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ORIGINAL ARTICLE

The 2017 IUIS Phenotypic Classification for Primary Immunodeficiencies

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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,

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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.

Fig. 1 Immunodeficiencies affecting cellular and humoral immunity. **a** ▶ Severe combined immunodeficiencies defined by T cell lymphopenia. **b** Combined immunodeficiencies. * T cell lymphopenia in SCID is defined by CD3+ T cells < 300/μL. AD: autosomal dominant transmission; ADA: adenosine deaminase; Ag: antigen; AR: autosomal recessive transmission; β2m: bêta-2 microglobulin; Bc: B cells; CBC: complete blood count; CD: cluster of differentiation; CVID: common variable immunodeficiency; def: deficiency; EBV: Epstein Barr virus; HHV8: human herpes virus 8; HIGM: hyper IgM syndrome; HPV: human papillomavirus; Ig: immunoglobulins; MHC: major histocompatibility complex; Nl: normal; NK: natural killer; SCID: severe combined immunodeficiency; Tc: T cells; TCR: T cell receptor; Treg: regulatory T cells; XL: X-linked transmission

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I. Immunodeficiencies affecting cellular and humoral immunity.
(a) Severe combined immunodeficiencies SCID, defined by CD3 T cell lymphopenia*.

CD19 NL : SCID T- B+

SCID T-B+NK-

XL,

CD 132-

γc deficiency.

IL2RG

AR,

CD 132+

JAK-3 def.

JAK3

SCID T-B+NK+

IL7Rα .

IL7R

No γ/δ T cells:

CD3δ. *CD3D*

CD3ε. *CD3E*

CD3ζ . *CD247*

Nl γ/δ T cells :

CD45 def.

PTPRC

Coronin-1A def . *CORO1A*

Detectable thymus

Winged helix def. FOXN1.

Severe infections; abnormal thymic epithelium; congenital alopecia, nail dystrophy, neural tube defect.

CD19 ↓ : SCID T-B-

SCID T-B-NK-

ADA def . *ADA*

Chondrosternal dysplasia, deafness, may have pulmonary alveolar proteinosis, cognitive defects

Reticular dysgenesis. *AK2*

Granulocytopenia, Thrombocytopenia deafness.

SCID T-B-NK+

Microcephaly ?

Yes	No
- *With facial dysmorphism:* DNA ligase IV def . *LIG4* CERNUNNOS /XLF def. *NHEJ1.* Radiation sensitive - *Without facial dysmorphism:* DNA PKcs def. *PRKDC* Radiosensibility	RAG 1/2 def. (*RAG1/ RAG2*) DCLRE1C def. *DCLRE1C (ARTEMIS).* Radiosensibility

I. Immunodeficiencies affecting cellular and humoral immunity
(b) Combined Immunodeficiencies Generally Less Profound than Severe Combined Immunodeficiency

Low CD4: MHCII Expression ?

Absent :

MHC-II def.

RFXANK,CIITA, RFX5, RFXAP

Diarrhea, respiratory infections, liver/biliary tract disease

Present:

XL MAGT1 def.

MAGT1.

AR, LCK def. *LCK.*

Immune dysregulation, autoimmunity. Low Treg, restricted T cell repertoire, poor TCR signaling;

AD :UNC119 def.

UNC119

Low CD8

CD8 def . *CD8A*

Maybe asymptomatic. CD8 Absent.

Nl MHC I on lymphocytes.

ZAP-70 def. *ZAP70* May have immune dysregulation, autoimmunity. Nl Ig. CD4: Low fonction

Absent MHC I on lymphocytes.

MHC-I def .

TAP2, TAP1 or *TAPBP*

Vasculitis, pyoderma gangrenosum. Nl Ig.

B2M

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

Low Bc:

DOCK8 def. *DOCK8.*Severe Eczema. Cutaneous viral and staphylococcal infections; severe atopy; cancer ,diathesis. High IgE, Low IgM, eosinophilia. Low NK with poor function. Low CD27+ memory Bc Poor peripheral Bc tolerance.

MST1 def . *STK4.*Intermittent neutropenia; bacterial, viral (HPV), candidal infections; EBV lymphoproliferation; autoimmune cytopenias; lymphoma; congenital heart disease. Low T and B. High Ig. Low terminal differentiated effector memory cells, low naïve Tc, poor proliferation.

IL21 def. *IL21.* Severe early onset colitis. Low IgG. Tc : NL / low function.

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

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

Ig : often NL

CD3γ def. *CD3G* TCR low.

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

TCRα def .*TRAC.* Recurrent viral, bacterial, fungal infections; immune dysregulation and autoimmunity; diarrhea. Absent TCRαβ; all Tc are γδ; poor proliferation.

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

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

LAT def . LAT. Adenopathy, splenomegaly, autoimmunity. High Ig . T and B : NL to low

Ig Low

DOCK2 def. *DOCK2.* Low Tc; NL NK but defective function. Poor interferon responses in hematopoietic and non-hematopoietic cells. IgG NL or low; poor antibody responses.

CARD11 deficiency (LOF). *CARD1.* *Pneumocystis jirovecii* pneumonia, bacterial & viral infections .Ig:Absent/low.Tc:NL number, poor proliferation

BCL10 def. *BCL10.* Recurrent bacterial and viral infections, candidiasis, gastroenteritis. Low memory T and Treg cells, poor Ag and anti-CD3 prolif. Decreased memory and switched Bc

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

ICOS def. *ICOS.* Autoimmunity, gastroenteritis, granulomas (CVID).

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

RelB deficiency.*RELB.*Tc:poor diversity, poor function

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

Normal Ig but Poor Specific Antibody response

IL21R def . *IL21R.* Recurrent infections; Pneumocystis, Cryptosporidium. Tc: low cytokine production; poor antigen proliferation.

MALT1 def. *MALT1.* Bacterial, fungal and viral infections. Impaired Tc proliferation and antibody response

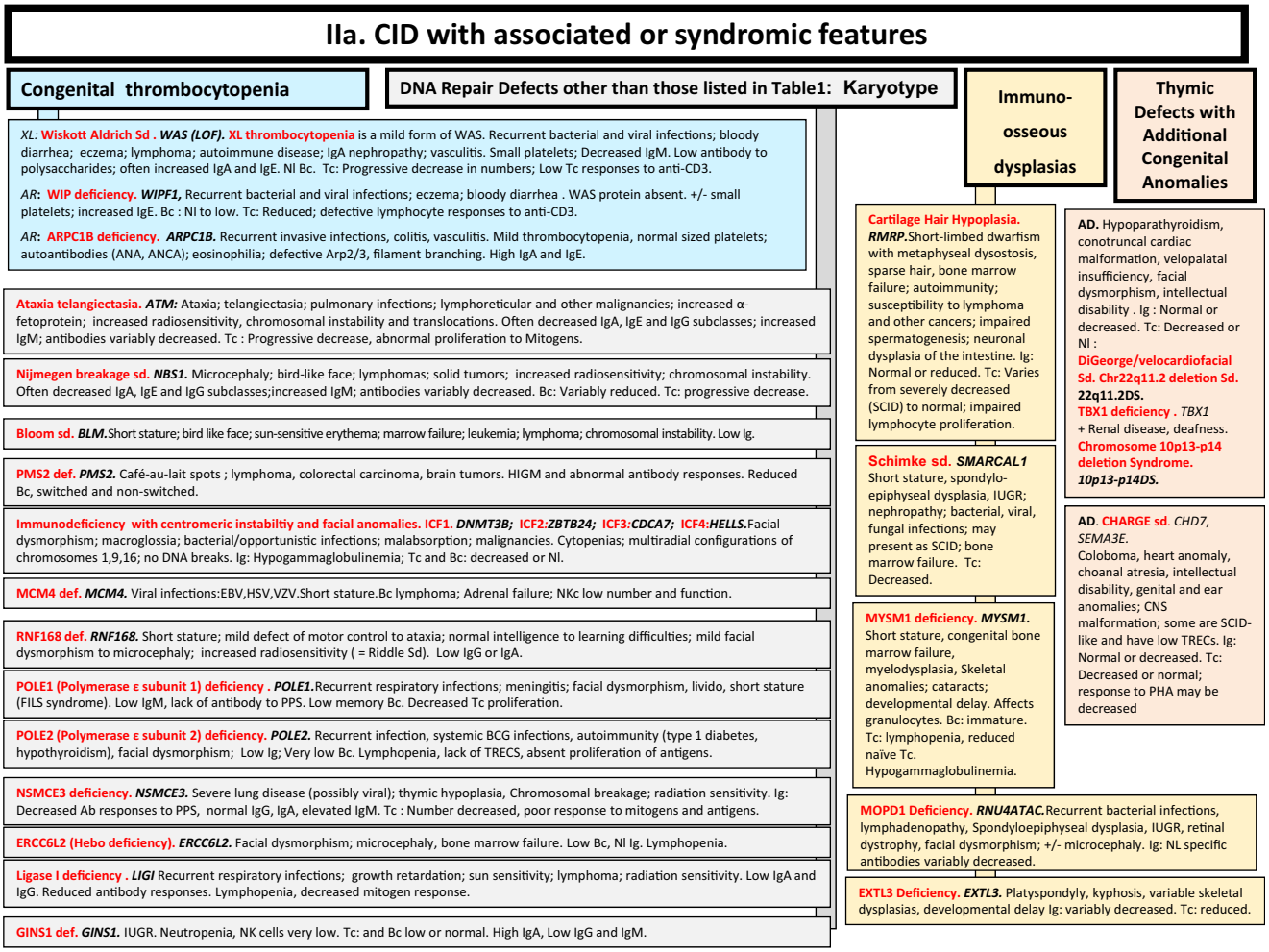

Fig. 2 **a**, **b** CID with associated or syndromic features. Ab: antibody; AD: autosomal dominant transmission; ANA: anti-nuclear antibodies; ANCA: anti-neutrophil cytoplasm antibodies; AR: autosomal recessive transmission; Bc: B cells; BCG: Bacillus Calmette-Guerin; BCR: B cell receptor; CD: cluster of differentiation; 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; Ig: immunoglobulins; IUGR: intrauterine growth retardation; LOF: loss-of-function; MDS: myelodysplasia; Nl: normal; NK: natural killer; PHA: phytohemagglutinin; PPS: polysaccharides; SCID: severe combined immunodeficiency; sd: syndrome; Tc: T cells; TCR: T cell receptor; TREC: T cell receptor excision circle; XL: X-linked transmission

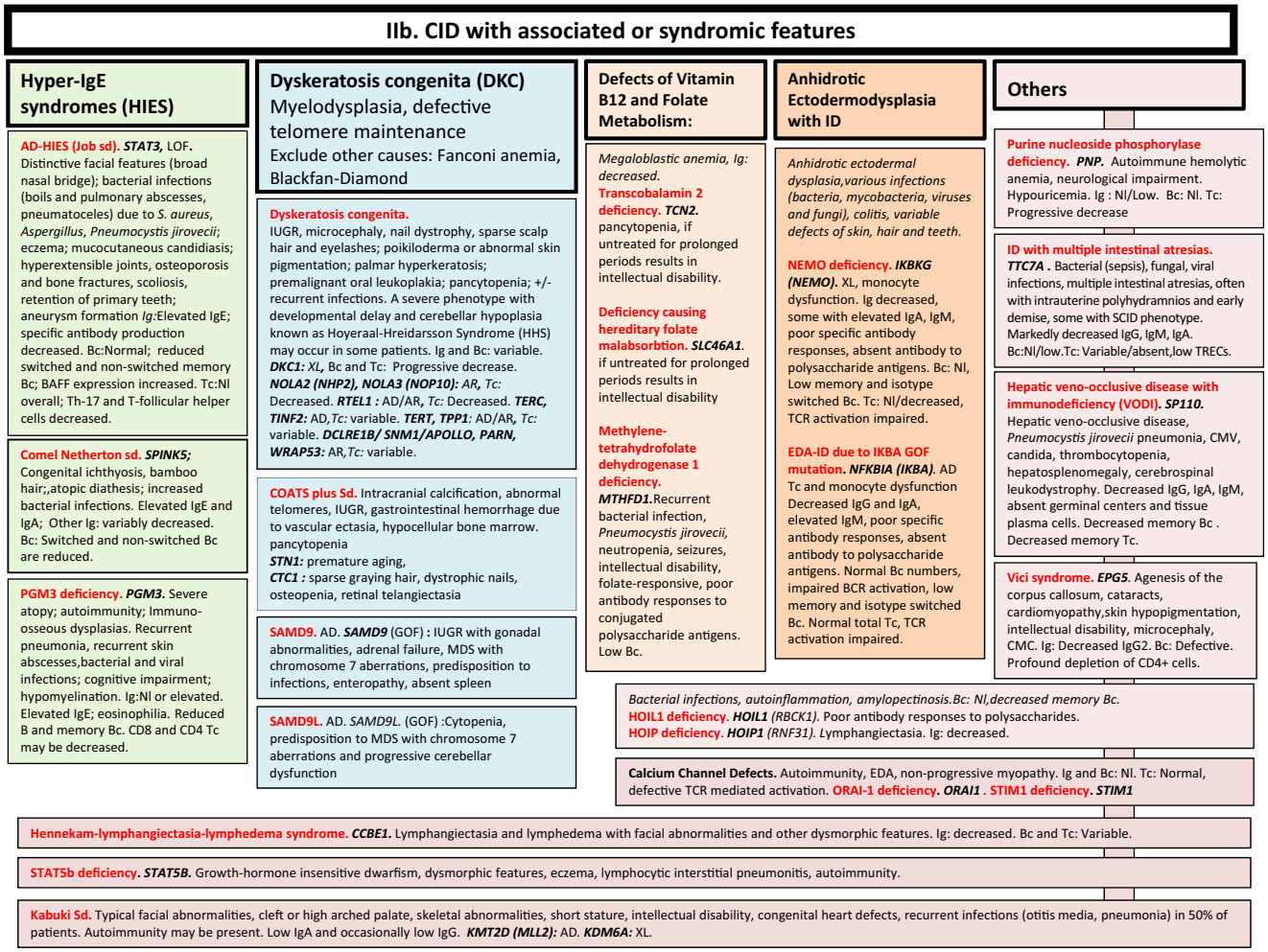

Fig. 2 (continued)

III. Predominantly Antibody deficiencies, a: Hypogammaglobulinemia

Serum Immunoglobulin Assays : IgG, IgA, IgM, IgE

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)

B 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

PI3KR1 def. *PIK3R1.* ProBc: Decreased

AD
E47 transcription factor def. *TCF3.*

B >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

AD. Severe bacterial infections; EBV susceptibility.
PIK3CD mutation (GOF). *PIK3CD GOF*. Decreased pro-Bc.
PIK3R1 deficiency (LOF). *PIK3CD*. Pro-Bc present and low memory Bc.

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

CD81 deficiency. *CD81*. Recurrent infections, may have glomerulonephritis.

TACI deficiency. *TNFRSF13B* *(TACI).* 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. Hypogammaglobulenia, absent IgA.

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

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

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

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

NFKB1 deficiency. *NFKB1*. AD. Recurrent sinopulmonary infections, COPD, EBV proliferation, autoimmunity, autoinflammation. Ig normal or low, Bc low or normal, low memory Bc.

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

IKAROS deficiency. *IKZF1*. AD. Recurrent sinopulmonary infections. Low or normal Bc potentially reducing levels with age.

ATP6AP1 deficiency. *ATP6AP1*. XL. Hepatopathy, leukopenia, low copper. Leukopenia and hypogammagl.

III. Predominantly Antibody deficiencies. b: Other Antibody deficiencies

Serum Immunoglobulin Assays : IgG, IgA, IgM, IgE

Severe Reduction in Serum IgG and IgA with Nl/elevated IgM and Normal Numbers of Bc : Hyper IgM Syndromes

AID deficiency. *AICDA.*
Bacterial infections, enlarged lymph nodes and germinal centers.

UNG deficiency. *UNG.*
Enlarged lymph nodes and germinal centers.

INO80. *INO80* .
Severe bacterial infections.

MSH6. *MSH6* .
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 Nl Numbers of Bc

Selective IgA deficiency. *Unknown.*
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. 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.
May be asymptomatic. One or more IgG and/or IgA subclasses as well as IgE may be absent.

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

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

High Bc numbers due to constitutive NF-κB activation

CARD11 GOF .
CARD11. AD. BENTA syndrome

Splenomegaly,
lymphadenopathy,
poor vaccine responses.

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

Compliance with Ethical Standards

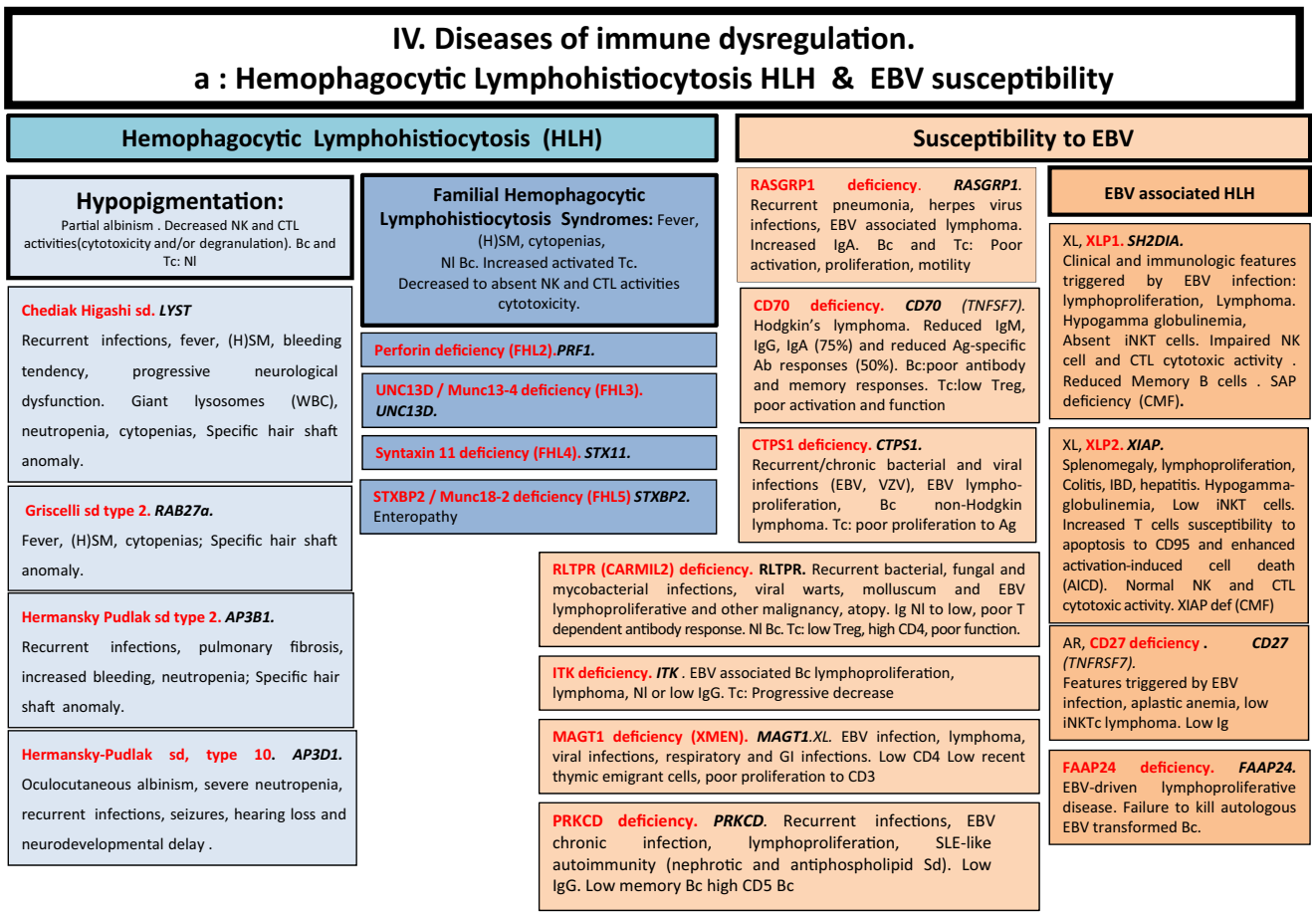

Fig. 4 Diseases of immune dysregulation. **a** Hemophagocytic lymphohistiocytosis. **b** Other diseases of immune dysregulation. Ab: antibody; AD: autosomal dominant transmission; Ag: antigen; ALPS: autoimmune lymphoproliferative syndrome; APS: autoimmune polyendocrinopathy syndrome; AR: autosomal recessive 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; HLH: hemophagocytic lymphohistiocytosis; (H)SM: (hepato)splenomegalia; 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 erythematous disease; Tc: T cells; TCR: T cell receptor; XL: X-linked transmission

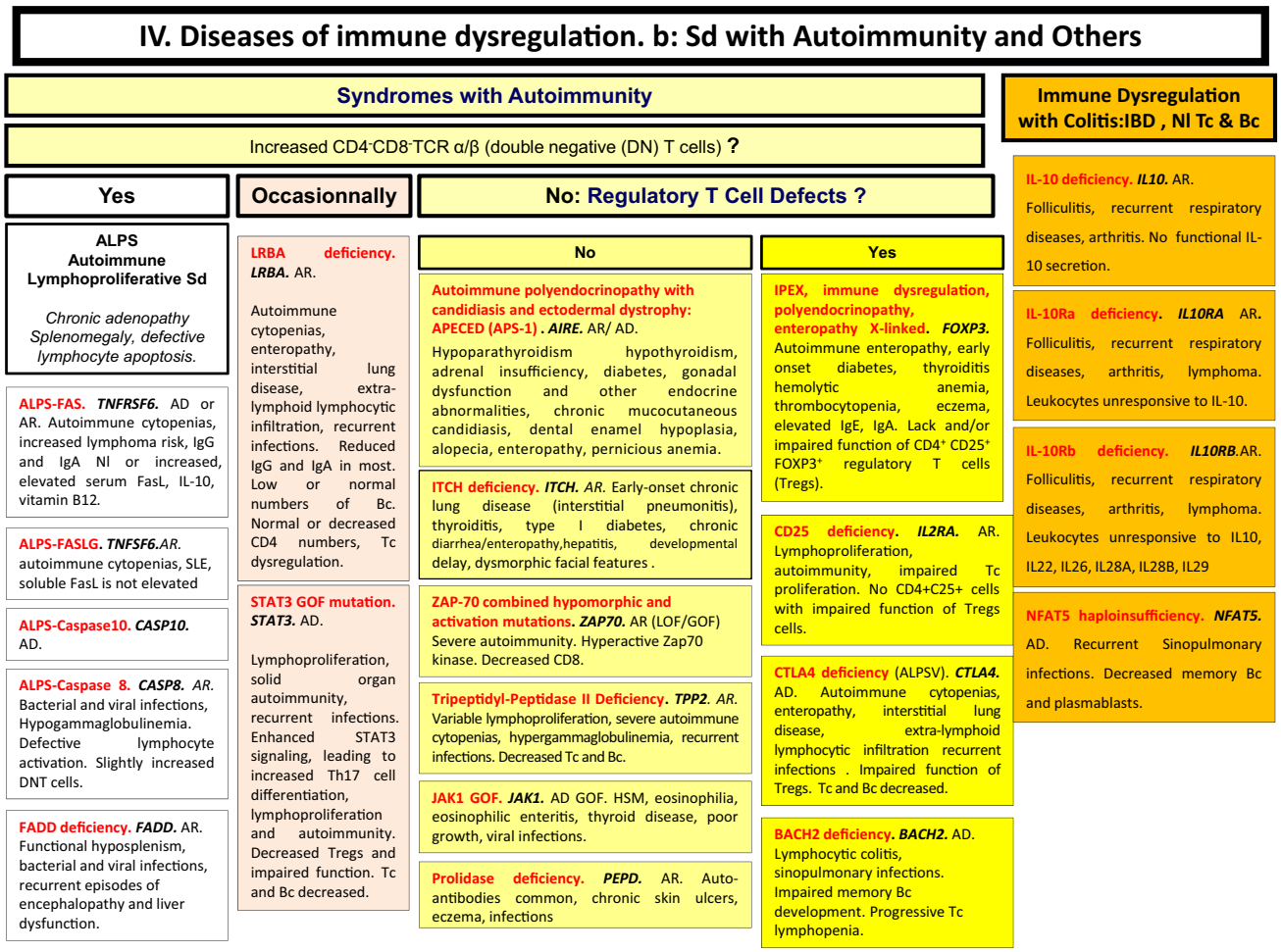

Fig. 4 (continued)

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; CMF: flow cytometry; CMML: chronic myelomonocytic leukemia; def: deficiency; DHR: dihydrorhodamine-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 (without anti-PMN)

Syndrome associated

Shwachman-Diamond syndrome. *SBDS*. *AR.* **_DNAJC21_.** *AR.*
Pancytopenia, exocrine pancreatic insufficiency, chondrodysplasia

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, O_2^- production.

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

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

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

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

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

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

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

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

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

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

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

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

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

X-linked neutropenia/ myelodysplasia WAS GOF. *WAS.* 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.

V. Congenital defects of phagocyte. b : Functional defects

Syndrome associated

Cystic fibrosis. *CFTR.* *AR.*
Pancreatic insufficiency, Respiratory infections, elevated sweat chloride

Papillon-Lefèvre . *CTSC.*
Periodontitis, palmoplantar hyperkeratosis

Localized juvenile periodontitis . *FPR1.*
Periodontitis only

β-Actin . *ACTB*
Mental retardation.

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

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.

LAD III. *FERMT3*
Severe bacterial infections and severe bleeding disorder; osteopetrosis (severe cases). Platelet aggregation assay.

No Syndrome associated: DHR assay (or NBT test)?

Normal

GATA2 def (MonoMac sd) . *GATA2,* AD.
Susceptibility to Mycocbacteria, Papilloma Viruses, Histoplasmosis, Lymphedema. Pulmonary alveolar proteinosis, myelodysplasia/AML/ CMML . Monocytopenia. Low NK.

Specific granule deficiency. *C/EBPE.*
Bilobed nuclei

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

Granulomas obstructing respiratory, urinary or gastrointestinal tracts. Inflammatory bowel disease (Crohn's like disease) and perianal disease : up to 30 %

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 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

Rac 2 def . *RAC2.*
Poor wound healing. LAD phenotype.

G6PD def Class I. *G6PD.*
Reduced DHR. Infections.

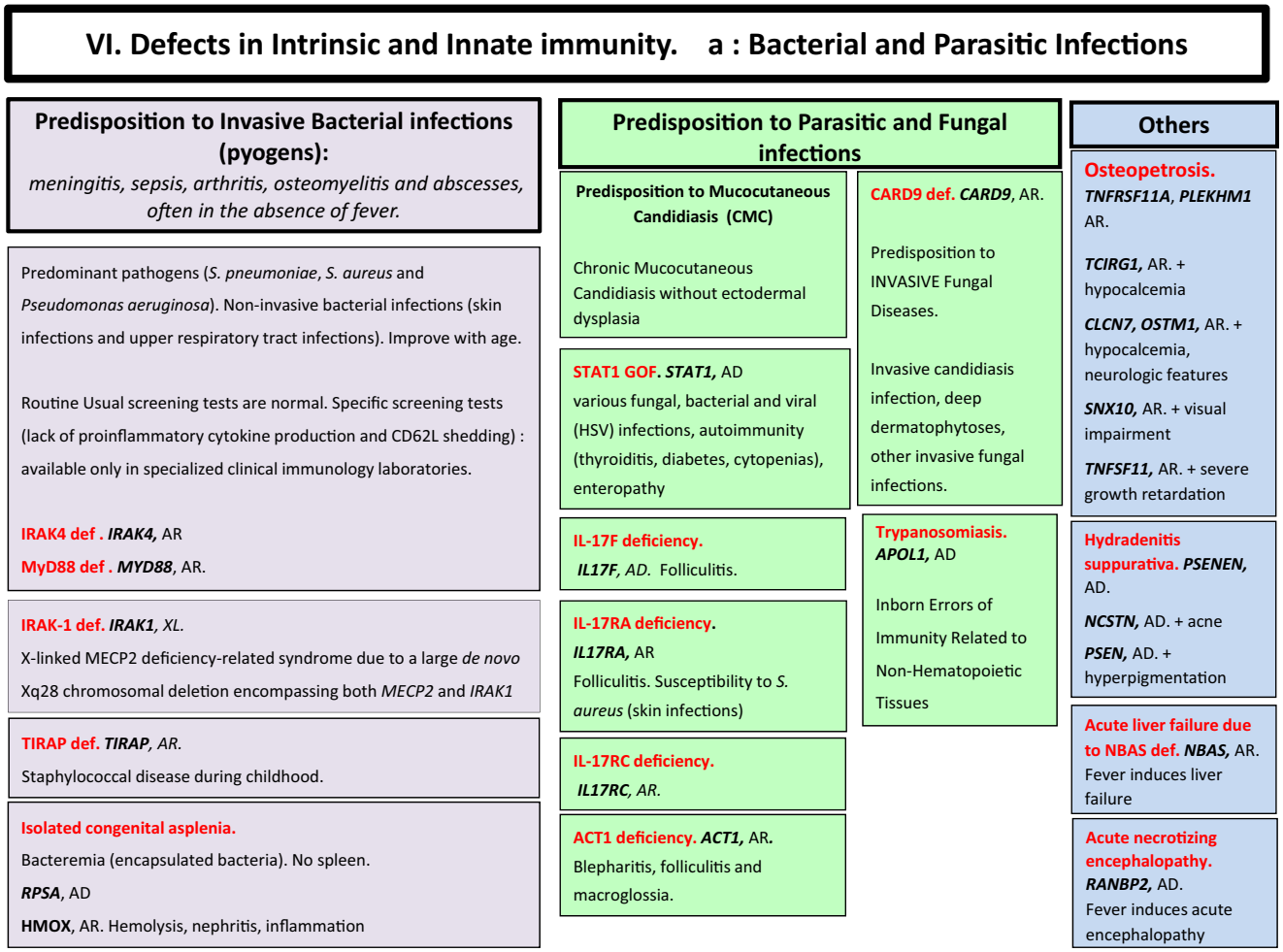

Fig. 6 Defects in intrinsic and innate immunity. **a** Bacterial and parasitic infections. **b** MSMD and viral infection. AD: autosomal dominant transmission; AR: autosomal recessive transmission; BCG: Bacillus Calmette-Guerin; CD: cluster of differentiation; CMC: chronic mucocutaneous candidiasis; 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

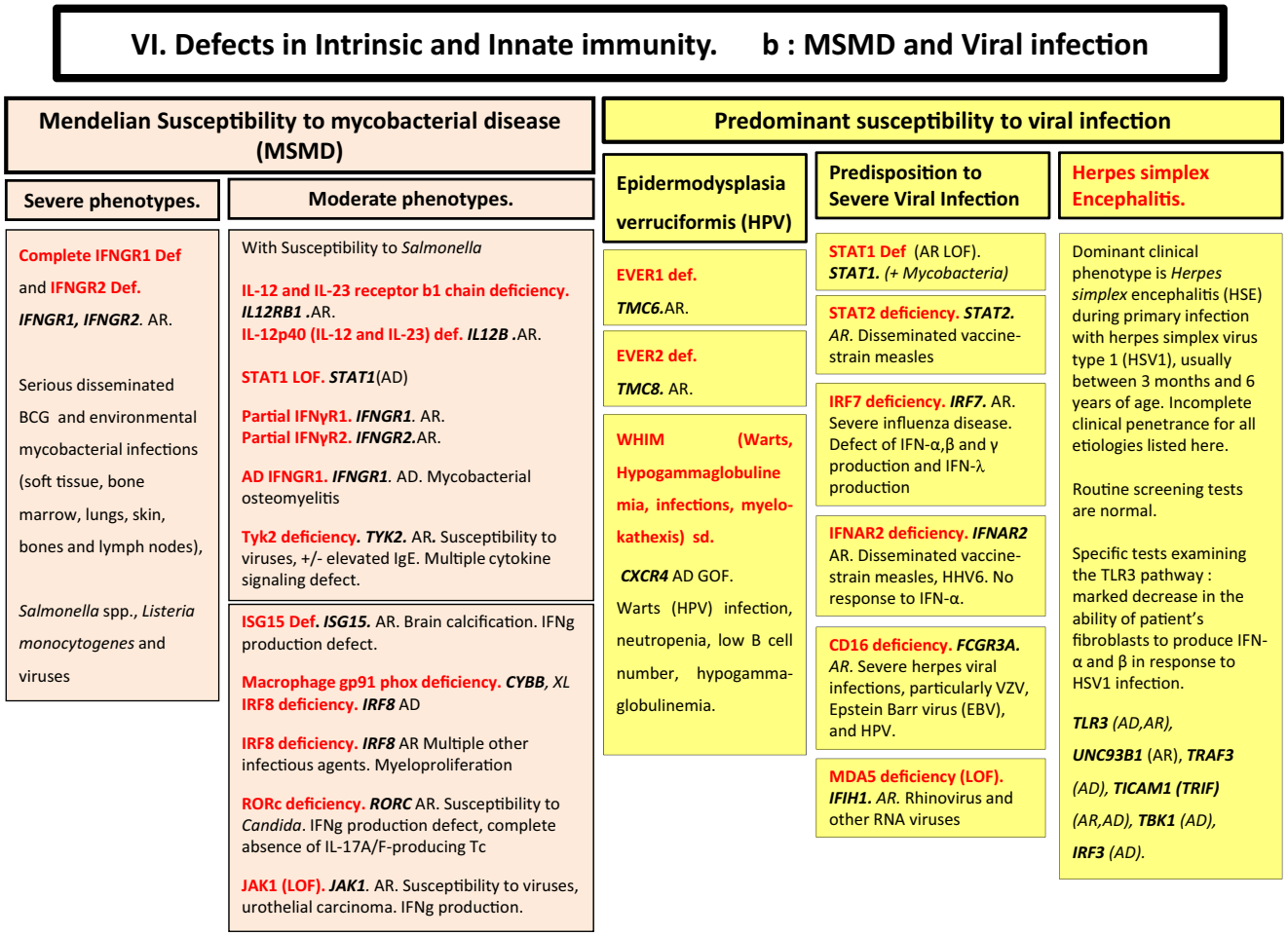

Fig. 6 (continued)

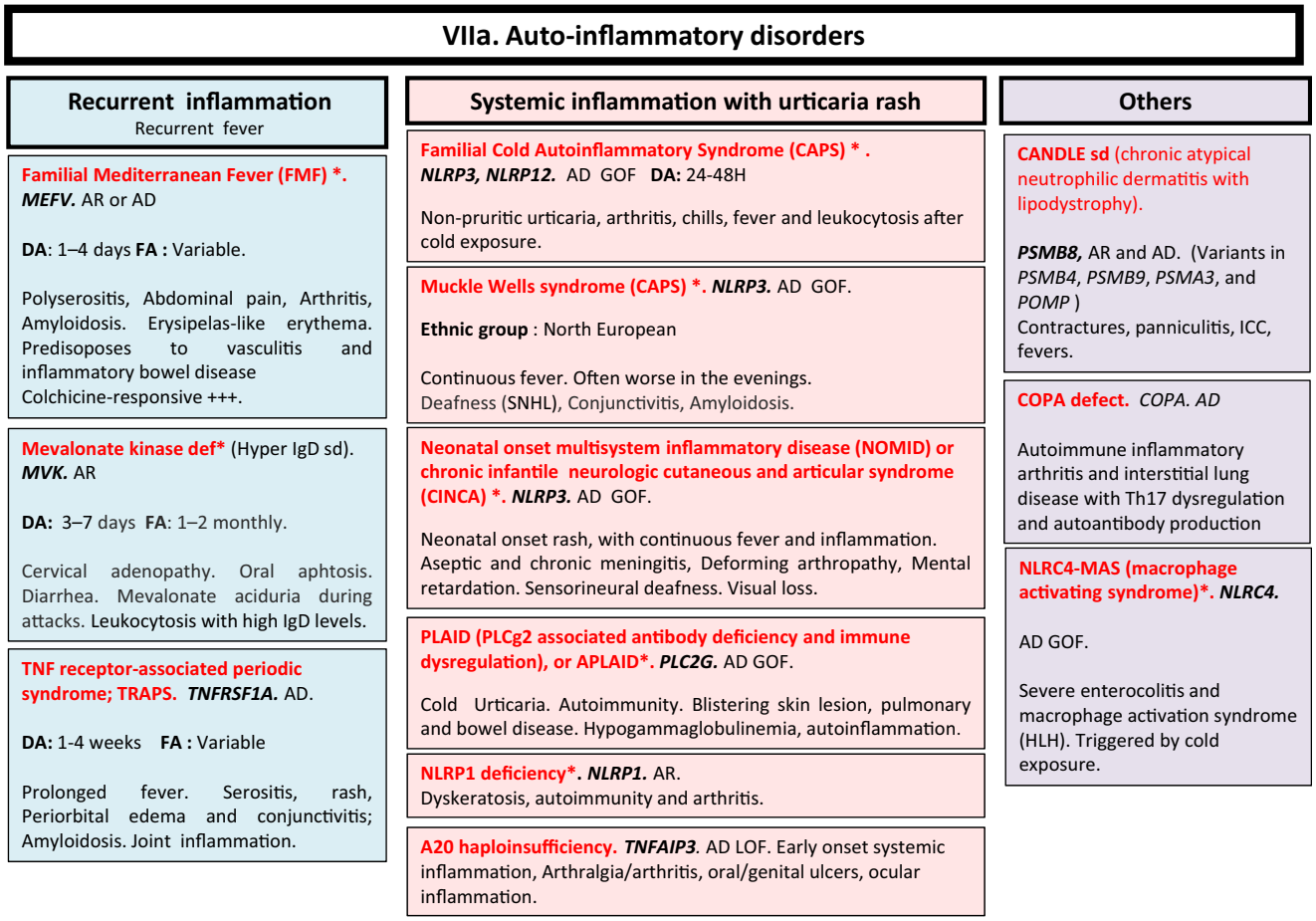

Fig. 7 **a**, **b** Autoinflammatory disorders. *Diseases affecting the inflammasome. AD: autosomal dominant transmission; AR: autosomal recessive transmission; BSN: bilateral striatal necrosis; CAPS: cryopirin-associated periodic syndrome; DA: duration of inflammation episode; FA: frequency of inflammation episode; FCL: familial chilblain lupus; GOF: gain-of-function; HLH: hemophagocytic lymphohistiocytosis; HSM: hepatosplenomegalia; 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

Pyogenic sterile arthritis, pyoderma gangrenosum, acne (PAPA) syndrome, hyperzincemia and hyper-calprotectinemia. *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

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 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)

Spondyloenchondro-dysplasia with immune dysregulation (SPENCD). *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.

Fig. 7 (continued)

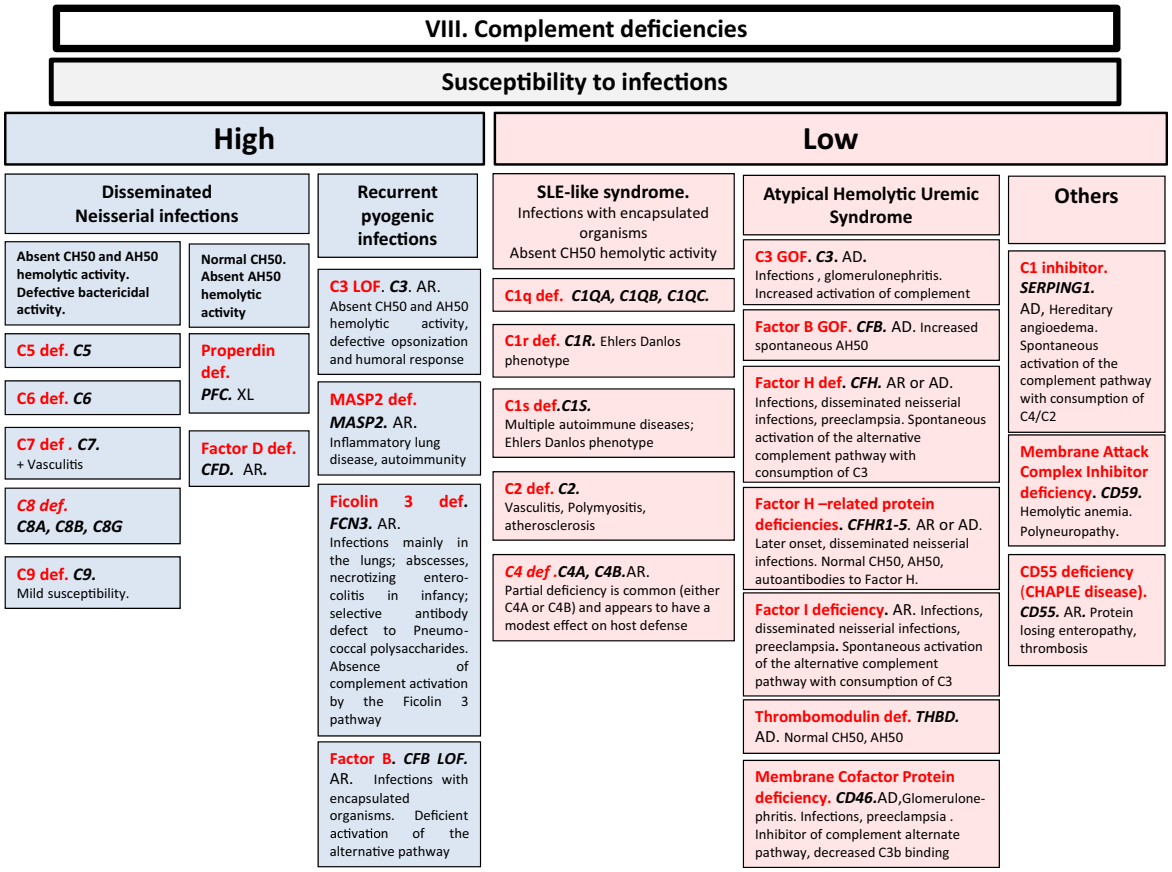

Fig. 8 Complement deficiencies. AD: autosomal dominant transmission; AH50: alternate pathway hemolytic activity; AR: autosomal recessive transmission; CH50: complement hemolytic activity; def: deficiency; LOF: loss-of-function; sd: syndrome; SLE: systemic lupus erythematosus; XL: X-linked transmission

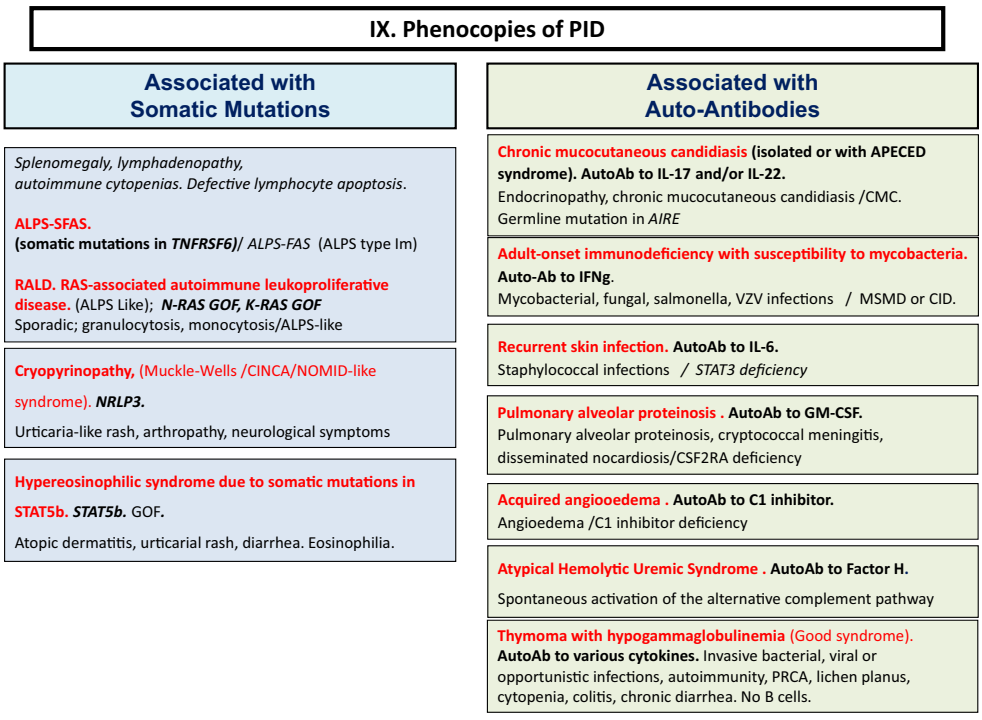

Fig. 9 Phenocopies of PID. ALPS: autoimmune lymphoproliferative syndrome; AutoAb: auto-antibodies; CID: combined immunodeficiency; CMC: chronic mucocutaneous candidiasis; GOF: gain-of-function; MSMD: Mendelian susceptibility to mycobacterial disease; PRCA: pure red cell aplasia

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

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, Benhsaien 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, Benhsaien I, El Bakkouri J, Bousfiha AA. Primary immunodeficiency classification on smartphone. J Clin Immunol. 2017;37(1):1–2.