The 2022 update of IUIS Phenotypical Classification for Human Inborn Errors of Immunity

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Abstract

The International Union of Immunological Societies (IUIS) expert committee (EC) on Inborn Errors of Immunity (IEI) report here the 2022 updated phenotypic classification, which accompanies and complements their genotypic classification.

This phenotypic classification is aimed for clinicians at the bedside and focuses on clinical features and laboratory phenotypes. In this classification,485 IEI underlying phenotypes as diverse as infection, malignancy, allergy, auto-immunity, and auto-inflammation, are described, including 55 novel monogenic defects and 1 phenocopy due to autoantibodies. Therefore, all 485 diseases of the genetic classification are presented in this paper in the form of colored tables with essentially clinical or immunological phenotype entries.

Introduction

Human Inborn Errors of Immunity (IEI) comprise a large group of disorders presenting damaging germline variants in the immune pathway. They can be dominant or recessive, autosomal or X-linked, and with complete or incomplete penetrance. Clinical features are dominated by 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. Based on stringent criteria applied by the International Union of Immunological Societies (IUIS) expert committee, 55 novel monogenic defects and 1 phenocopy have been added in the classification, bringing out the total number of genetic defects to 485[1]. If most IEI are individually rare, they are collectively more common than generally thought [2].

Since 2013, the (IUIS) expert committee on Primary Immunodeficiencies PID (IEI) proposes every other year a phenotypic classification of all these disorders, in parallel with a genotypic catalog which facilitates both research on, and diagnosis of, these conditions worldwide [1]. The phenotypic classification is organized in diagnosis algorithms, based on the clinical and laboratory features observed in these patients. This phenotypic classification is also adapted for smartphone applications [3].

Here, we report an update of the phenotypic classification of IEI, based on the 2022 IEI classical classification [1]. This tree-based decision-making process is aimed to physicians, regardless of their familiarity with IEI. Its purpose is to guide the physician towards the most probable diagnosis based on the clinical and laboratory features of their patient.

Methodology

All disorders indexed in the 2022 update of the IUIS IEI classification [1] are included in phenotypic algorithms 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 exponential number of diseases, several categories have been splitin two or three sub-figures to be more informative.

Disease names are presented in red and genes in bolditalic. 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 atypical presentation.

Results

Algorithms for the 2022 update of IUIS phenotypical classification are presented in 22 figures (Figs 1a-10).

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, as more and more reports show a spectrum of atypical presentations related to hypomorphic mutations of those genes or incomplete penetrance.

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.

Conclusion

This phenotypic classification of IEI forms a diagnostic resource, aimed to complement the 2022 IUIS genotypic classification. These figures were designed as user-friendly diagnosis orientation tools for physicians and biologists who are not experts in the field of IEI. Our aim is to help them to reach a probable diagnosis for patients with clinical or biological features evocative of IEI and guide them in exploration of such patients.

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

References

1. IUIS classification 2022 (to be precised)
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Figure legends

Fig. 1Immunodeficiencies affecting cellular and humoral immunity. (a) Severe combined immunodeficiencies defined by T cell lymphopenia. (b) Combined immunodeficiencies. * T cell lymphopenia in SCID is definedby CD3+ Tcells < 300/µL.Ab: antibody;AD: autosomal dominant transmission; ADA:adenosine deaminase; Adp: Adenopathies; Ag: antigen; AR: autosomal recessivetransmission; β2m: bêta-2 microglobulin; Bc: B cells; CBC: completeblood count; CD: cluster of differentiation; CMV: cytomegalovirus; CVID: common variableimmunodeficiency; def: deficiency; EBV: Epstein Barr virus;Eo: Eosinophilia;GOF: gain-of-function mutation; HHV8:human herpes virus 8; HIGM: hyper IgM syndrome;HLH: hemophagocyticlymphohistiocytosis; HPV: humanpapillomavirus;HSCT: haematopoietic stem cell transplantation; HSM: Hepatosplenomegaly;Ig: immunoglobulins; MHC: major histocompatibilitycomplex; Nl: normal; NK: natural killer;PHA phytohemagglutinin;PJP: Pneumocystis jiroveci pneumonia;SCID: severe combinedimmunodeficiency; SLE: systemic lupus erythematosus;Tc: T cells; TCR: T cell receptor; T_{EMRA}: effector memory T cells expressing CD45RA; Treg: regulatory Tcells; XL: X-linked transmission

Fig. 2 CID with associated or syndromic features. Ab: antibody;AD: autosomal dominant transmission; AD DN: Autosomal dominant transmission with dominant negative effect; ANA: anti-nuclear antibodies;ANCA: anti-neutrophil cytoplasm antibodies; AR: autosomal recessivetransmission; Bc: B cells; BCG: Bacillus Calmette-Guerin; BCR: B cellreceptor; CD: cluster of differentiation;CID: combined immunodeficiency of T and B cells; CMV: cytomegalovirus; CNS:central nervous system; def: deficiency; DNA: desoxyribonucleic acid;EBV: Epstein Barr virus; EDA: anhidrotic ectodermal dysplasia;GOF: gain-of-function; HIES: hyper IgE syndrome; FILS: facialdysmorphism, immunodeficiency, livedo and short stature; ID:immunodeficiency; Ig: immunoglobulins; IL-6: Interleukin-6; IUGR: intrauterine growthretardation; LOF: loss-of-function;MCC: mucocutaneous candidiasis; Nl: normal;NK: natural killer; PHA: phytohemagglutinin; PPS: polysaccharides;RTE : recent thymic emigrantT-cell; SCBMS : seizures, cortical blindness, and microcephaly syndrome;SCID: severe combined immunodeficiency; sd: syndrome; Tc: T cells;TCR: Tcell receptor; TREC: Tcell receptor excision circle; XL: X-linkedtransmission

Fig. 3 Predominantly antibody deficiencies. (a)Hypogammaglobulinemias.(b) Other antibody deficiencies.AD: autosomal dominant transmission; AR:autosomal recessive transmission;Bc:Bcells; BENTA:Bcell expansion withNF-κB and T cell anergy; CD: cluster of differentiation; CMF: flow cytometry;COPD: chronic obstructive pulmonary disease; DC: dendritic cell;def: deficiency; EBV:Epstein Barr virus; GC: germinal centers;GOF: gain-of-function; Hx: patient history; Ig: immunoglobulins;Nl: normal;PJP: Pneumocystis jiroveci pneumonia;SLE: systemic lupus erythematosus;Treg: regulatory T cells; XL: X-linked transmission

Fig. 4 Diseases of immune dysregulation. (a)Hemophagocyticlymphohistiocytosis and EBV susceptibility.(b)Syndromes withautoimmunity and others. Ab:antibody; AD: autosomal dominant transmission; Ag: antigen; AIHA: Autoimmune hemolytic anemia; ALPS:autoimmune lymphoproliferative syndrome; APS: autoimmunepolyendocrinopathy syndrome; AR: autosomal recessive transmission; Bc:B cells; CD: cluster of differentiation; CMF: flow cytometry; CTL: cytotoxicT lymphocytes; def: deficiency; DNT: double negative Tcells; EBV: EpsteinBarr virus; FHL: familial hemophagocyticlymphohistiocytosis; GOF: gain-of-function; GN: glomerulonephritis; HLH: hemophagocyticlymphohistiocytosis; (H)SM:(hepato)splenomegalia; IBD: inflammatory bowel disease; Ig: immunoglobulin;IL-10: interleukin-10; ITP: immune thrombocytopenic purpura;JIA: Juvenile idiopathic arthritis; LOF: loss-of-function; MIS-C: Multisystem inflammatory syndrome; iNKT: invariant NKTcells; NK: natural killer cells; Nl: normal; sd: syndrome; SLE: systemic lupuserythematous disease;T1D: Type 1 diabetes;Tc: T cells; TCR: T cell receptor; XL: X-linkedtransmission

Fig. 5 Congenital defects of phagocyte number, function, or both. (a) Neutropenia. (b) Functional defects of phagocytes. AD: autosomaldominant transmission; AML: acute myeloid leukemia; AR: autosomalrecessive transmission; BCG: Bacillus Calmette-Guerin;BM : bone marrow; CD: cluster ofdifferentiation; CGD: chronic granulomatous disease; CMF: flow cytometry;CMML: chronic myelomonocytic leukemia; def: deficiency; DHR:dihydrorhodamine-1,2,3; GM-CSF: Granuocytes/Monocytes colony stimulation factor; GOF: gain-of-function; IBD: Inflammatory bowel disease; IUGR: intrauterinegrowth retardation; LAD: Leukocyte adhesion deficiency; MDS: myelodysplasia; NBT: nitroblue of tetrazolium;NK: natural killer cells; WBC: white blood cells; XL: X-linkedtransmission

Fig. 6 Defects in intrinsic and innate immunity. (a)Viralinfections. (b)Bacterial and parasitic infections and otherdefects AD: autosomal dominanttransmission; AR: autosomal recessive transmission; BCG: BacillusCalmette-Guerin; CD: cluster of differentiation; CMC: chronicmucocutaneous candidiasis; CMV: cytomegalovirus; EBV: EpsteinBarr virus; GOF: gain-of-function; IFNg: interferongamma;HHV6: human herpes virus type 6; HLH: hemophagocyticlymphohistiocytosis;HPV: human papillomavirus; HSV: herpes simplex virus; LOF: loss-of-function; MSMD:Mendelian susceptibility to mycobacterial disease; NK: natural killercells; RNA: ribonucleic acid; sd: syndrome; Tc: T cells; TLR3: Toll-likereceptor type 3; VZV: varicella zoster virus; XL: X-linked transmission.

Fig. 7Autoinflammatory disorders. Ab: antibody;AD: autosomal dominant transmission; ANCA: Anti-neutrophilic cytoplasmic autoantibody; AR: autosomalrecessive transmission;Bc: B cells; BSN: bilateral striatal necrosis; CAPS: cryopirinassociatedperiodic syndrome;CNS: central nervous system; DA: duration of acute inflammation episode;dsDNA: double-stranded Desoxyribonucleixacid; FA:

frequency of acute inflammation episode; FCL: familial chilblain lupus;GOF: gain-of-function; HLH: hemophagocyticlymphohistiocytosis;HSM: hepatosplenomegalia; ICC: intracranial calcifications;IFN: interferon;IL:interleukin; ISG: immune serum globulin; KREC: kappa-deleting element recombination circle;LOF: loss-of-function; sd: syndrome; Nl: normal;NK: natural killer;SLE: systemic lupuserythematosus; SMS: Singleton-Merten syndrome; SNHL: sensorineuralhearing loss; SP: spastic paraparesis; TB: tuberculosis; Tc: T cells;TORCH: toxoplasmosis, other,rubella, cytomegalovirus, and herpes infection; TREC: T-cell recombination excision circles.

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

Fig. 9Bone marrow failure disorders. AD: autosomal dominant transmission;AR: autosomal recessivetransmission; Bc: B cells; BMFS: Bone marrow failure syndrome; CNS:central nervous system; DKC: Dyskeratosiscongenita; GI: Gastrointestinal; GOF: gain-of-function;IUGR: intrauterine growthretardation; MDS: myelodysplasia; sd: syndrome; Tc: T cells; XL: X-linked transmission

Fig. 10Phenocopies of PID.ALPS: autoimmunelymphoproliferative syndrome;AutoAb: auto-antibodies; BM :bone marrow;CID:combined immunodeficiency;CMC: chronic mucocutaneouscandidiasis; GOF: gain-of-function;IFN: interferon;LOF: loss-of-function;MSMD:Mendeliansusceptibility to mycobacterialdisease; PRCA: pure red cellaplasia

I. Immunodeficiencies affecting cellular and humoral immunity.
(a) Severe Combined Immunodeficiencies SCID, defined by CD3 T cell lymphopenia. Low TRECS

CD19 NL : SCID T- B+

SCID T-B+NK+

IL7Rα . *IL7R* AR.

No γ/δ T cells:
CD3δ*. *CD3D* AR
CD3ε*. *CD3E* AR
CD3ζ . *CD3Z*** AR

Nl γ/δ T cells :
CD45*
PTPRC AR

LAT def* . *LAT* AR.
Typical SCID or CID with adenopathy, splenomegaly, autoimmunity. High Ig.

Winged helix def*.
***FOXN1*.** AR
Severe infections, abnormal thymic epithelium, congenital alopecia, nail dystrophy, neural tube defect. Ig: decreased. Tc: Very low.

Coronin-1A def*. *CORO1A* AR.
Detectable thymus

PAX1 def*. *PAX1* AR (LOF)
Omenn's-like syndrome (erythroderma, lymphocytosis, eosinophilia, ↓ proliferation to PHA, severe/recurrent infections). No thymus, Tc deficiency not corrected by HSCT despite donor chimerism. Otofaciocervical syndrome type 2. Nl IgM, ↓ IgA, Nl to ↑ IgE.

LCP2/SLP76 def. *SLP76*** AR (LOF)
Early-onset skin abscesses, rash recurrent infections, autoimmunity, neutrophil dysfunction, platelets dysfunction, ↓Tc proliferation to PHA, anti-CD3/CD28 stimulation, ↓ NK cell degranulation, ↓Actin polymerization. ↑ IgM, ↓ IgA. ↓ ↓ CD4+, ↑CD8+ Tc. Nl but ↓ class-switched memory and transitional Bc, ↑ naïve and immature Bc.

ITPKB def. *ITPKB*** AR
Failure to thrive. Recurrent bacterial/fungal infections.
Leuko/lymphopenia/neutropenia/anemia/ thrombocytopenia. Nl IgM, A; ↓ IgG.

SCID T-B+NK-

γc def. *IL2RG*
XL,
CD 132 def

JAK-3 def . *JAK3*
AR,
CD 132+

CD19 ↓ : SCID T-B-

SCID T-B-NK+

Microcephaly ?

Yes	No
Radiation sensitivity - *With facial dysmorphism:* **DNA ligase IV def . *LIG4*** AR **CERNUNNOS /XLF def*.** ***NHEJ1*** AR. - *Without facial dysmorphism:* **DNA PKcs def*. *PRKDC*** AR Variable Ig levels	Increased risk of graft rejection, possibly due to activated NK cells **RAG 1/2 def** **(*RAG1/ RAG2*)** AR **DCLRE1C def** ***DCLRE1C*** AR **(*ARTEMIS*).** + Radiation sensitivity **Omenn sd (hypomorphic mutations).** Erythroderma, Alopecia, Adp, HSM, Eo ↑, IgE↑

SCID T-B-NK-

ADA def . *ADA* AR
Chondrosternal dysplasia, deafness, may have pulmonary alveolar proteinosis, cognitive defects

Reticular dysgenesis. *AK2* AR
Neutropenia, deafness. Some have anemia and thrombocytopenia.

Activated Rac2 defect*. *RAC2,*
AD GOF
Recurrent bacterial and viral infections, lymphoproliferation; neutropenia

I. Immunodeficiencies affecting cellular and humoral immunity

(b) Combined Immunodeficiencies: generally less profound than SCID

Low CD4: MHC-II Expression ?

Absent

MHC-II def. ***RFXANK, CIITA, RFX5, RFXAP.*** AR Failure to thrive, respiratory and gastrointestinal infections, liver/biliary tract disease

Present

LCK def. ***LCK.*** *AR* Immune dysregulation, auto-immunity. Low Treg, restricted T cell repertoire, poor TCR signaling.↑IgM.

UNC119 def. ***UNC119.*** *AD*

Polymerase δ def*. AR. **POLD1** or **POLD2**. Recurrent respiratory tract infections, skin infections, warts and molluscum, short stature, intellectual disability. Low Bc, Low Ig.

COPG1 def*. ***COPG1*** AR. Recurrent pneumonia, viral respiratory infections, bronchiectasis, chronic EBV, CMV viremia, failure to thrive. Nl IgM, G, A. Poor/absent Ig responses to vaccines . Impaired Tc and Bc proliferation

SASH3 def*. ***SASH3*** XL. Immune dysregulation, recurrent sinopulmonary, cutaneous and mucosal infections, refractory autoimmune cytopenias, eczema, autoimmunity,, ↓proliferation/cell cycle progression, ↑ apoptosis. ↓ Bc, ↓ NK. ↓ IgG and IgA. ↓specific Ab responses.

Low CD8

CD8 def *. ***CD8A*** AR. Recurrent infections .Maybe asymptomatic.CD8 Absent.

Nl MHC -I on lymphocytes.

ZAP-70 def. ***ZAP70*** AR (LOF/GOF). May have immune dysregulation, autoimmunity. Nl Ig. CD4: Low fonction ***Combined hypomorphic and activating mutations:*** Severe autoimmunity . Nl or decreased CD4 and Bc. Nl IgA, low IgM, IgG Nl or low.

Absent MHC -I on lymphocytes.

MHC-I def . ***TAP2, TAP1*** **or** ***TAPBP*** AR. Vasculitis, pyoderma gangrenosum. Nl Ig.

B2M* AR. Sinopulmonary infections, cutaneous granulomas. Nl Ig. Hypoprotidemia. Absent β2m associated proteins MHC-I, CD1a, CD1b, CD1c.

Low Bc

DOCK8 def. ***DOCK8*** AR. Severe Eczema. Cutaneous viral and staphylococcal infections; severe atopy; cancer ,diathesis. High IgE, Low IgM, eosinophilia.↓NK with poor function.↑Bc, ↓memory Bc Poor peripheral Bc tolerance. ↑ exhausted CD8+ TEM cells

IKAROS def.* (CD154). ***IKZF1***. AD. 0pportunistic infections, including P.jirovecii, bacterial, viral and other fungal infections. Increased risk fo T-ALL. Agammaglobulinemia, high recent thymic emigrant/naive/Th0 cells; low-absent memory T cells

IL21 def.** ***IL21*** AR. Severe early onset colitis. Tc : NL / low function. Hypogamma-globulinemia, poor specific antibody responses;↑ IgE

NIK def.** ***MAP3K14*** AR. Bacterial, viral and Cryptosporidium infections.↓: NK, Ig levels & switched memory Bc. **Tc** :Ag poor proliferation

STK4 def . ***STK4*** AR. Intermittent neutropenia, bacterial, viral (HPV, EBV, molluscum), candidal infections, lymphoproliferation, autoimmune cytopenias, lymphoma, congenital heart disease. ↓ : CD4 Tc, naïve Tc, ↑ TEM and TEMRA cells, poor proliferation. ↓: memory Bc, IgM & Ab responses. ↑IgG, IgA, IgE.

Moesin def.* ***MSN.*** XL. Recurrent infections with bacteria, varicella; neutropenia. ↓ Ig over time. Tc: defective migration, proliferation.

MAN2B2 def.** ***MAN2B2*** AR. Recurrent infections, vasculitis, arthritis, failure to thrive, neurodevelopmental delay; congenital disorder of glycosylation. Nl IgM, ↓ IgA, ↑ IgE. ↓Tc (↓ naïve, ↑ T_{EMRA}), ↓TCR proliferation.

Ig : often NL

ITK deficiency. ***ITK*** AR. EBV associated Bc lympho-proliferation, lymphoma, immune dysregulation. Nl or low IgG. Progressive CD4 T cell lymphopenia; reduced T cell activation

RelA haploinsufficiency*. ***RELA,*** AD. Chronic mucocutaneous ulceration. Impaired NFkB activation; reduced production of inflammatory cytokines

CD3γ def*. ***CD3G*** AR. TCR low. Autoimmunity

TCRα def* .*TRAC* AR. Recurrent viral, bacterial, fungal infections; diarrhea; immune dysregulation and autoimmunity. Absent TCRαβ except for a minor CD3-dim TCRαβ population; poor proliferation.

OX40 def.** ***TNFRSF4*** AR. Kaposi's sarcoma, impaired immunity to HHV8. Low memory Bc. Tc : low Ag specific memory CD4+.

FCHO1 def*. ***FCHO1*** AR. failure to thrive. Lymphoproliferation. Tc: Low. Bc & Ig : Nl Increased activation-induced T-cell death, defective clathrin-mediated endocytosis

RHOH def.** ***RHOH*** AR. HPV infection, lung granulomas, molluscum contagiosum, lymphoma. Low naïve T cells, restricted repertoire, poor proliferation to CD3.

I. Immunodeficiencies affecting cellular and humoral immunity

(b) Combined Immunodeficiencies: generally less profound than SCID (continued)

Low Immunogmobulins

CD40 ligand def. (CD154). XL, ***CD40LG***. or **CD40 def.** AR, ***CD40.***
Opportunistic infections, biliary tract and liver disease, *Cryptosporidium*.. Neutropenia, HIGM: IgM normal or high, other Ig isotypes low**.** Bc: sIgM$^+$, IgD$^+$ cells present, absent sIgG$^+$, IgA$^+$ and IgE$^+$ cells. Tc: NL to low.

DOCK2 def. *DOCK2.* Early invasive herpes viral, bacterial infections, Nl NK number, but defective function. Poor interferon responses. IgG NL or low; poor antibody responses.

IKBKB def. *IKBKB* AR**.** Recurrent bacterial, viral and fungal infections. Opportunistic infections. Bc : poor fonctions. absent Treg and γδ T cells; impaired TCR activation.

CARD11 deficiency (LOF). *CARD11* AR LOF**.** *P neumocystis jirovecii* pneumonia, bacterial & viral infections . Ig:Absent/low.Tc:NL number, poor proliferation .

BCL10 def. *BCL10.* *R***ecurrent bacterial and viral infections, candidiasis, gastroenteritis. Tc: few memory T and Treg cells, poor Ag and anti-CD3 proliferation. Bc: Decreased memory and switched Bc

IKBKA def. *IKKα*** AD/AR (also known as *IKK1* or *CHUK*)
Recurrent infections (Staphylococcus aureus, mucocutaneous candidiasis, epidermodysplasia verruciformis due to HPV), absent secondary lymphoid tissues, lymphocytic infiltration of intestine and liver, skeletal abnormalities, failure to thrive, ↓ NK function. Nl Tc, Nl NK panhypogammaglobulinemia.

C-REL def. *REL.*** Recurrent infections with bacteria, mycobacteria, salmonella and opportunistic organisms. Defective innate immunity. Low Ig. Tc: decreased memory CD4, poor proliferation.

ICOS def. *ICOS* AR. Recurrent infections, autoimmunity, gastroenteritis, granulomas.

IKAROS def*. (CD154). *IKZF1*. AD DN,
0pportunistic infections, including *P.jirovecii*, bacterial, viral and other fungal infections. Increased risk fo T-ALL.
Agammaglobulinemia, high recent thymic emigrant/naive/Th0 cells; low-absent memory T cells

IKZF2 def. (HELIOS)*. *IKZF2* AD/AR
Recurrent upper respiratory infections pneumonia, thrush, mucosal ulcers, chronic lymphadenopathy, SLE, Evan's syndrome, EBV-associated HLH, lymphoma. ↑activated/exhausted T cells, ↓ Tfh cells, ↓ NKc, Nl Tregs. Nl Bc, but low switched memory.

IKZF3 def*. *IKZF3* AD. EBV susceptibility, recurrent sinopulm/resp infections, PJP, warts, B cell lymphoma. Nl Tc and NKc, abnormal Bc development, severe hypogammaglobulinemia.

TFRC deficiency* *TFRC* AR**.** Recurrent infections. Neutropenia, thrombocytopenia. Bc:Nl number, low memory Bc. Tc: Nl number, poor proliferation

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

ICOSL def. *ICOSL*** AR. Recurrent respiratory tract viral infections. hypogammaglobulinemia, and Low Tc, slowly progressive neutropenia

Normal Ig but Poor Specific Antibody response

MALT1 def. *MALT1* AR.
Bacterial, fungal and viral infections.

Impaired Tc proliferation.

RelB def. *RELB*** AR.

Recurrent infections

Tc: poor diversity, ↓ proliferation to mitogens; no response to Ag;

Bc: marked increase

II. CID with Associated or Syndromic features

Congenital thrombocytopenia

XL: **Wiskott Aldrich Sd or XL thrombocytopenia *WAS (LOF)***.

Recurrent bacterial and viral infections; bloody diarrhea; eczema; lymphoma; autoimmune disease; IgA nephropathy; vasculitis. Small platelets; Decreased IgM. Low antibody to polysaccharides; often increased IgA and IgE. Nl Bc. Tc: Progressive decrease in numbers; Low Tc responses to anti-CD3.

Patients with XL-thrombocytopenia have later onset of complications and more favourable life expectancy but eventually develop similar complications as observed in WAS

AR: **WIP deficiency*. *WIPF1,*** WAS protein absent. +/- small platelets; increased IgE. Bc : Nl to low. Tc: Reduced; defective lymphocyte responses to anti-CD3.

AR: **Defective Arp2/3-mediated filament branching. *ARPC1B.*** Recurrent invasive infections, colitis, vasculitis. Mild trombocytopenia, normal sized platelets; autoantibodies (ANA, ANCA); eosinophilia. High IgA and IgE.

DNA Repair Defects other than those listed in Table1: Karyotype

Ataxia telangiectasia. *ATM* AR. Ataxia; telangiectasia; pulmonary infections; lymphoreticular and other malignancies; increased α-fetoprotein; increased radiosensitivity, chromosomal instability and translocations. Often decreased IgA, IgE and IgG subclasses; increased IgM; antibodies variably decreased. Tc : Progressive decrease, abnormal prolif to Mitogens.

Nijmegen breakage Sd. *NBS1* AR. Microcephaly; bird-like face; lymphomas; solid tumors; increased radiosensitivity; chromosomal instability. Often decreased IgA, IgE and IgG subclasses;increased IgM; antibodies variably decreased. Bc: Variably reduced. Tc: progressive decrease.

Bloom sd. *BLM* AR. Short stature; bird like face; sun-sensitive erythema; marrow failure; leukemia; lymphoma; chromosomal instability. Low Ig.

AR : **Immunodeficiency with centromeric instabiltiy and facial anomalies: ICF1. *DNMT3B;* ICF2:*ZBTB24;* ICF3:*CDCA7;***
ICF4:*HELLS.* Facial dysmorphism; macroglossia; bacterial/opportunistic infections; malabsorption; malignancies. Cytopenias; multiradial configurations of chromosomes 1,9,16; no DNA breaks. Ig: Hypogammaglobulinemia; Tc and Bc: decreased or Nl.

MCM4 def. *MCM4* AR. Viral infections:EBV,HSV,VZV.short stature.Bc lymphoma; Adrenal failure; NKc low number and function.

PMS2 def. *PMS2* AR. Café-au-lait spots ; lymphoma, colorectal carcinoma, brain tumors. HIGM and abnormal antibody responses. Reduced Bc, switched and non-switched.

BMFS2 (Hebo def). *ERCC6L2* AR. Facial dysmorphism; microcephaly, learning difficulties. Bone marrow failure.

AR. Short stature; mild defect of motor control to ataxia; normal intelligence to learning difficulties; mild facial dysmorphism to microcephaly; ↑radiosensitivity. ↓ IgG or IgA.

NSMCE3 deficiency*. *NSMCE3* AR. Severe lung disease (possibly viral); thymic hypoplasia, Chromosomal breakage; radiation sensitivity. Ig: Decreased Ab responses to PPS, normal IgG, IgA, normal to elevated IgM. Tc : Low, poor responses to mitogens and antigens.

GINS1 def*. *GINS1* AR. IUGR. Neutropenia, NK cells very low. Tc and Bc: low or normal. High IgA, Low IgG and IgM.

POLE1 (Polymerase ε subunit 1) deficiency (FILS syndrome). ***POLE1*** AR. Recurrent respiratory infections; meningitis; facial dysmorphism, livido, short stature. Low IgM, lack of antibody to PPS. Low memory Bc. Decreased Tc proliferation.

Ligase I deficiency *. *LIGI* AR. Recurrent bacterial and viral infections; growth retardation; sun sensitivity; lymphoma; radiation sensitivity. Macrocytic red blood cells. Hypogammaglobulinemia. Reduced Ab response. Lymphopenia, increased γδTc, decreased mitogen response.

POLE2 (Polymerase ε subunit 2) deficiency. *POLE2* AR.** Recurrent infection, disseminated BCG infections, autoimmunity (type 1 diabetes, hypothyroidism), facial dysmorphism; Low Ig; Very low Bc. Lymphopenia, lack of TRECS, absent proliferation of antigens.

MCM10 def. *MCM10* AR (LOF).** Severe CMV infection, phenocopies *GINS1* and *MCM4* deficiencies. NKc low number and function. ↓ IgG, Nl IgM/A. Mild lymphopenia (↓ T memory cells), ↓Bc. HLH-like biomarkers.

Immuno-Osseous Dysplasias

Cartilage Hair Hypoplasia *RMRP* AR. Short-limbed dwarfism with metaphyseal dysostosis, sparse hair, bone marrow failure; autoimmunity; susceptibility to lymphoma and other cancers; impaired spermatogenesis; neuronal dysplasia of the intestine. Ig: Nl or ↓. Tc: Varies from ↓↓ (SCID) to Nl; impaired lymphocyte proliferation.

Schimke Sd *SMARCAL1* AR. Short stature, spondilo-epiphyseal dysplasia, IUGR; nephropathy; bacterial, viral, fungal infections; may present as SCID; bone marrow failure. Tc: ↓

MOPD1 Deficiency. *RNU4ATAC* AR. Recurrent bacterial infections, lymphadenopathy, Spondyloepiphyseal dysplasia, IUGR, retinal dystrophy, facial dysmorphism; +/- microcephaly. short stature. Ig: ↓ , specific antibodies variably decreased

Immunoskeletal dysplasia with neurodevelopmental abnormalities. *EXTL3* AR. Short stature; cervical spinal stenosis, neuro-developmental impairment. Eosinophilia; Ig: variably ↓ Tc: ↓

MYSM1 def* *MYSM1* AR. Short stature, congenital bone marrow failure, myelodysplasia. Skeletal anomalies; cataracts; developmental delay. Affects granulocytes. Bc: immature. Tc: lymphopenia, reduced naïve Tc. Hypogammaglobulinemia

II. CID with Associated or Syndromic features (continued)

Thymic Defects with Additional Congenital Anomalies

FOXN1 haploinsufficiency. *FOXN1* AD.
Recurrent, viral and bacterial respiratory tract infections; skin involvement (eczema, dermatitis), nail dystrophy. T cell lymphopenia may normalize by adulthood.

CHARGE Sd. *CHD7* AD/***SEMA3E*** AD.
Coloboma, heart anomaly, choanal atresia, intellectual disability, genital and ear anomalies; CNS malformation; some are SCID-like and have low TRECs. Ig: Normal or decreased. Tc: Decreased or normal; response to PHA may be decreased

Hypoparathyroidism, conotruncal cardiac malformation, velopalatal insufficiency, facial dysmorphism, intellectual disability . Ig : Normal or decreased. Tc: ↓or Nl May have low TRECs at NBS.
DiGeorge/velocardiofacial Sd. Chr22q11.2 deletion Sd. 22q11.2DS AD.
TBX1 deficiency . *TBX1* AD.

Jacobsen Sd. *11q23del* AD. Recurrent respiratory infections; multiple warts; facial dysmorphism, growth retardation. Lymphopenia, Low NK, Bc and switched memory Bc. Hypogammaglobulinemia.

Chromosome 10p13-p14 deletion Syndrome. *10p13-p14DS.* AD.
Hypoparathyroidism; renal disease; deafness; growth retardation; facial dysmorphism; cardiac defects may be present

Anhidrotic Ectodermodysplasia with ID

Anhidrotic ectodermal dysplasia,various infections (bacteria, mycobacteria, viruses and fungi), colitis, variable defects of skin, hair and teeth.

NEMO deficiency. *IKBKG (NEMO).* XL, monocyte dysfunction. Ig decreased, some with elevated IgA, IgM, poor specific antibody responses, absent antibody to polysaccharide antigens. Bc: Nl, Low memory and isotype switched Bc. Tc: Nl/decreased, TCR activation impaired.

EDA-ID due to IKBA GOF mutation. *NFKBIA (IKBA).* AD Tc and monocyte dysfunction Decreased IgG and IgA, elevated IgM, poor specific antibody responses, absent antibody to polysaccharide antigens. Normal Bc numbers, impaired BCR activation, low memory and isotype switched Bc. Normal total Tc, TCR activation impaired.

EDA-ID due to IKBK GOF mutation* *IKBB.* AD. Low Tc. Bc: Nl number, poor function. Low Ig.

Hyper-IgE Syndromes (HIES)

AD-HIES (Job sd). *STAT3.* AD LOF. Distinctive facial features (broad nasal bridge); bacterial infections (boils and pulmonary abscesses, pneumatoceles) due to *S. aureus*, *Aspergillus*, *Pneumocystis jirovecii*; eczema; mucocutaneous candidiasis; hyperextensible joints, osteoporosis and bone fractures, scoliosis, retention of primary teeth; aneurysm formation. IgE ↑↑; specific antibody production↓. Bc:Normal; reduced switched and non-switched memory Bc; BAFF expression ↑. Tc:Nl overall; Th-17 & T-follicular helper cells ↓

IL6R deficiency*. *IL6R* AR.
Recurrent pyogenic infections, cold, abscesses, high circulating IL-6 Levels.

IL6ST deficiency. *IL6ST*
AR (LOF, partial deficiency)* : Bacterial infections, boiles, eczema, pulmonary abscesses, pneumatoceles, bone fractures, scoliosis, retention of primary teeth, craniosynostosis. ↓B-cell memory.
AR (LOF, complete deficiency)* : Fatal Stuve-Weidemann-like syndrome; skeletal dysplasia, lung dysfunction, renal abnormalities, thrombocytopenia, dermatitis, eczema. Defective acute phase response. Complete unresponsiveness to IL-6 family cytokines. Death *in utero* or *in neonatal* period occurred for most affected individuals.
AD : HIES – STAT3-like; dermatitis/eczema, eosinophilia, recurrent skin infections, pneumonia, bronchiectasis, pneumatoceles with severe secondary pulmonary aspergillosis, connective tissue defects, phenocopies aspects of IL6R and IL11R deficiencies. Nl/low IgG and IgA, Nl IgM, hyper IgE. Nl Tc numbers, ↓ to Nl NKc, Nl Bc, ↓ memory Bc.

ZNF341 deficiency. *ZNF341.* AR. Phenocopy of AD-HIES: Mild facial dysmorphism, early onset eczema, MCC, bacterial skin infections, abscesses, recurrent bacterial respiratory infections (S. aureus), lung abscesses and pneumatoceles, hyperextensible joints,
bone fractures and retention of primary teeth

Comel Netherton Sd; *SPINK5* AR. Congenital ichthyosis, bamboo hair,atopic diathesis; ↑ bacterial infections, failure to thrive. ↑ IgE and IgA; Other Ig: variably decreased. Bc: Switched and non-switched Bc are↓.

ERBIN deficiency. *ERBB21P*** AD. Recurrent respiratory infections, susceptibility to S. aureus, eczema, hyperextensible joints, scoliosis, arterial dilatation in some. Moderately increased IgE; increased Treg.

PGM3 deficiency. *PGM3* AR. Severe atopy; autoimmunity; skeletal anomalies: short stature, brachydactyly, dysmorphic facial features. Recurrent pneumonia, recurrent skin abscesses,bacterial and viral infections; cognitive impairment; delayed CNS myelination in some. Ig:Nl or elevated. Elevated IgE; eosinophilia.
Reduced B and memory Bc. CD8 and CD4 Tc may be↓.

CID with early-onset asthma, eczema and food allergies, autoimmunity ID with atopic dermatitis (CADINS). *CARD11* AD LOF (dominant negative).
Variable atopy, cutaneous viral infections, recurrent respiratory infections, lymphoma.
Eosinophilia, ↓Tc proliferation. Nl to low Bc.

Loes-Dietz syndrome. *TGFBR1, TGFBR2* AD. Recurrent respiratory infectons, eczema, food allergies, hyperextensible joints, scoliosis, retention of primary teeths; aortic aneurisms.

II. CID with Associated or Syndromic Features (continued)

Defects of Vitamin B12 and Folate Metabolism

Megaloblastic anemia,

Ig: decreased.

Transcobalamin 2 deficiency. ***TCN2*** AR.

pancytopenia, if untreated for prolonged periods results in intellectual disability.

Deficiency causing hereditary folate malabsorbtion. ***SLC46A1*** AR. failure to thrive, if untreated for prolonged periods results in intellectual disability

Methylene-tetrahydrofolate dehydrogenase 1 deficiency ***MTHFD1*** AR.

Recurrent bacterial infection, *Pneumocystis jirovecii; failure to* thrive; neutropenia; seizures, intellectual disability; folate-responsive

↓ Bc, ↓ antibody responses to conjugated polysaccharide antigens.

Others

Purine nucleoside phosphorylase deficiency. ***PNP*** AR.
Autoimmune haemolytic anemia, neurological impairment. Hypouricemia. Ig : Nl/Low. Bc: Nl. Tc: Progressive decrease

Calcium Channel Defects, AR . Autoimmunity, EDA, non-progressive myopathy. Ig and Bc: Nl. Tc: Normal, defective TCR mediated activation.
ORAI-1 deficiency*. ***ORAI1*** . **STIM1 deficiency*.** ***STIM1.***
CRACR2A deficiency.** ***CRACR2A*.**
Later onset CID with chronic diarrhea, recurrent lower respiratory tract infections, including pneumonia. Panhypogamma.

ID with multiple intestinal atresias. ***TTC7A*** AR. Bacterial (sepsis), fungal, viral infections, multiple intestinal atresias, often with intrauterine polyhydramnios and early demise, some with SCID phenotype. Markedly decreased IgG, IgM, IgA. Bc:Nl/low.Tc: Variable/absent, low TRECs (may present with SCID at birth)

Hepatic veno-occlusive disease with immunodeficiency (VODI). ***SP110*** AR. Hepatic veno-occlusive disease, *Pneumocystis jirovecii* pneumonia, CMV, candida, thrombocytopenia, hepatosplenomegaly, cerebrospinal leukodystrophy. Decreased IgG, IgA, IgM, absent germinal centers and tissue plasma cells. Decreased memory Bc . Decreased memory Tc.

STAT5b deficiency. ***STAT5B.*** AR. Growth-hormone insensitive dwarfism, dysmorphic features, eczema, lymphocytic interstitial pneumonitis, autoimmunity. Hypergammaglobulinemia, High IgE.
AD DN: Growth failure and eczema only. High IgE.

Vici syndrome. ***EPG5*** AR. Agenesis of the corpus callosum, cataracts, cardiomyopathy, skin hypopigmentation, intellectual disability, microcephaly, CMC. Ig: Decreased IgG2. Bc: Defective. Profound depletion of CD4+ cells.

Wiedemann-Steiner Sd. ***KMT2A (MLL).*** AD. Respiratory infections; short stature; hypertelorism; hairy elbows; developmental delay, intellectual disability. Hypogammaglobulinemia, decreased memory Bc.

Kabuki Sd. ***KMT2D (MLL2).*** AD. ***KDM6A:*** XL.
Typical facial abnormalities, cleft or high arched palate, skeletal abnormalities, short stature, intellectual disability, congenital heart defects, recurrent infections (otitis media, pneumonia) in 50% of patients. Autoimmunity may be present.
Low IgA and occasionally low IgG.

Immunodeficiency, developmental delay and hypohomocysteinemia, IMDDHH*. Activating de-novo mutations in *NFE2L2.* AD. Recurrent respiratory and skin infections, growth retardation, developmental delay; white matter cerebral lesions, decreased level of homocysteine; increased expression of stress response genes. Hypogammaglobulinemia. Bc: Decreased switched-memory Bc.

BCL11B deficiency. ***BCL11B.*** AD. Congenital abnormalities: neonatal teeth, dysmorphic facies; absent corpus callosum; neurocognitive deficits. Tc : Low, poor proliferation.

Hennekam-lymphangiectasia-lymphedema syndrome*. ***CCBE1*** AR/ ***FAT4*** AR. Lymphangiectasia and lymphedema with facial abnormalities and other dysmorphic features. Ig: decreased. Bc and Tc: Variable.

Tricho-Hepato-Enteric syndrome. ***TTC37*** AR/***SKIV2L*** AR*.
Respiratory infections, IUGR, wooly hair, early onset intractable diarrhea, liver cirrhosis, platelet abnormalities. Impaired IFNγ production, Hypogammaglobulinemia, low antibody responses.
Bc: Variably low switched-memory Bc.

DIAPH1 def*. ***DIAPH1*** AR.
Seizures, cortical blindness, microcephaly syndrome (SCBMS), recurrent bacterial/viral/fungal infections, defective cytoskeletal organization/mitochondrial dysfunction in SCBMS pathogenesis, ↓ Tc activation/proliferation. ↓naive Tc, ↓RTE's, ↑naïve/trans Bc, ↓memory Bc, ↓IgM, Nl IgG, variable IgA.

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, gastro-intestinal or skin. → B Lymphocyte (CD19+) enumeration (CMF)

Bc absent

Severe bacterial infection. All Ig isotypes decreased.

X-Linked Agammaglobulinemia. *BTK*. Some patients have detectable Ig. ProBc: Nl

AR :

μ heavy chain Def. *IGHM*

Igα def*. *CD79A*, Igβ def*. *CD79B*

BLNK def*. *BLNK*, λ5 def. *IGLL1*,** ProBc: Nl

E47 transcription factor def*. *TCF3* Severe, failure to thrive.

p85 def. *PIK3R1*.** Cytopenia. ProBc:↓

p110δ def. *PIK3CD*.** Autoimmune complications.

ZIP7 def*. *SLC39A7*. Early onset infections, blistering dermatosis, thrombocytopenia

AD

E47 transcription factor def*. *TCF3*.

Hoffman syndrome*. *TOP2B*. Facial dysmorphism, limb anomalies

FNIP1 def*. *FNIP1* AR (LOF). Early onset recurrent sinopulmonary infections, bronchiectasis, congenital heart defects, severe or intermittent neutropenia, Crohn disease, developmental delay, increased AMPK activity. Mild Tc lymphocytosis.

PU.1 def*. *SPI1* AD. Sinopulmonary infections with encapsulated bacteria, viral infections in some patients .Nl Tc and NKc. ↓↓conventional DCs.

Bc >1 % : Commun Variable Immunodeficiency Phenotype

CVID with no gene defect specified.
Clinical phenotypes vary: most have recurrent infections, some have polyclonal lymphoproliferation, autoimmune cytopenias and/or granulomatous disease

PIK3CG deficiency*. *PIK3CG* AR LOF. cytopenia/lymphopenia, eosinophilia, lymphadenopathy, splenomegaly, recurrent infections, HLH-like; ↑ inflammatory markers. ↓Treg, ↓CD8. Nl Bc, ↓memory Bc.

Activated p110δ syndrome (APDS2). *PIK3R1*. AD GOF. Similar to APDS1 + Developmental delay.

Activated p110δ syndrome (APDS1). *PIK3CD* . AD GOF. AutoimmunitySevere bacterial infections. EBV± CMV viremia, Lymph-adenopathy, lympho-proliferation, lymphoma. ↓memory Bc and ↑ transitional Bc.

PTEN Deficiency (LOF). *PTEN*. *AD.* Lymphoproliferation, Autoimmunity. Developmental delay.

ATP6AP1 deficiency. *ATP6AP1*. XL. Hepatopathy, leukopenia, low copper. Variable Ig findings.

Mannosyl-oligosaccharide glucosidase deficiency (MOGS)*. *MOGS* *(GCS1)* AR. Low bacterial and viral infections in comparison to the level of hypogamma, severe neurologic disease, also known as congenital disorder of glycosylation type IIb (CDG-IIb).

IKAROS haploinsufficiency. *IKZF1* AD. Recurrent sinopulmonary infections; autoimmunity. Decreased pro-Bc.

IKZF2 def (HELIOS)*. *IKZF2* AD/AR. Recurrent upper respiratory infections pneumonia, thrush, mucosal ulcers, chronic lymphadenopathy, SLE, Evan's syndrome, EBV-associated HLH, lymphoma. ↑activated Tc↓ NKc. Nl Bc but low switched memory.

ARHGEF1 deficiency. *ARHGEF*** *AR.* Recurrent infections, bronchiectasis.

SH3KBP1 deficiency *SH3KBP1*** *(CIN85) XL.* Severe bacterial infections.

SEC61A1 deficiency.* *SEC61A1* *AD.* Severe recurrent respiratory tract infections

TRNT1 deficiency. *TRNT1* AR. Congenital sideroblastic anemia, deafness, developmental delay. B cell deficiency and Hypogamma.

IKZF3 def*. *IKZF3* AD. EBV susceptibility, recurrent sinopulm/resp infections, PJP, warts, B cell lymphoma. Abnormal Bc development, severe hypogamma.

CTNNBL1 def. *CTNNBL1*.** AR (LOF). Autoimmune cytopenias, recurrent infections, hyperplastic GC's. Progressive severe hypogamma, ↓Tc, reduced memory Bc.

TWEAK deficiency. *TWEAK*** *(TNFSF12)* AD. Pneumonia, bacterial infections, warts, thrombocytopenia. Neutropenia. Low IgM and A, lack of anti-pneumococcal antibody.

TNFSF13 def. *TNFSF13*** (APRIL) AR LOF. Chronic but mild infections., Alopecia areata. Nl T/NKc, Nl Bc counts, ↑IgM+/↓sw memory Bc, ↓blood plasmablasts.

CD19 deficiency*. *CD19* *AR.* Recurrent infections, may have glomerulonephritis.

CD20 deficiency. *CD20*** *AR.* Recurrent infections. Low IgG, Nl or elevated IgM and IgA

CD21 deficiency*. *CD21* *AR.* Recurrent infections. Low IgG, impaired anti-pneumococcal response.

CD81 deficiency*. *CD81* *AR.* Recurrent infections, may have glomerulonephritis. Phenocopy of CD19 deficiency.

RAC2 deficiency. *RAC2*** *AR.* Recurrent sinopulmonary infections, poststreptococcal glomerulonephritis; urticaria. Some have selective IgA def.

TACI deficiency. *TNFRSF13B* *(TACI)* AD or AR . Variable clinical expression and penetrance for monoallelic variants.

BAFF receptor deficiency*. *TNFRSF13C* *(BAFF-R)* AR. Variable clinical expression. Low IgG and IgM.

IRF2BP2 deficiency. *IRF2BP2*** AD. Recurrent infections, possible autoimmunity and inflammatory disease. Hypogammaglobulinemia, absent IgA.

NFKB1 deficiency. *NFKB1* AD. Recurrent sinopulmonary infections, COPD, EBV proliferation, autoimmune cytopenias, alopecia and autoimmune thyroiditis. Ig Nl or↓, Bc ↓ or Nl, ↓ memory Bc.

NFKB2 deficiency. *NFKB2* AD. Recurrent sinopulmonary infections, alopecia and endorinopathies (ie, central adrenal insufficiency). Low Bc.

POU2AF1 def . *POU2AF1*** AR. Recurrent respiratory infections, possible chronic viral infection Nl Tc. Nl Bc, ↓switched memory Bc, alter Bc phenotype.

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 : Hyper IgM Syndromes

AID deficiency.

AICDA. AR or AD.

Bacterial infections, enlarged lymph nodes and germinal centers. Nl memory Bc, but lacking somatic hypermutation in AR form.

UNG deficiency. ***UNG*** *AR.*

Enlarged lymph nodes and germinal centers.

INO80 def*. ***INO80*** *AR.*

Severe bacterial infections.

MSH6 def. ***MSH6*** *AR.*

Family or personal history of cancer. Variable IgG, defects, increased IgM in some, Nl Bc, low switched memory Bc.

Isotype, Light Chain, or Functional Deficiencies with Generally Normal Numbers of Bc

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.

Transient hypogammaglobuliemia of infancy. **Unknown.**
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. May be asymptomatic. 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: Nl.

Ig heavy chain mutations and deletions.
Mutation or chromosomal deletion at 14q32 AR.
May be asymptomatic. One or more IgG and/or IgA subclasses as well as IgE may be absent.

Selective IgM deficiency. ***Unknown*.** Pneumococcal / bacterial infections. Absent serum IgM.

Kappa chain deficiency*. ***IGKC*** *AR.*
Asymptomatic. All immunoglobulins have lambda light chain.

High Bc numbers due to constitutive NF-κB activation

CARD11 GOF . ***CARD11.*** AD GOF . BENTA syndrome.
Splenomegaly, lymphadenopathy, poor vaccine responses.

IV. Diseases of immune dysregulation.
(a) Hemophagocytic Lymphohistiocytosis and EBV susceptibility

Familial Hemophagocytic Lymphohistiocytosis (FHL)

FHL With Hypopigmentation:

Partial albinism . Bc and Tc: Nl
↓↓ NK and CTL activities : cytotoxicity and/or degranulation

Griscelli Sd type 2. *RAB27A* AR.
Fever, HSM, cytopenias; Specific hair shaft anomaly

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

Hermansky Pudlak sd type 2. *AP3B1* AR.
Recurrent infections, pulmonary fibrosis, increased bleeding, neutropenia; Specific hair shaft anomaly.

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

FHL Syndromes without Hypopigmentation :

Fever, HSM, cytopenias,
Nl Bc. Increased activated Tc.
↓↓ NK and CTL activities : cytotoxicity and/or degranulation

Perforin deficiency (FHL2).*PRF1* AR.

UNC13D / Munc13-4 deficiency (FHL3). *UNC13D* AR.

Syntaxin 11 deficiency (FHL4). *STX11* AR.

STXBP2 / Munc18-2 deficiency (FHL5) *STXBP2* AR or AD. Enteropathy

SLC7A7 deficiency. *SLC7A7* AR.
Lysinuric protein intolerance, bleeding tendency, alveolar proteinosis Hyper-inflammatory response of macrophages. Nl Tc and NK cell function

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

RHOG deficiency. *RHOG*** AR.
↓Total CD4+ and CD8+ T cells, mild ↓Bc; ↑ IgM, IgG

Susceptibility to EBV

RLTPR (CARMIL2) deficiency. RLTPR AR**.** Recurrent bacterial, fungal and mycobacterial infections, viral warts, molluscum and EBV lymphoproliferative and other malignancy, atopy. Ig Nl to ↓, poor T dependent antibody response. Nl Bc. Tc: ↓ Treg, high CD4, poor function.

CTPS1 deficiency. *CTPS1* AR. Recurrent/chronic bacterial and viral infections (EBV, VZV), EBV lympho-proliferation, B cell non-Hodgkin lymphoma. Tc: poor proliferation to Ag

XL magnesium EBV and neoplasia (XMEN). *MAGT1* *XL.* EBV infection, lymphoma, viral infections, respiratory and GI infections. Glycosylation disorder. Some patients can present with neurological manifestations. Low CD4 Low recent thymic emigrant cells, poor proliferation to CD3. High B cells, high DN T cells.

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

RASGRP1 deficiency*. *RASGRP1* AR. Recurrent pneumonia, herpes virus infections, EBV associated lymphoma. Decreased NK cell function; high IgA. Bc and Tc: Poor activation, proliferation, motility

CD70 deficiency*. *CD70* *(TNFSF7)* AR. Hodgkin lymphoma, autoimmunity in some patients. 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

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

TET2 deficiency. *TET2***. AR LOF. ALPS-like (↑ sCD25, sFasL, IL10), recurrent viral infections, lymphadenopathy, HSM, autoimmunity (cytopenias, B-cell lymphoma (EBV+ HL-like), failure to thrive, developmental delay, EBV viremia, DNA hypermethylation, defective FAS-mediated apoptosis. Variable (hyper-/ hypogamma, ↓response to pneumococcal vaccine). ↑ DNT, ↓Th1, Th17, Tfh cells. ↓Memory Bc.

EBV associated HLH

XLP1. *SH2DIA.* XL,
Clinical and immunologic features triggered by EBV infection: lymphoproliferation,
Aplastic anemia, Lymphoma.

Hypogammaglobulinemia,
Absent iNKT cells. Impaired NK cell and CTL cytotoxic activity . Reduced Memory Bc .
SAP deficiency (FCM).

XL, **XLP2. *XIAP.***
Splenomegaly, lympho-proliferation, Colitis, 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)

AR, **CD27 deficiency . *CD27*** *(TNFRSF7).*
Features triggered by EBV infection, aplastic anemia,
low iNKTc lymphoma. Low Ig

IV. Diseases of immune dysregulation. (b) Syndromes with Autoimmunity and Others

Syndromes with Autoimmunity

ALPS: Autoimmune Lymphoproliferative Sd
Chronic adenopathy Splenomegaly, defective lymphocyte apoptosis.

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-Caspase 8*. *CASP8.* *AR.* Bacterial and viral infections, Hypogammaglobulinemia. Defective lymphocyte activation. Slightly increased DNT cells.

ALPS-Caspase10*. *CASP10.* AD.

Regulatory T Cell Defects ?

No

APECED : Autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy (APS-1) . *AIRE.* AR/ AD. Hypoparathyroidism hypothyroidism, adrenal insufficiency, diabetes, gonadal dysfunction and other endocrine abnormalities, chronic mucocutaneous candidiasis, dental enamel hypoplasia, alopecia, enteropathy, pernicious anemia.

JAK1 GOF. *JAK1.*** AD GOF. HSM, eosinophilic enteritis, thyroid disease, poor growth, viral infections. Eosinophilia,

FADD deficiency.* *FADD.* AR. Functional hyposplenism, bacterial and viral infections, recurrent episodes of encephalopathy and liver dysfunction.

PDCD1 deficiency. *PDCD1.*** AR. Tuberculosis, autoimmunity (T1D, hypothyroidism and JIA), fatal pulmonary autoimmunity, HSM, ↑IgG/IgA, anti-insulin autoAb. Mildly lymphopenia. ↑DNT. Nl Bc.

ITCH deficiency. *ITCH.* *AR.* Early-onset chronic lung disease (interstitial pneumonitis), thyroiditis, type I diabetes, chronic diarrhea, enteropathy, and hepatitis, developmental delay, dysmorphic facial features.

Tripeptidyl-Peptidase II Deficiency. *TPP2.*** *AR.* Variable lymphoproliferation, severe autoimmune cytopenias, hypergammaglobulinemia, recurrent infections. Decreased Tc and Bc.

Prolidase deficiency. *PEPD.* AR. Chronic skin ulcers, eczema, infections. Auto-abs common.

SOCS1 deficiency. *SOCS1.* AD (haploinsufficiency). Recurrent bacterial infections, severe multisystemic autoimmunity, ITP, AIHA, SLE, GN, HSM, psoriasis, arthritis, thyroiditis, hepatitis, risk of COVID19/MIS-C, neutropenia, lymphopenia, incomplete penetrance. ↓CD4/CD8 Tc. ↑naïve Bc; ↓sw memory.

Yes

IPEX, immune dysregulation, polyendocrinopathy, enteropathy X-linked. *FOXP3* XL. Autoimmune enteropathy, early onset diabetes, thyroiditis hemolytic anemia, thrombocytopenia, eczema, ↑IgE/IgA. Lack and/or impaired function of $CD4^+$ $CD25^+$ $FOXP3^+$ Tregs.

LRBA deficiency. *LRBA.* AR. Recurrent infections, inflammatory bowel disease, autoimmunity. ↓IgG/IgA in most. ↓ or Nl Bc. ↓ or Nl CD4 numbers, Tc dysregulation.

STAT3 GOF mutation. *STAT3.* AD. Lymphoproliferation, solid organ autoimmunity, recurrent infections. Enhanced STAT3 signaling, leading to increased Th17 cell differentiation, lymphoproliferation and autoimmunity. ↓ Tregs and impaired function. ↓ Tc and Bc.

FERMT1 deficiency. *FERMT1* AR. Dermatosis (congenital blistering, skin atrophy, photosensitivity, skin fragility, and scaling). Intracellular accumulation of IgG, IgM, IgA, and C3 in colloid bodies under the basement membrane

IKAROS GOF*. *IKZF1.* AD GOF. Multiple autoimmune features (diabetes, colitis, thyroiditis), allergy, lymphoproliferation, Evans Syndrome, recurrent infections. Normal/mildly decreased Bc.

CTLA4 deficiency (ALPSV). ***CTLA4*** AD. Autoimmune cytopenias, enteropathy, interstitial lung disease, extra-lymphoid lymphocytic infiltration recurrent infections . Impaired function of Tregs. ↓ Tc and Bc.

BACH2 deficiency. *BACH2* AD. Lymphocytic colitis, sinopulmonary infections. Impaired memory Bc development. Progressive Tc lymphopenia.

CD25 deficiency*. *IL2RA* AR. Lymphoproliferation, autoimmunity, impaired Tc proliferation. No CD4+C25+ cells with impaired function of Tregs cells.

CD122 deficiency. *IL2RB* AR. Lymphoproliferation, lymphadenopathy, HSM, AIHA, dermatitis, enteropathy. Hypergamma, viral (EBV, CMV) infections

DEF6 deficiency*. *DEF6* AR. HSM, enteropathy, cardiomyopathy, recurrent infections. ↓Tc, ↓ or Nl Bc.

Immune Dysregulation with Colitis

IL-10R deficiency. AR. Folliculitis, recurrent respiratory diseases, arthritis, lymphoma.
IL10RA Leukocytes unresponsive to IL-10.
IL10RB. Leukocytes unresponsive to IL10, IL22, IL26, IL28A, IL28B, IL29

RIPK1 deficiency. *RIPK1.* AR. Reccurrent infections, progressive polyarthritis. Low Tc , low or nl Bc.

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

TGFB1 deficiency*. *TGFB1.* AR. Recurrent viral infections, microcephaly, and encephalopathy. Decreased T cell proliferation in response to anti-CD3

ELF4 deficiency*. *ELF4 .* XL. Early onset mucosal autoinflammation/ IBD, fevers and ulcers, hyper inflammatory macrophages. Nl IgM, G, A. ↓responses to live viral vaccines. Nl Tc and Bc.

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

V. Congenital defects of phagocyte number, function, or both. (a) Neutropenia (without anti-PMN)

Syndrome associated

Shwachman-Diamond Syndrome.
DNAJC21 *AR.* ***EFL1**** *AR.* Pancytopenia, exocrine pancreatic insufficiency. ***SBDS*** *AR.* +chondrodysplasia
SRP54 deficiency*. ***SRP54*** AD. Neutropenia and exocrine pancreatic insufficiency .

Glycogen storage disease type 1b. ***G6PT1*** *AR.* Fasting hypoglycemia, lactic acidosis, hyperlipidemia, hepatomegaly.

3-Methylglutaconic aciduria.
CLPB *AR.* Neurocognitive developmental aberrations, microcephaly, hypoglycemia, hypotonia, ataxia, seizures, cataracts, IUGR.

Clericuzio syndrome (Poikiloderma with neutropenia).
C16ORF57 *(USB1) AR.* Retinopathy, developmental delay, facial dysmorphism, poikiloderma.

JAGN1 deficiency. ***JAGN1*** *AR.* Osteopenia. Myeloid maturation arrest.

WDR1 deficiency. ***WDR1***
AR. Poor wound healing, severe stomatitis, neutrophil nuclei herniate. Mild neutropenia.

SMARCD2 deficiency. ***SMARCD2*** *AR.* Developmental aberrations, bones defect, myelodysplasia

G6PC3 deficiency (SCN4). ***G6PC3*** *AR.* Structural heart defects, urogenital abnormalities, inner ear deafness, and venous angiectasias of trunks and limbs. Affected fonctions: Myeloid differentiation, chemotaxis, O_2^- production.

Cohen syndrome. ***COH1*** *AR.* Dysmorphism, mental retardation, obesity, deafness.

Barth Syndrome (3-Methylglutaconic aciduria type II). ***TAZ*** *XL.* Cardiomyopathy, myopathy, growth retardation.

VPS45 deficiency (SCN5). ***VPS45*** AR. Extramedullary hematopoiesis, bone marrow fibrosis, nephromegaly.

Specific granule deficiency*. ***CEBPE*** AR (LOF).
Neutrophils with bilobed nuclei. Chronic neutropenia.

TLR8 def*. ***TLR8.*** XL GOF. Lymphoproliferation, infectious susceptibility, progressive autoinflammatory disease. BM failure, proinflammatory phenotype with activated Tc, elevated serum cytokines associated with impaired Bc maturation.

HYOU1 deficiency.** ***HYOU1*** *AR.* Hypoglycemia, inflammatory complications.

P14/LAMTOR2 deficiency.** ***LAMTOR2*** *AR.* Partial albinism, growth failure. Hypogammaglobulinemia, reduced CD8 cytotoxicity.

No syndrome associated

Elastase deficiency. (SCN1). ***ELANE*** *AD.* Susceptibility to MDS/leukemia. Severe congenital neutropenia or cyclic neutropenia (perform CBC twice weekly/ 4 weeks).

HAX1 deficiency (Kostmann Disease) (SCN3). **HAX1**
AR. Cognitive and neurological defects in patients with defects in both HAX1 isoforms, susceptibility to MDS/leukemia

X-linked neutropenia/ myelodysplasia WAS GOF. ***WAS*** XL GOF.
Myeloid maturation arrest, monocytopenia, variable lymphoid anomalies .

G-CSF receptor deficiency*. ***CSF3R*** *AR.*
Stress granulopoiesis disturbed

Neutropenia with combined immune deficiency *. ***MKL1*** *AR.*
Mild thrombocytopenia. Lymphopenia.

CXCR2 deficiency*. ***CXCR2*** AR LOF.
Profound neutropenia, myelokathexis, recurrent gingivitis, oral ulcers. Hypergammaglobulinemia (↑IgG, IgA, IgM). Nl CD4+ Tc, variable CD8+ Tc, Nl NKc. Nl Bc.

GFI 1 deficiency (SCN2).** ***GFI1***
AD.
B/T lymphopenia

V. Congenital defects of phagocyte. (b) Functional defects

Syndrome associated

Cystic fibrosis. *CFTR.* AR.

Pancreatic insufficiency,

Respiratory infections, elevated

sweat chloride

Papillon-Lefèvre . *CTSC* AR.

Periodontitis, palmoplantar

hyperkeratosis in some patients

Localized juvenile periodontitis

. *FPR1* AR. Periodontitis only

β-Actin . *ACTB* AD.

Mental retardation, short stature

Leukocyte adhesion deficiency

Skin infections evolve to large ulcers.
Leukocytosis with neutrophilia
(WBC > 25000)

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. Severity of the disease correlates with the degree of deficiency in CD18 (FCM). (WBC 20,000–150,000 with 60–85 % neutrophils)

LAD II (Congenital disorder of glycosylation, type IIc). *SLC35C1*
Recurrent infections. Mild LAD type 1 features with hh-blood group, growth retardation, developmental
delay , facial dysmorphism (depressed nasal bridge).

LAD III
FERMT3
Severe bacterial infections and
severe bleeding disorder. Platelet aggregation assay.

No Syndrome associated:

DHR assay (or NBT test) ?

Normal

GATA2 def. *GATA2,* AD.

Susceptibility to Mycocbacteria,

Papilloma Viruses, Histoplasmosis,

Lymphedema. Alveolar proteinosis,

myelodysplasia/ AML/ CMML .

Multi lineage cytopenias. Low NK.

Pulmonary alveolar proteinosis.

CSF2RA, *AR.* ***CSF2RB****, XL.*

Affected cells: Alveolar

macrophages. Affected fonction:

GM-CSF signaling

Abnormal

CGD: 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
Granulomata obstructing respiratory, urinary or gastrointestinal tracts. Inflammatory bowel disease (Crohn's like disease) and perianal disease : up to 30 %
Pathogens : typically catalase negative bacteria (*S. aureus* and gram-negative bacilli, *Aspergillus*, *Candida*); other: *Burkholderia cepacia,Chromobacterium violaceum, Nocardia*, and invasive *Serratia marcescens*. BCG adverse effects in up to 20 %. Microscopic granulomas.

XL CGD: ***CYBB*** ($gp91^{phox}$)
NCF1 ($p47^{phox}$) , AR
CYBA ($p22^{phox}$), AR
NCF4 ($p40^{phox}$), AR
NCF2 ($p67^{phox}$), AR
CYBC1** , AR

G6PD def Class I. *G6PD* XL. Infections.

Rac 2 def* . *RAC2* AD LOF. Poor wound healing. LAD phenotype (leukocytosis).

VI. Defects in Intrinsic and Innate immunity. (a) Predisposition to Viral infection

Predisposition to Herpes simplex Encephalitis

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.

UNC93B1 (AR), ***TRAF3***** *(AD),* ***TICAM1 (TRIF)**** *(AR,AD),* ***TBK1**** *(AD),* ***IRF3**** *(AD)*

SNORA31* . AD. Forebrain HSV-1 encephalitis.

TLR3 *(AD,AR)* + severe pulmonary influenza, VZV

DBR1* (AR) + other viral infections of the brainstem

Mollaret's meningitis : recurrent lymphocytic meningitis due to HSV2, history of multiple episodes of meningitis.
ATG4A** . AD
MAP1LC3B2**. AD

Predisposition to HPV

Epidermodysplasia verruciformis

HPV group B1 infections and cancer of the skin

EVER1 def. ***TMC6.*** AR.

EVER2 def. ***TMC8.*** AR.

CIB1 def. ***CIB1.*** AR.

WHIM (Warts, Hypogammaglobulinemia, infections, myelo-kathexis) sd.

CXCR4 AD GOF. Warts (HPV) infection, neutropenia, low B cell number, hypogamma-globulinemia.

RHOH def.** ***RHOH*** AR.
HPV infection, lung granulomas, molluscum contagiosum, lymphoma. Low naïve T cells, restricted repertoire, poor proliferation to CD3.

Predisposition to Severe Viral Infection

STAT1 def. AR LOF. ***STAT1.*** *(+ Mycobacteria)*

STAT2 def. ***STAT2.*** *AR.*

Disseminated vaccine-strain measles

MDA5 def (LOF)*. ***IFIH1.*** *AR.*

Rhinovirus and other RNA viruses

IFNAR1 def*. ***IFNAR1*** AR.

Severe disease caused by Yellow Fever vaccine and Measles vaccine

IFNAR2 def*. ***IFNAR2*** AR.

Disseminated vaccine-strain measles, HHV6. No response to IFN-α.

RNA poymerase III def*. ***POLR3A. POLR3C. POLR3F.*** AD. Severe VZV infection.

IRF7 def.** ***IRF7.*** AR.
IRF9 def*. ***IRF9.*** AR.
Severe influenza disease.

IL-18BP def.** ***IL18BP.*** AR.

Fulminant viral hepatitis

ZNFX1 def. ***ZNFX1.*** AR.

Severe infections by RNA/DNA viruses, causing early-onset, systemic, severe, acute inflammation with major dysfunctions of liver, brain, kidneys, lungs, virally triggered inflammatory episodes (HLH), intermittent monocytosis, mycobacterial disease (BCGosis, disseminated TB),

TLR7 def. ***TLR7 .*** XL.

Severe COVID19

CD16 def*. ***FCGR3A.*** *AR.*

Severe herpes viral infections, particularly VZV, EBV, and HPV.

CD28 def*. ***CD28*** AR.

Susceptibility to HPV infection. Nl Tc, ↓NKc, Nl Bc. Nl serum IgM,G,A.

NOS2 def.** ***NOS2 .*** AR. Severe susceptibility to CMV-induced disease, fatal pneumocystis pneumonia secondary to CMV, apparent intact responses to infection with other herpes viruses (EBV, VZV, HSV). ↓CD4+ Tc; ↓NKc (mostly all immature cells), Nl CD8+ Tc. ↓Bc.

VI. Defects in Intrinsic and Innate immunity. (b) Predisposition to Bacterial, Fungal and Parasitic Infections

Predisposition to Invasive Bacterial infections (pyogens):

Meningitis, sepsis, arthritis, osteomyelitis and abscesses, often in the absence of fever.

Predominant pathogens (*S. pneumoniae*, *S. aureus* and *Pseudomonas aeruginosa*). Non-invasive bacterial infections (skin infections and upper respiratory tract infections). Improve with age. Routine Usual screening tests are normal. Specific screening tests (lack of proinflammatory cytokine production and CD62L shedding) : available only in specialized clinical immunology laboratories.

IRAK4 def . *IRAK4,* AR

MyD88 def . *MYD88*, AR.

IRAK-1 def. *IRAK1***, *XL.* X-linked MECP2 deficiency-related syndrome due to a large *de novo* Xq28 chromosomal deletion encompassing both *MECP2* and *IRAK1*

TIRAP def. *TIRAP***, *AR.*
Staphylococcal disease during childhood.

Isolated congenital asplenia.
Bacteremia (encapsulated bacteria). No spleen.

RPSA, AD.
HMOX*, AR. Hemolysis, nephritis, inflammation

Predisposition to Parasitic and Fungal infections

Predisposition to Mucocutaneous Candidiasis (CMC)

without ectodermal dysplasia

STAT1 GOF. *STAT1,* AD
various fungal, bacterial and viral (HSV) infections, autoimmunity (thyroiditis, diabetes, cytopenias), enteropathy

IL-17RA deficiency. *IL17RA,* AR. Folliculitis. Susceptibility to *S.aureus* (skin infections) and chronic bacterial infections.

IL-17RC deficiency. *IL17RC*, *AR.*

IL-17F deficiency*. *IL17F*, *AD.* Folliculitis.

ACT1 deficiency*. *ACT1,* AR. Blepharitis, folliculitis and macroglossia.

JNK1 haploinsufficiency* def*. *MAPK8. AD (haplo-insufficiency).
Connective tissue disorder (similar to Ehlers-Danlos syndrome). ↓ Th17 cells *ex vivo, in vitro,* ↓ responses of fibroblasts to IL-17A, IL-17F

CARD9 def. *CARD9*, AR.

Predisposition to INVASIVE Fungal Diseases.
Invasive candidiasis infection, deep dermatophytoses, other invasive fungal infections.

Trypanosomiasis *APOL1,* AD. Trypanosomiasis.

Mendelian Susceptibility to Mycobacterial Disease: MSMD

Severe phenotypes :

Complete IFNGR1 Def and **IFNGR2 Def. *IFNGR1, IFNGR2***.
AR. Serious disseminated BCG and environmental mycobacterial infections (soft tissue, bone marrow, lungs, skin, bones and lymph nodes), *Salmonella* spp., *Listeria monocytogenes* and viruses
IFNG deficiency*. *IFNG.* AR LOF.

Moderate phenotypes:

With Susceptibility to *Salmonella*
IL-12 and IL-23 receptor b1 chain def. *IL12RB1* .AR.
IL-12p40 (IL-12 and IL-23) def. *IL12B* .AR.
IL-12Rb2 deficiency. *IL12RB2***. *AR*
IL-23R deficiency. *IL23R***. *AR.*
STAT1 LOF *STAT1*(AD)
Partial IFNγR1, *IFNGR1*. AR. **Partial IFNγR2, *IFNGR2.***AR.
AD IFNGR1 *IFNGR1*. AD. Mycobacterial osteomyelitis
SPPL2a deficiency*. *SPPL2A.* AR.
Tyk2 deficiency, *TYK2.* AR.
Susceptibility to viruses, +/- elevated IgE. multiple cytokine signaling defect. ***P1104A TYK2 homozygosity*** MSMD or tuberculosis.

Macrophage gp91 phox def. *CYBB*, *XL*
IRF8 def. *IRF8* AD.
ISG15 def. *ISG15.* AR. Brain calcification. IFNg production defect.
IRF8 def. *IRF8* AR. Multiple other infectious agents. Myeloproliferation
RORγt def*. *RORC* AR. Susceptibility to *Candida*. IFNg productiondefect, complete absence of IL-17A/F-producing Tc
JAK1 (LOF)*, *JAK1*. AR. Susceptibility to viruses, urothelial carcinoma. ↓ IFNg production.
T-bet def. *TBX21.*** AR LOF. Upper airway inflammation

Others

Hydradenitis suppurativa.

PSENEN, AD.

NCSTN, AD. + acne

PSEN, AD. + hyperpigmentation

Acute liver failure due to NBAS def. *NBAS,* AR.

Fever induces liver failure

Acute necrotizing encephalopathy.

RANBP2, AD.

Fever induces acute encephalopathy

IRF4 haploinsufficiency*.

IRF4, AD.

Whipple's disease

VII. Auto-inflammatory disorders

Recurrent inflammation
Recurrent fever

Familial Mediterranean Fever (FMF) *.*MEFV.* AR or AD (Usually M694del variant)**. DA**: 1–4 days **FA :** Variable. Polyserositis, Abdominal pain, Arthritis, Amyloidosis. Erysipelas-like erythema. Predisposes to vasculitis and inflammatory bowel disease .
Colchicine-responsive +++.

TNF receptor-associated periodic syndrome; TRAPS. *TNFRSF1A.* AD.
DA: 1-4 weeks **FA :** Variable Prolonged fever. Serositis, rash, Periorbital edema and conjunctivitis. Amyloidosis. Joint inflammation.

Bacterial infections, autoinflammation, amylopectinosis. Bc: Nl,decreased memory Bc.
HOIL1 deficiency. ***RBCK1*** AR.
Poor Ab responses to polysaccharides.
HOIP deficiency*. ***RNF31*** AR.
Lymphangiectasia. Ig: decreased.

RIPK1 def. *RIPK1.* AD.
Regular/prolonged fevers, lymphadenopathy, spleno/ hepatomegaly, ulcers, arthralgia, GI features, ↑inflammation markers, ↑pro-inflammatory cytokines. Responsive to Tocilizumab (not IL1/TNF blockade). ↓/Nl $CD4^+$ Tc , Nl/↑$CD8^+$ Tc, ↑DN T cells.

Mevalonate kinase def* (Hyper IgD sd). ***MVK.*** AR.
DA: 3–7 days **FA**: 1–2 monthly. Cervical adenopathy. Oral aphtosis. Diarrhea. Mevalonate aciduria during attacks. Leukocytosis with high IgD levels.

CEBPE deficiency*. *CEBPE.* AR GOF. **DA:** 4–5 days **FA**: 2–4 weeks, later more seldom. Recurrent abdominal pain, aseptic fever, systemic inflammation; abscesses, ulceration, infections; mild bleeding diathesis. Mild lymphopenia, ↓naïve Tc, ↑T_{EMRA} cells.

C2orf69 def. *C2orf69.* AR.
Brain abnormalities (hypomyelination, microcephaly), liver dysfunction, early onset severe and recurrent autoinflammation, leukoencephalopathy with recurrent seizures, often fatal.

ZNFX1 def. *ZNFX1.* AR. Severe infections by RNA/DNA viruses, causing early-onset, systemic, severe, acute inflammation with major dysfunctions of liver, brain, kidneys, lungs, virally triggered inflammatory episodes (HLH), intermittent monocytosis, mycobacterial disease (BCGosis, disseminated TB)

TBK1 def*. *TBK1* AR. chronic systemic autoinflammation (polyarthritis, vasculitis, delayed neurocognitive development, treated with TNF inhibitors.

Systemic inflammation with urticaria rash

Familial Cold Autoinflammatory Syndrome (CAPS) . *NLRP3, NLRP12.* AD GOF.
DA: 24-48H, non-pruritic urticaria, arthritis, chills, fever and leukocytosis after cold exposure.

Muckle Wells syndrome (CAPS) *
NLRP3. AD GOF.
Ethnic group: North European.
Continuous fever. Often worse in the evenings. Urticaria, Deafness (SNHL), Conjunctivitis, Amyloidosis.

A20 haploinsufficiency *TNFAIP3*. AD LOF.
Arthralgia, mucosal ulcers, ocular inflammation.

PLAID (PLCg2 associated antibody deficiency and immune dysregulation), or APLAID*.
PLC2G. AD GOF.
Cold Urticaria. Impaired humoral immunity. Hypogammaglobulinemia, autoinflammation.

Neonatal onset multisystem inflammatory disease (NOMID) or chronic infantile neurologic cutaneous and articular syndrome (CINCA) *.
NLRP3. AD GOF.
Neonatal onset rash, with continuous fever and inflammation. Aseptic and chronic meningitis, chronic arthropathy. Mental retardation, Sensorineural deafness. and Visual loss in some patients.

NLRP1 deficiency*. *NLRP1.* AR.
Dyskeratosis, autoimmunity and arthritis.

Type 1 Interferonopathies

Progressive encephalopathy, ICC, Cerebral atrophy, HSMG, leukodystrophy , Thrombocytopenia, Elevated hepatic transaminases . Chronic cerebrospinal fluid (CSF) lymphocytosis

Aicardi-Goutieres Syndromes
TREX1 AR-AD (+SLE, FCL),
RNASEH2A, RNASEH2B (+SP),
RNASEH2C AR.
SAMHD1 AR *(+ FCL)*,
ADAR1 (+BSN, SP),
IFIH1 GOF AD (+ SLE, SP, SMS),
DNASE2 AR,
LSM11* AR LOF,
RNU7-1 AR LOF

ADA2 deficiency. *CECR1* AR.
Polyarteritis nodosa, childhood-onset, early-onset recurrent ischemic stroke and fever, Lived o racemosa, some patients develop hypogammaglobulinemia

ATAD3A def*. *ATAD3A*
AD or AR.
Predominant neuro defects (development delay, spasticity), elevated ISG expression, increased serum type 1 IFNs.

USP18 def *.
USP18 AR.
TORCH like syndrome.

STAT2 def*. *STAT2* AR GOF. Severe fatal early onset autoinflammation (skin ulceration, fever, seizures, intracranial calcification, multiorgan dysfunction, abnormal neurodevelopment; phenocopy of USP18 def. ↑ serum IFN-α, IL6, TNFa. ↑Tc, ↓NKc. Nl Bc. low/normal Ig levels.

STING-associated vasculopathy with onset in infancy (SAVI). *TMEM173.*
AD: Early-onset inflammatory disease, Skin vasculopathy, inflammatory lung disease, systemic autoinflammation and ICC, FCL.
AR GOF : failure to thrive, early onset rash, fever, dyspnea, interstitial lung disease/pneumonitis, polyarthritis, autoAbs, clubbing, increased inflammatory markers, IFN gene signature , phenocopy of SAVI due to AD GOF *TMEM173* variants.

VII. Auto-inflammatory disorders (continued)

Sterile inflammation (skin / bone / joints)

Predominant on the bone / joints

Pyogenic sterile arthritis, pyoderma gangrenosum, acne (PAPA) syndrome, hyperzincemia and hyper-calprotectinemia. ***PSTPIP1*** *(C2BP1)* AD.
DA: 5 days
FA: Fixed interval : 4-6 weeks
Destructive arthritis, Pyoderma gangrenosum, inflammatory skin rash, Myositis. Acute-phase response during attacks

Chronic recurrent multifocal osteomyelitis and congenital dyserythropoieticanemia (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

DIRA (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

Predominant on the skin

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 diarrhea and skin lesions. Severe bacteremia. Defective TNFα production.

SLC29A3 mutation. ***SLC29A3*** . AR. Hyperpigmentation hypertrichosis, histiocytosis-lymphadenopathy plus syndrome

Otulipenia/ORAS*. ***OTULIN.*** AR. Neonatal onset of recurrent fever, Arthralgia, lipodystrophy. Dermatitis, diarrhea, Neutrophilia

AP1S3 deficiency*. ***AP1S3.*** AR.
Pustular psoriasis

HCK1 def.** ***HCK1.*** AD GOF. Cutaneous vasculitis and chronic pulmonary inflammation/ fibrosis, inflammatory leukocyte infiltration of the lungs and skin, anemia, HSM, respiratory failure, clinical improvement with ruxolitinib.

Others

CANDLE Sd (chronic atypical neutrophilic dermatitis with lipodystrophy)/PRAAS. ***PSMB8,*** AR and AD.
Contractures, panniculitis, ICC, fevers. ***PSMG2,*** AR.
Panniculitis, lipodystrophy, AIHA.

NLRP1 GOF. ***NLRP1*** AD GOF.
Palmoplantar carcinoma, corneal scarring; recurrent respiratory papillomatosis. Increased IL1β.

COPA defect. ***COPA*** *AD.* Autoimmune inflammatory arthritis and interstitial lung disease with Th17 dysregulation and autoantibody production

T-cell lymphoma subcutaneous panniculitis-like (TIM3 deficiency). ***HAVCR2*** AR. Panniculitis, HLH, polyclonal cutaneous T cell infiltrates or T-cell lymphoma

Pediatric systemic lupus erythematosus. ***DNASE1L3*** AR. Very early onset SLE, reduced complement levels, autoantibodies (dsDNA, ANCA), lupus nephritis, hypocomplementemic urticarial vasculitis syndrome.

PRAAS with immunodeficiency*. ***PSMB9*** AD GOF.
Severe autoinflammation (neonatal-onset fever, a chilblain-like skin rash, myositis, pulmonary hypertension, basal ganglia calcification), periodic inflammatory exacerbation, immunodeficiency, ↑ IL-6, IL-18, IP-10, IFN- α, ↑ liver enzymes in blood and CSF. Mild pancytopenia. ↓IgG and Bc. ↓TREC and KREC.↓monocytes, CD8 T, and γδ Tc.

NLRC4-MAS (macrophage activating syndrome)*. ***NLRC4*** AD GOF. Severe enterocolitis and macrophage activation syndrome (HLH). Triggered by cold exposure.

OAS1 def*. ***OAS1.*** AD GOF.
Pulmonary alveolar proteinosis, skin rash.

Spondyloenchondro-dysplasia with immune dysregulation (SPENCD). ***ACP5*** AR. Short stature, SP, ICC, SLE-like auto-immunity (Sjögren's syndrome, hypothyroidism, inflammatory myositis, Raynaud's disease and vitiligo), hemolytic anemia, thrombocytopenia, skeletal dysplasia, possibly recurrent bacterial and viral infections.

XL reticulate pigmentary disorder. ***POLA1*** XL. Hyper-pigmentation, reticulate pattern. Inflammatory lung and Gastroenteritis or colitis. Corneal scarring, characteristic facies

CDC42 def. ***CDC42*** AD. Neonatal onset: pancytopenia, fever, rash, HSM, systemic inflammation, myelofibrosis/proliferation, HLH, multisystemic inflammatory disease.↑serum inflammatory markers, failure to thrive, neurodevelopmental delay. ↓ NK function (cytox). Nl or ↓ Tc. Nl or ↓ Bc.

ALPI deficiency*. ***ALP1.*** AR. / **TRIM22 def*.** ***TRIM22.***
AR. Inflammatory bowel disease.

NCKAP1L def*. ***NCKAP1L.*** AR LOF. Recurrent URTI, skin rashes/abscesses, ulcers, anti dsDNA Abs, SLE-like, lymphadenopathy, fever, HLH-like, failure to thrive, immunodeficiency coupled with atopy, lymphoproliferation, hyperinflammation and cytokine overproduction (↑Th1), ↓Tc proliferation, cytoskeletal defects. Nl/↑ Ig levels. Nl Tc, possibly immature NK cells but intact function. Nl Bc.

SYK def*. ***SYK.*** AD GOF. Recurrent infections, multi-organ inflammatory disease (colitis, arthritis, dermatitis), inflammation in multiple tissues (gut, skin, CNS, lung, liver), diffuse large B cell lymphoma. Dysgamma (↓ IgM, IgG).

IKBKG (NEMO exon 5 deletion) def*. ***IKBKG.*** XL.
fever, skin rash, systemic autoinflammation, infections, CNS involvement, panniculitis, uveitis, hepatosplenomegaly, ectodermal dysplasia.Hypogamma, Bc lymphopenia.

VIII. Complement deficiencies

Level of Infection susceptibility ?

High Susceptibility

Disseminated Neisserial infections

Absent CH50 and AH50 hemolytic activity. Defective bactericidal activity.

C6 def. ***C6*** AR.

C7 def . ***C7*** AR.

+ Vasculitis

C8 def.

C8A, C8B, C8G AR.

C9 def. ***C9*** AR.

Mild susceptibility.

Normal CH50.

Absent AH50 hemolytic activity

Properdin def.

PFC XL.

Factor D def.

CFD AR.

Recurrent pyogenic infections

C3 LOF. ***C3*** AR.
Absent CH50 and AH50 hemolytic activity, defective opsonization and humoral response

MASP2 def. ***MASP2*** AR.
Inflammatory lung disease, autoimmunity

Ficolin 3 def. ***FCN3*** AR.
Infections mainly in the lungs; abscesses, necrotizing entero-colitis in infancy; selective antibody defect to Pneumo-coccal polysaccharides. Absence of complement activation by the Ficolin 3 pathway

Factor B. ***CFB LOF.*** AR.
Infections with encapsulated organisms. Deficient activation of the alternative pathway

Low Susceptibility

SLE-like syndrome. Infections with encapsulated organisms

Absent CH50 hemolytic activity

C1q def. ***C1QA, C1QB, C1QC.*** AR.

C1r def. ***C1R.*** AR.
Ehlers Danlos phenotype

C1s def.*C1S.* AR.
Multiple autoimmune diseases; Ehlers Danlos phenotype

C2 def. ***C2.*** AR.
Vasculitis, Polymyositis, atherosclerosis

Complete C4 def .
C4A+C4B.AR.
Partial deficiency is common (either C4A or C4B) and appears to have a modest effect on host defense

Atypical Hemolytic Uremic Syndrome

C3 GOF. ***C3*** AD. Glomerulonephritis.
Increased activation of complement

Factor B GOF. ***CFB.*** AD. Increased spontaneous AH50. Atypical hemolytic-uremic Sd.

Factor H def. ***CFH.*** AR or AD. Infections, disseminated neisserial infections, preeclampsia. Spontaneous activation of the alternative complement pathway with consumption of C3

Factor H –related protein deficiencies.
CFHR1-5. AR or AD. Later onset, disseminated neisserial infections. Normal CH50, AH50, autoantibodies to Factor H.

Factor I deficiency. AR. Infections, disseminated neisserial infections, preeclampsia. Spontaneous activation of the alternative complement pathway with consumption of C3

Thrombomodulin def. ***THBD.*** AD.
Normal CH50, AH50

Membrane Cofactor Protein deficiency.
CD46 AD. Glomerulone-phritis. Infections, preeclampsia . Inhibitor of complement alternate pathway, decreased C3b binding

Others

C1inhibitor. ***SERPING1*** AD.

Hereditary angioedema.

Spontaneous activation of the complement pathway with consumption of C4/C2

Membrane Attack Complex Inhibitor deficiency.
CD59 AR.

Hemolytic anemia.
Polyneuropathy.

CD55 deficiency (CHAPLE disease). ***CD55*** AR.

Protein losing enteropathy, thrombosis

Periodontal Ehlers Danlos.
C1R,C1S. AD GOF.

Hyperpigmentationskin fragility.
Normal CH50.

IX. Bone marrow failure

Fanconi anemia
CNS, skeletal, skin, cardiac, GI, urogenital anomalies.

Increased chromosomal breakage, pancytopenia.

Fanconi anemia Type A-W:

-AR

FANCA, FANCC, BRCA2, FANCD2, FANCE, FANCF, XRCC9,FANCI, BRIP1, FANCL, FANCM, PALB2, RAD51C, SLX4,ERCC4, RAD51, BRCA1, UBE2T, XRCC2, MAD2L2,RFWD3,

-XL

FANCB

Dyskeratosis congenita (DKC)
Myelodysplasia, short telomeres.

Exclude other causes:
Fanconi anemia,
Blackfan-Diamond

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. ***RTEL1 :*** AD, *Tc:* Decreased. ***TERC, TINF2, ACD :*** AD,*Tc:* variable. ***TERT, TPP1:*** AD/AR, *Tc:* variable. ***DCLRE1B/ SNM1/APOLLO, WRAP53*, DCAB1:*** AR,*Tc:* variable.

Hoyeraal-Hreidarsson Syndrome (HHS)
Severe phenotype with developmental delay and cerebellar hypoplasia.

AR, ***RTEL1, PARN, ACD***

Bone marrow failure sd

(BMFS)

Myelodysplasia

SRP72- deficiency.**

SRP72, AD

Bone marrow failure and

congenital nerve deafness

BMFS5*

TP53, AD

Erythroid hypoplasia,

B-cell deficiency

Others

MIRAGE sd. ***SAMD9*** AD GOF. I
UGR with gonadal abnormalities, adrenal failure, MDS with chromosome 7 aberrations, predisposition to infections, enteropathy, absent spleen

Ataxia pancytopenia sd. *SAMD9L* AD 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 AR. premature aging,
CTC1 AR. sparse graying hair, dystrophic nails, osteopenia, retinal telangiectasia,

Osteopetrosis. *TNFRSF11A*, *PLEKHM1* AR.
TCIRG1, AR. + hypocalcemia
CLCN7, OSTM1, AR. + hypocalcemia, neurologic features
SNX10, AR. + visual impairment
TNFSF11, AR. + severe growth retardation

MECOM def. *MECOM* AD LOF. Congenital hypomegakaryocytic thrombocytopenia, clinodactyly, cardiac and renal malformations, Bc deficiency, radioulnar synostosis and presenile hearing loss.

X. Phenocopies of PID

Associated with Somatic Mutations

Splenomegaly, lymphadenopathy, autoimmune cytopenias.
Defective lymphocyte apoptosis.

ALPS-SFAS
(somatic mutations in *TNFRSF6)*/ *ALPS-FAS*
(ALPS type Im)

RALD. RAS-associated autoimmune leukoproliferative disease. (ALPS Like); ***N-RAS GOF, K-RAS GOF.*** Sporadic; granulocytosis, monocytosis/ALPS-like

Cryopyrinopathy, (Muckle-Wells /CINCA/NOMID-like syndrome).
NRLP3.
Urticaria-like rash, arthropathy, neurological symptoms

Hypereosinophilic syndrome due to somatic mutations in STAT5b. ***STAT5b.*** GOF.
Atopic dermatitis, urticarial rash, diarrhea. Eosinophilia.

TLR8 def*. ***TLR8.*** GOF. Lymphoproliferation, Infectious susceptibility, progressive autoinflammatory disease. BM failure, proinflammatory phenotype with activated Tc, elevated serum cytokines associated with impaired Bc maturation.

Late adulthood onset treatment-refractory inflammatory syndrome VEXAS.
UBA1. LOF.

Often fatal, fevers, cytopenias, dysplastic bone marrow, neutrophilic cutaneous and pulmonary inflammation, chondritis and vasculitis, inflammatory syndrome or hematologic condition, ↑ serum inflammatory markers. ↓peripheral lymphocyte counts, loss of immature Bc.

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, cryptococcal meningitis, disseminated nocardiosis/CSF2RA deficiency

Acquired angiooedema .
AutoAb to C1 inhibitor.
Angioedema /C1 inhibitor deficiency

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

Thymoma 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.

Severe COVID-19.
Neutralizing AutoAb to type 1 IFNs (IFNa, IFNw). Severe, l
ife-threatening infection with SARS-CoV-2.