):1078–87.

5. Jeddane L, Ouair H, Benhsaïen I, El Bakkouri J, Bousfiha AA. Primary immunodeficiency classification on smartphone. J Clin Immunol. 2017;37(1):1–2.