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ARTICLE

The 2024 update of IUIS phenotypic classification of human inborn errors of immunity

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Here, we report the 2024 update of the phenotypic classification by the International Union of Immunological Societies (IUIS) expert committee (EC) on inborn errors of immunity (IEI), which accompanies and complements the 2024 genotypic classification. The aim of this classification is to help diagnosis for clinicians at the bedside and focuses on clinical features and basic laboratory phenotypes of specific IEI. In this update, 559 IEI are described, including 67 novel monogenic defects and 2 new phenocopies. This phenotypic classification is presented in the form of decision trees when possible, with essential clinical or immunological phenotype entries.

Introduction

Human inborn errors of immunity (IEI) include a large group of disorders resulting from genetic defects that compromise innate and adaptive immunity, non-hematopoietic cell-mediated immunity, as well as immune regulation. They can be dominantly or recessively inherited, autosomal or X-linked, and with complete or incomplete penetrance of the clinical phenotype. Patients can present with increased susceptibility to a broad or narrow spectrum of infectious diseases, as well as autoimmune, autoinflammatory, allergic, and/or malignant diseases. The number of disorders being discovered is growing at an unprecedented rate since the development of next-generation sequencing, including not only rare but also common genetic defects (1). Progress in the molecular genetics and cellular immunology of IEI has resulted in the development of innovative, preventive, and therapeutic approaches (2).

In 2024, the International Union of Immunological Societies (IUIS) expert committee on IEI added 67 novel monogenic defects and 2 phenocopies in the classification (3). While most IEI are individually rare, as a group they represent a major cause of morbidity and mortality—particularly so in the case of childhood disease (4).

Since 2013, the IUIS IEI expert committee has periodically published an updated phenotypic classification of all these disorders, which facilitates the diagnosis of these conditions worldwide. Organized as diagnostic algorithms, this phenotypic classification was also adapted for smartphone applications (5).

Here, we report the 2024 update of the phenotypic classification of IEI reported and evaluated until June 2024. This decision tree–based process is aimed at physicians, regardless of their expertise in and knowledge of IEI. Its purpose is to guide

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the physician toward the most probable diagnosis based on the clinical and laboratory features of their patient.

Methodology

All disorders indexed in the 2024 update of the IUIS IEI classification (3) are included in phenotypic algorithms assigned to each of the 10 main groups/tables of the classification, except for phenocopies that were integrated in their respective phenotypic group. The same color was used for each group of similar conditions. Given the exponential number of diseases, several categories have been divided into two or three sub-figures to be more informative. New disorders or new genes causing a known disorder are highlighted with a red frame.

A new decision tree has been added in the first step to guide physician through the best fitted category based on the main clinical features (Fig. 1).

Disease names are presented in red (darker red for phenocopies) and genes in bold italic. The OMIM number for phenotype has been added and is preceded by a #. When no OMIM phenotype is available, an asterisk precedes the OMIM code for the gene.

An asterisk is added to highlight extremely rare disorders (<10 reported cases or kindreds to the best of our knowledge). However, the reader should keep in mind that some genes have only been very recently described and that the true prevalence of individual IEIs is unknown. A double asterisk indicates that only a single case or single kindred affected by the indicated genotype has been reported to date. In these cases, it is difficult to confirm that the observed phenotype would be reproducible in other patients carrying the same defect or if it is an atypical presentation.

Results

Algorithms for the 2024 update of IUIS phenotypic classification are presented in 21 figures (Figs. 1–21).

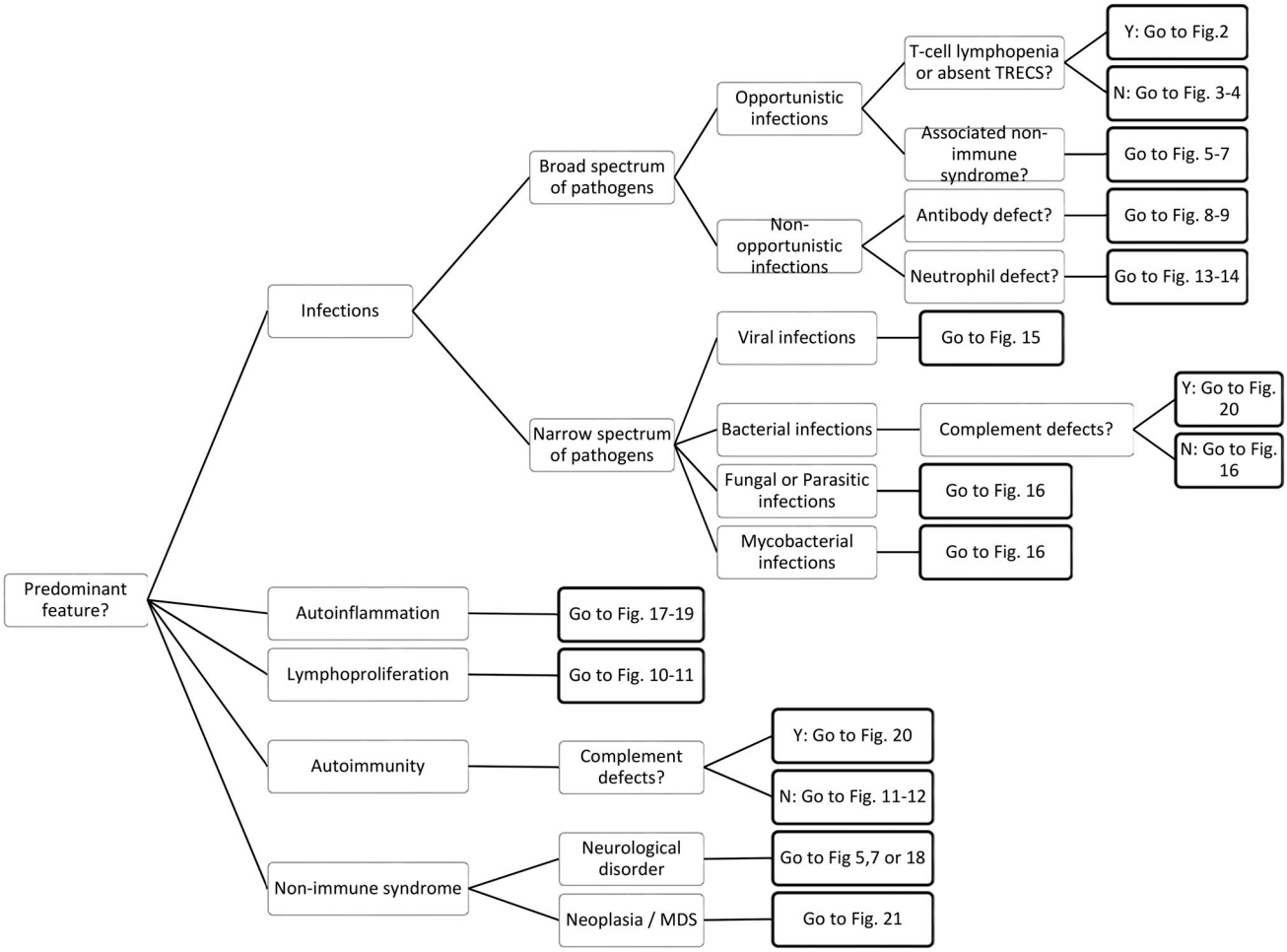

Figure 1. **Decision tree orienting through IEI classification categories.** MDS: myelodysplasia; N: No; TRECS: T cell receptor excision circles; Y: Yes. A searchable PDF file containing all figures in this article can be found under the "Supplements" tab.

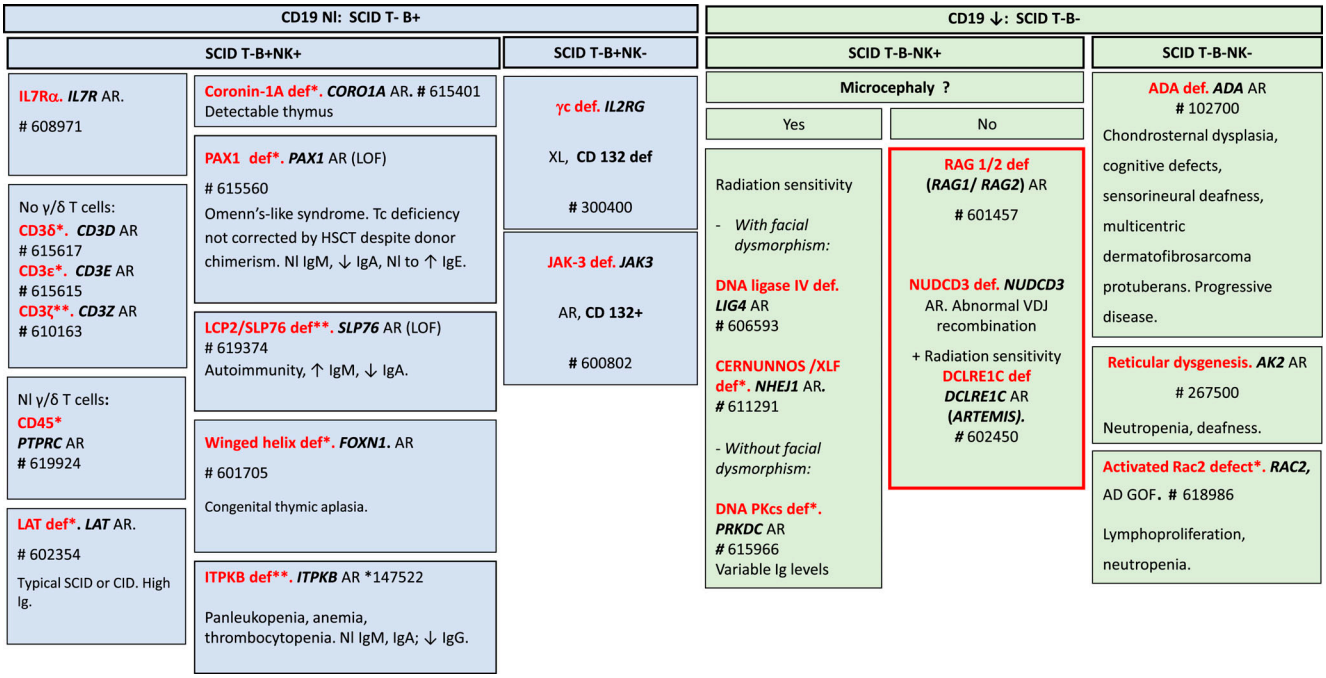

Figure 2. **Immunodeficiencies affecting cellular and humoral immunity.** Severe combined immunodeficiencies (SCID) defined by T cell lymphopenia. *T cell lymphopenia in SCID is defined by $CD3^+$ T cells <300/µl. Ab: antibody; AD: autosomal dominant inheritance; ADA: adenosine deaminase; Adp: adenopathies; Ag: antigen; AR: autosomal recessive; Bc: B cells; CD: cluster of differentiation; CID: combined immunodeficiency; def: deficiency; GOF: gain-of-function mutation; HSCT: hematopoietic stem cell transplantation; Ig: immunoglobulins; LOF: loss-of-function mutation; Nl: normal; NK: natural killer cells; SCID: severe combined immunodeficiency; Tc: T cells; TCR: T cell receptor; TREC: T cell receptor excision circles; XL: X-linked inheritance. A searchable PDF file containing all figures in this article can be found under the "Supplements" tab.

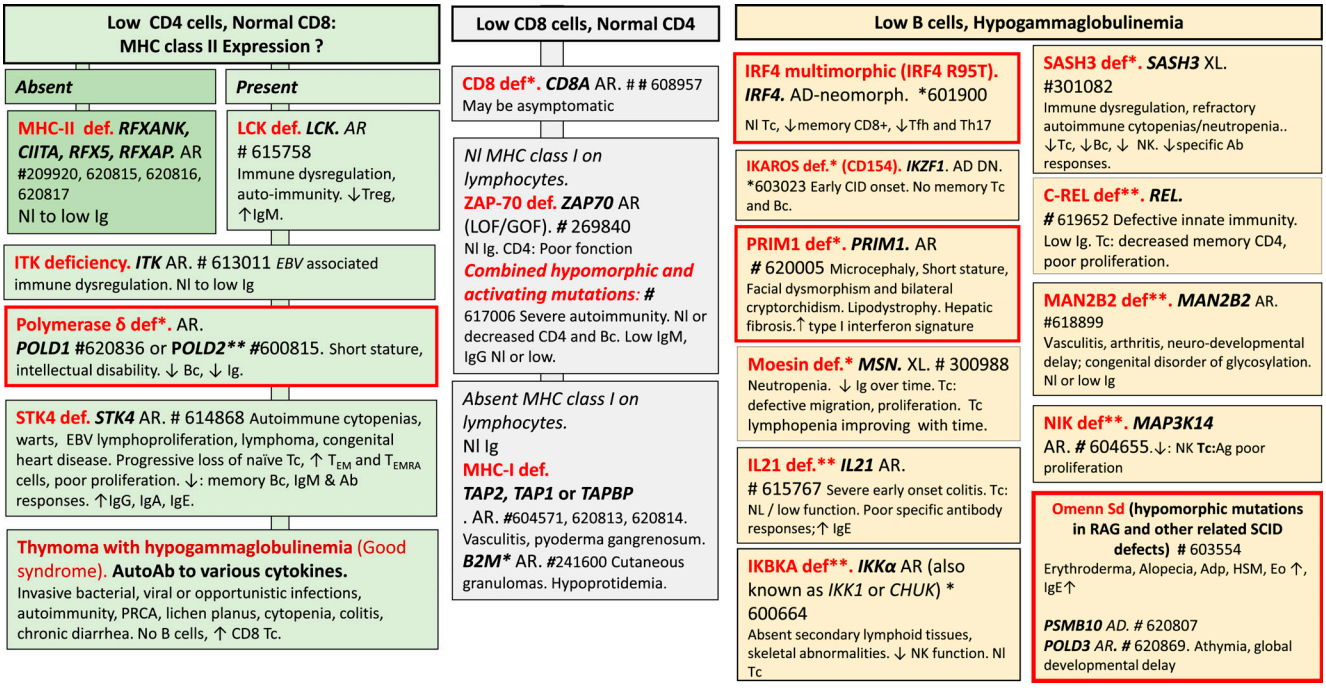

Figure 3. **Immunodeficiencies affecting cellular and humoral immunity.** Combined immunodeficiencies (2). *T cell lymphopenia in SCID is defined by $CD3^+$ T cells <300/µl. Ab: antibody; AD: autosomal dominant inheritance; AD DN: autosomal dominant inheritance with dominant negative effect; Adp: adenopathies; Ag: antigen; AR: autosomal recessive; β2m: β-2 microglobulin; Bc: B cells; CD: cluster of differentiation; CID: combined immunodeficiency; def: deficiency; EBV: Epstein-Barr virus; Eo: eosinophils; GOF: gain-of-function mutation; HSM: hepatosplenomegaly; Ig: immunoglobulins; LOF: loss-of-function mutation; MHC: major histocompatibility complex; Nl: normal; NK: natural killer cells; PRCA: pure red cell aplasia; SCID: severe combined immunodeficiency; Tc: T cells; T_{EM}: effector memory T cells; T_{EMRA}: effector memory T cells expressing CD45RA; Tfh: follicular helper T cells; Treg: regulatory T cells; XL: X-linked inheritance. A searchable PDF file containing all figures in this article can be found under the "Supplements" tab.

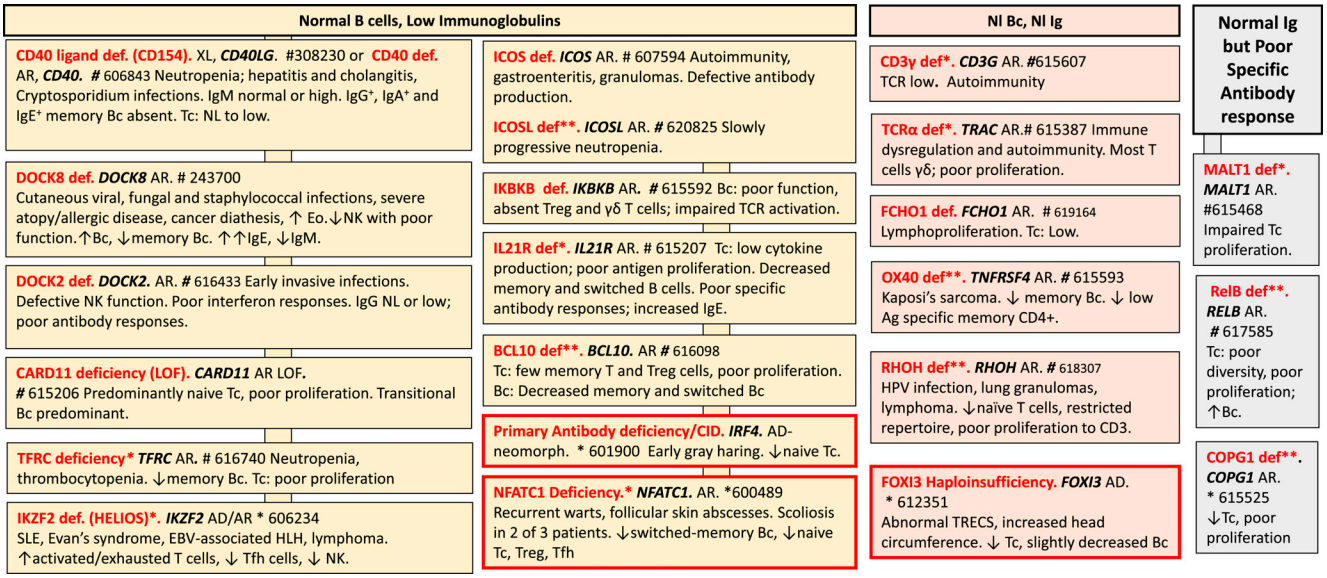

Figure 4. **Immunodeficiencies affecting cellular and humoral immunity.** Combined immunodeficiencies (3). *T cell lymphopenia in SCID is defined by $CD3^+$ T cells <300/μl. Ab: antibody; AD: autosomal dominant inheritance; Ag: antigen; AR: autosomal recessive; Bc: B cells; CD: cluster of differentiation; CID: combined immunodeficiency; def: deficiency; Eo: eosinophils; HLH: hemophagocytic lymphohistiocytosis; HPV: human papillomavirus; Ig: immunoglobulins; LOF: loss-of-function mutation; Nl: normal; NK: natural killer cells; SCID: severe combined immunodeficiency; SLE: systemic lupus erythematosus; Tc: T cells; TCR: T cell receptor; Tfh: follicular helper T cells; TREC: T cell receptor excision circles; XL: X-linked inheritance. A searchable PDF file containing all figures in this article can be found under the "Supplements" tab.

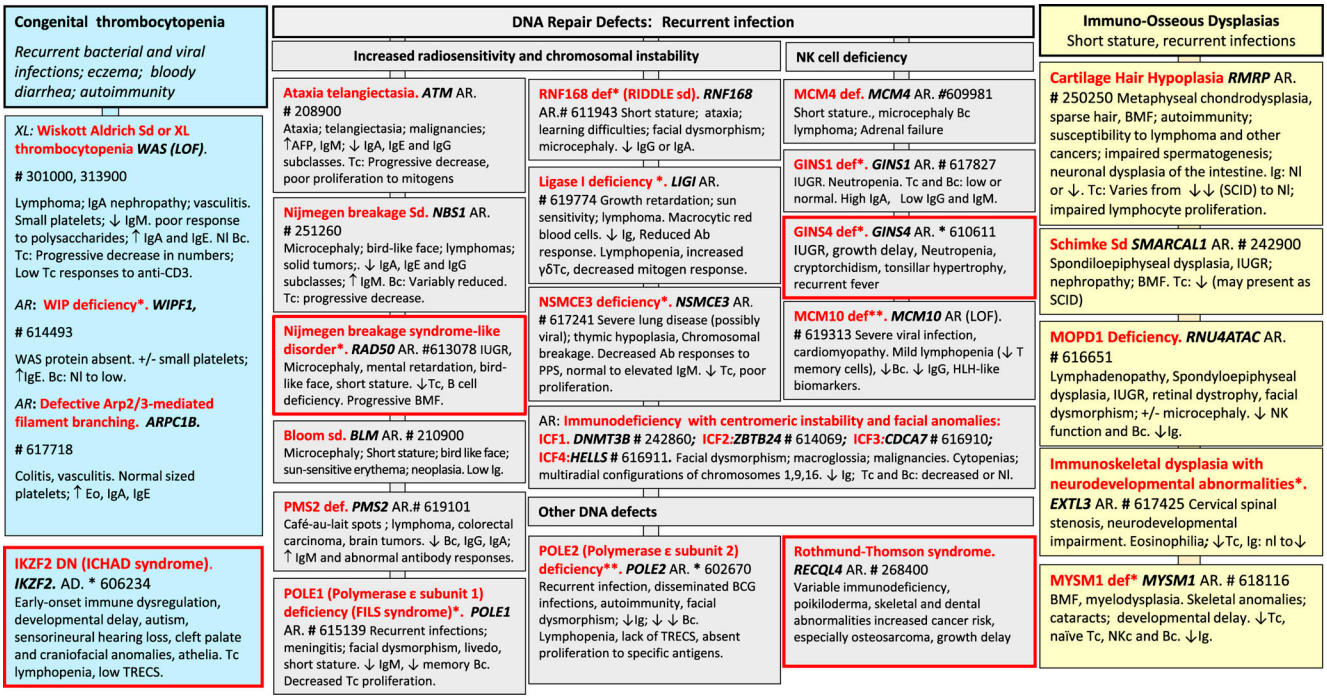

Figure 5. **CID with associated or syndromic features** (2). Ab: antibody; AD: autosomal dominant inheritance; AFP: α-fetoprotein; AR: autosomal recessive inheritance; Bc: B cells; BCG: Bacillus Calmette–Guerin; BMF: bone marrow failure; CD: cluster of differentiation; CID: combined immunodeficiency of T and B cells; def: deficiency; DNA: deoxyribonucleic acid; Eo: eosinophils; GOF: gain-of-function; HLH: hemophagocytic lymphohistiocytosis; FILS: facial dysmorphism, immunodeficiency, livedo and short stature; Ig: immunoglobulins; IUGR: intrauterine growth retardation; LOF: loss-of-function; Nl: normal; NK: natural killer; PPS: polysaccharides; SCID: severe combined immunodeficiency; sd: syndrome; Tc: T cells; TREC: T cell receptor excision circle; XL: X-linked inheritance. A searchable PDF file containing all figures in this article can be found under the "Supplements" tab.

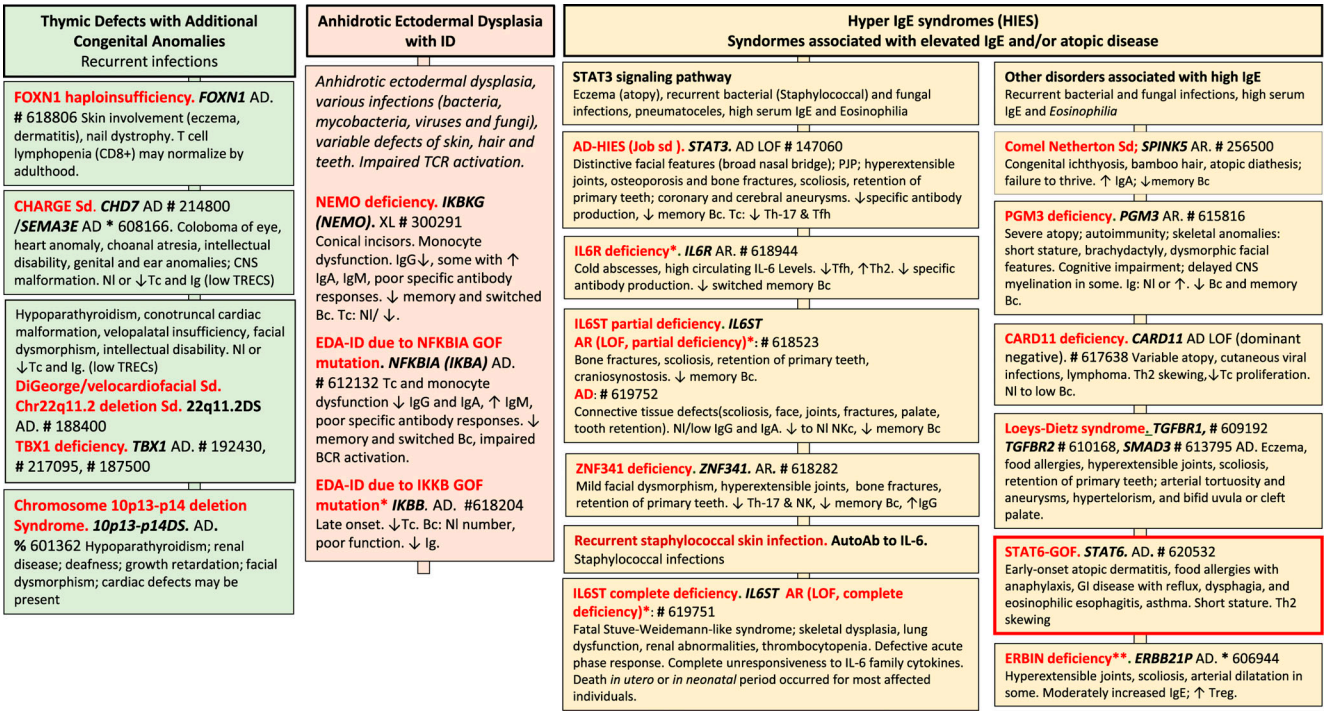

Figure 6. **CID with associated or syndromic features** (3). Ab: antibody; AD: autosomal dominant inheritance; AR: autosomal recessive inheritance; Bc: B cells; BCR: B cell receptor; CD: cluster of differentiation; CID: combined immunodeficiency of T and B cells; CNS: central nervous system; def: deficiency; EDA: anhidrotic ectodermal dysplasia; GI: gastrointestinal; GOF: gain-of-function; HIES: hyper IgE syndrome; ID: immunodeficiency; Ig: immunoglobulins; IL-6: Interleukin-6; LOF: loss-of-function; NI: normal; NK: natural killer; PJP: *Pneumocystis jiroveci* pneumonia; sd: syndrome; Tc: T cells; TCR: T cell receptor; Tfh: follicular helper T cells; TREC: T cell receptor excision circle; Treg: regulatory T cells; XL: X-linked inheritance. A searchable PDF file containing all figures in this article can be found under the "Supplements" tab.

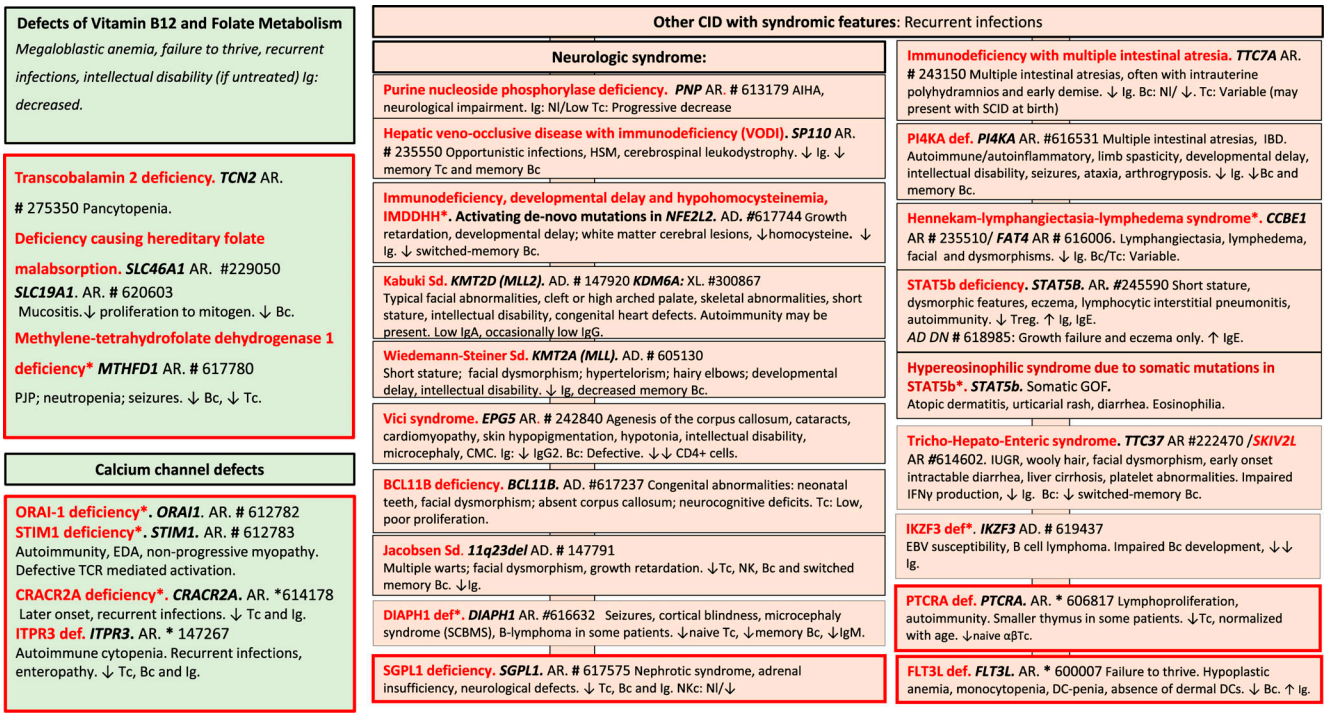

Figure 7. **CID with associated or syndromic features** (4). Ab: antibody; AD: autosomal dominant inheritance; AD DN: autosomal dominant inheritance with dominant negative effect; AIHA: autoimmune hemolytic anemia; AR: autosomal recessive inheritance; Bc: B cells; CD: cluster of differentiation; CID: combined immunodeficiency of T and B cells; DC: dendritic cells; def: deficiency; EBV: Epstein-Barr virus; EDA: anhidrotic ectodermal dysplasia; GOF: gain-of-function; Ig: immunoglobulins; IUGR: intrauterine growth retardation; LOF: loss-of-function; NI: normal; NK: natural killer; PJP: *Pneumocystis jiroveci* pneumonia; SCID: severe combined immunodeficiency; sd: syndrome; Tc: T cells; TCR: T cell receptor; Treg: regulatory T cells; XL: X-linked inheritance. A searchable PDF file containing all figures in this article can be found under the "Supplements" tab.

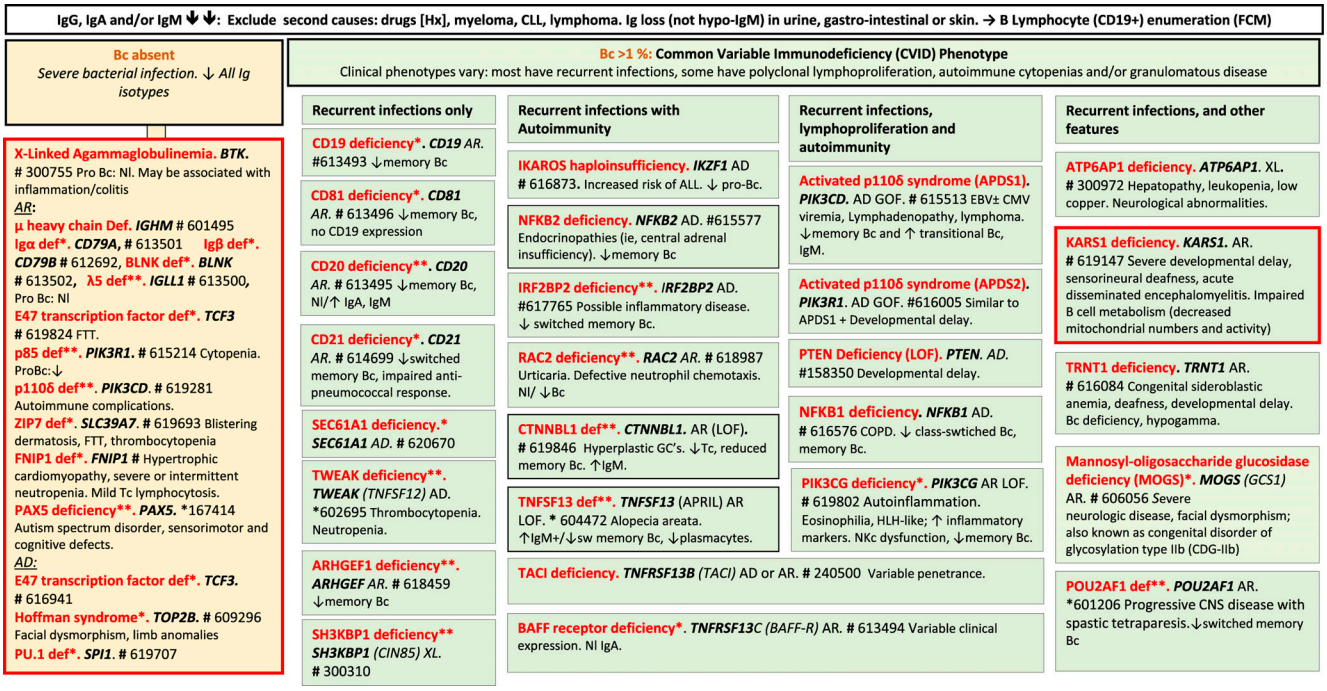

Figure 8. **Predominantly antibody deficiencies. Hypogammaglobulinemias.** AD: autosomal dominant inheritance; ALL: acute lymphoblastic leukemia; AR: autosomal recessive inheritance; Bc: Bcells; CD: cluster of differentiation; CLL: chronic lymphocytic leukemia; CMV: cytomegalovirus; CNS: central nervous system; COPD: chronic obstructive pulmonary disease; def: deficiency; EBV: Epstein-Barr virus; FCM: flow cytometry; FTT: failure to thrive; GC: germinal centers; GOF: gain-of-function; HLH: hemophagocytic lymphohistiocytosis; Hx: patient history; Ig: immunoglobulins; NKc: natural killer cells; Nl: normal; sw: switched; Tc: T cells; XL: X-linked inheritance. A searchable PDF file containing all figures in this article can be found under the "Supplements" tab.

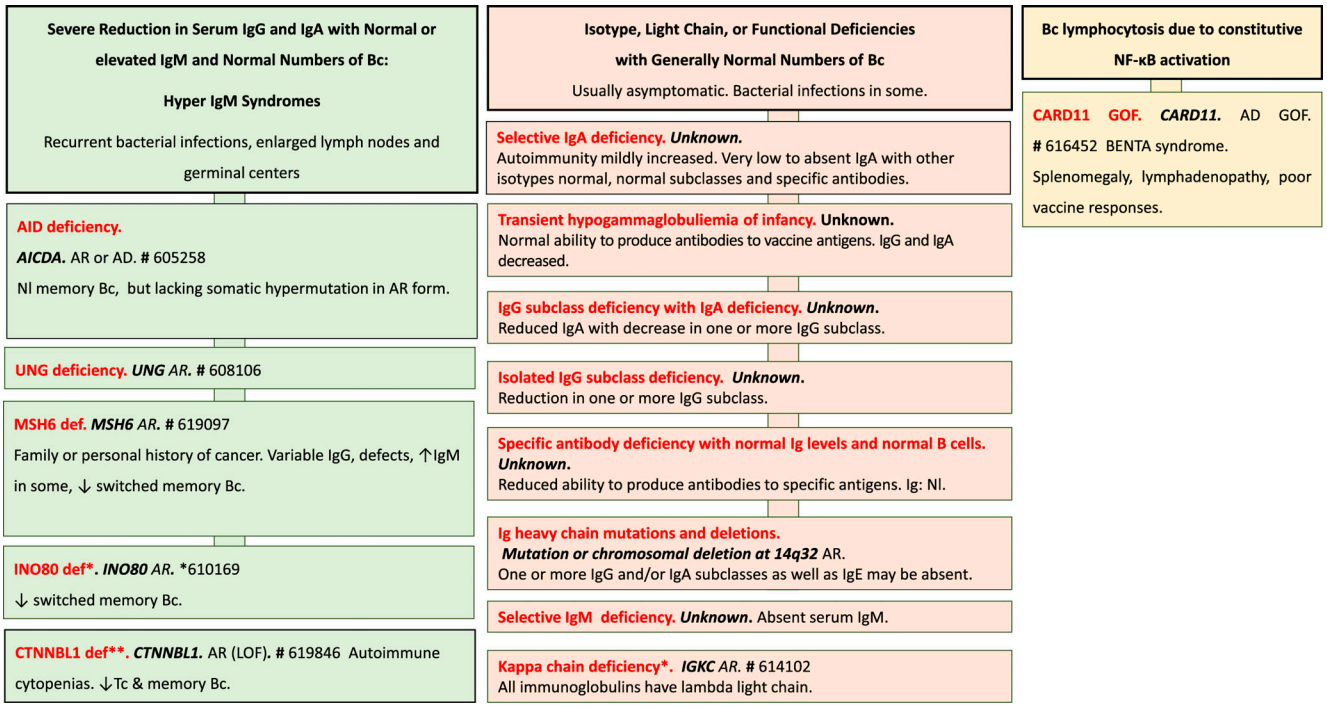

Figure 9. **Predominantly antibody deficiencies. Other antibody deficiencies.** AD: autosomal dominant inheritance; AR: autosomal recessive inheritance; Bc: Bcells; BENTA: B cell expansion with NF-κB and T cell anergy; CD: cluster of differentiation; def: deficiency; GOF: gain-of-function; Ig: immunoglobulins; NKc: natural killer cells; Nl: normal; Tc: T cells; XL: X-linked inheritance. A searchable PDF file containing all figures in this article can be found under the "Supplements" tab.

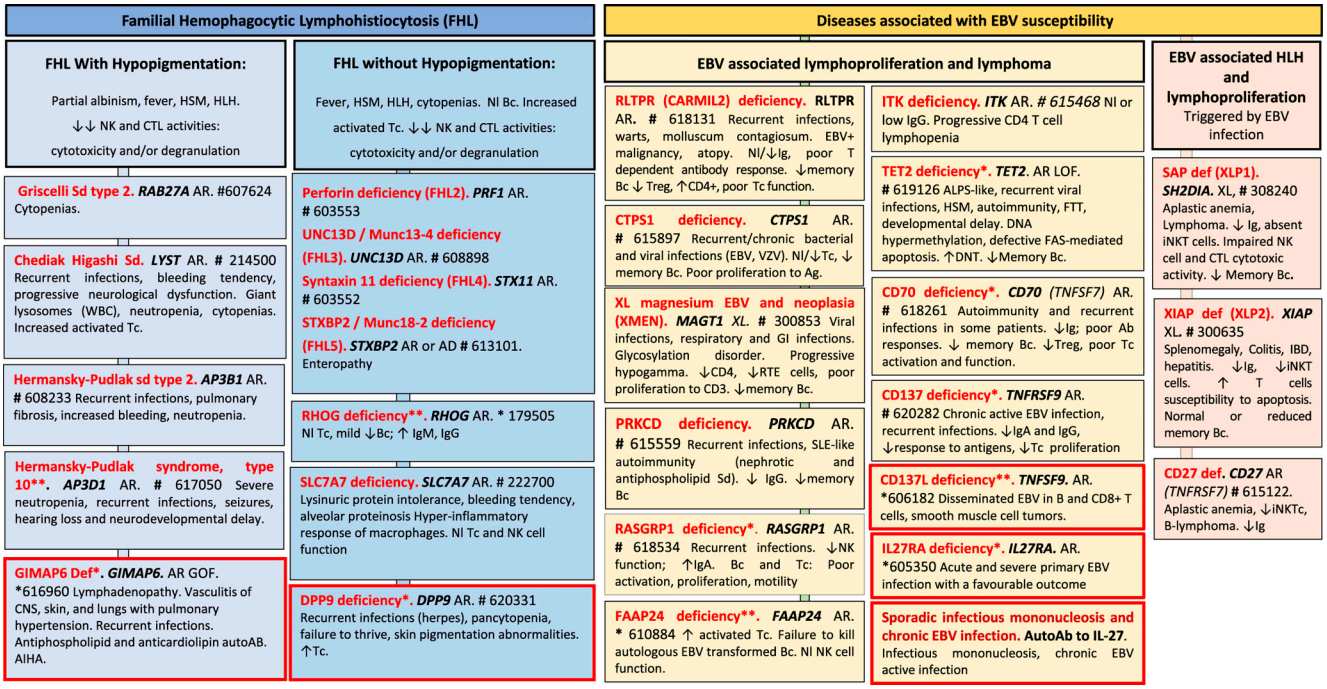

Figure 10. **Diseases of immune dysregulation** (2). Hemophagocytic lymphohistiocytosis and EBV susceptibility. Ab: antibody; AD: autosomal dominant inheritance; Ag: antigen; AIHA: autoimmune hemolytic anemia; ALPS: autoimmune lymphoproliferative syndrome; AR: autosomal recessive inheritance; Bc: B cells; CD: cluster of differentiation; CNS: central nervous system; CTL: cytotoxic T lymphocytes; def: deficiency; DNT: double-negative T cells; EBV: Epstein-Barr virus; FHL: familial hemophagocytic lymphohistiocytosis; FTT: failure to thrive; GI: gastrointestinal; GOF: gain-of-function; HLH: hemophagocytic lymphohistiocytosis; (H)SM: (hepato)splenomegaly; IBD: inflammatory bowel disease; Ig: immunoglobulin; LOF: loss-of-function; iNKT: invariant NK T cells; NK: natural killer cells; Nl: normal; RTE: recent thymic emigrant; sd: syndrome; Tc: T cells; Treg: regulatory T cells; VZV: varicella zona virus; WBC: white blood cells; XL: X-linked inheritance. A searchable PDF file containing all figures in this article can be found under the "Supplements" tab.

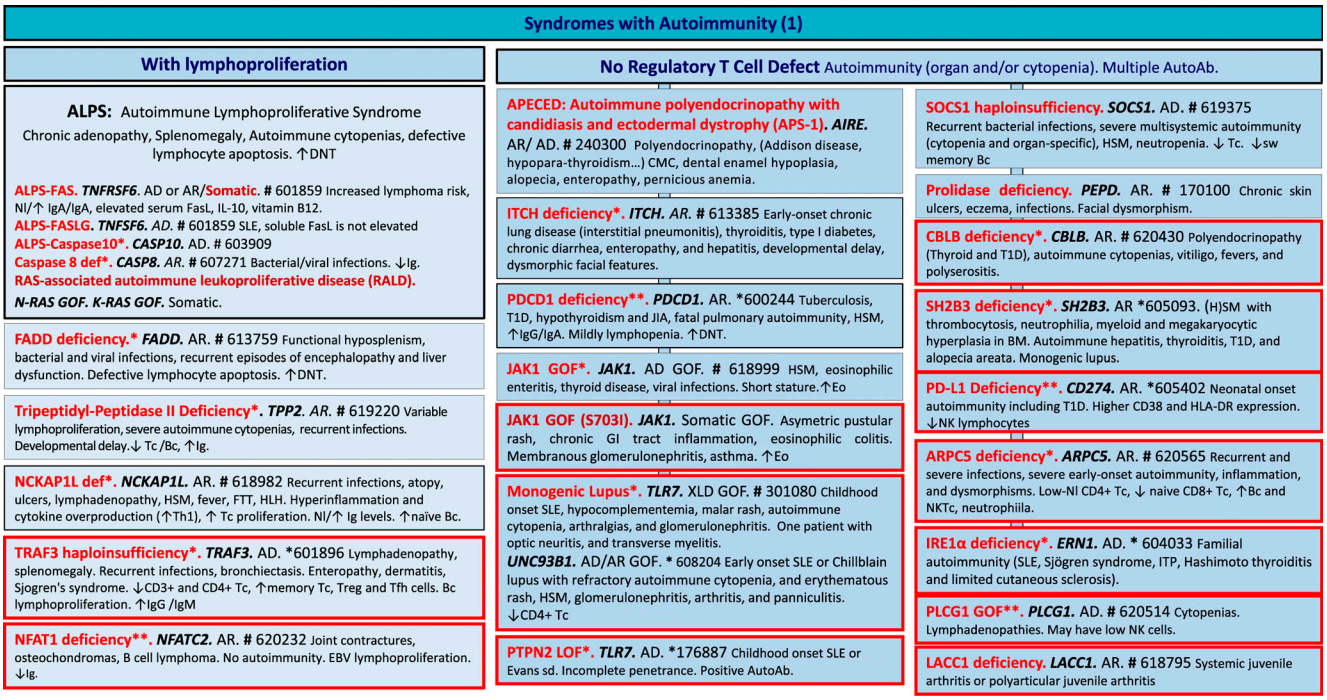

Figure 11. **Diseases of immune dysregulation** (3). Syndromes with autoimmunity and others. AD: autosomal dominant inheritance; ALPS: autoimmune lymphoproliferative syndrome; AR: autosomal recessive inheritance; Bc: B cells; BM: bone marrow; CD: cluster of differentiation; CMC: chronic mucocutaneous

candidiasis; def: deficiency; DNT: double-negative T cells; EBV: Epstein-Barr virus; Eo: eosinophils; FTT: failure to thrive; GI: gastrointestinal; GOF: gain-of-function; HLH: hemophagocytic lymphohistiocytosis; (H)SM: (hepato)splenomegaly; Ig: immunoglobulin; IL-10: interleukin-10; ITP: immune thrombocytopenic purpura; JIA: juvenile idiopathic arthritis; LOF: loss-of-function; NK: natural killer cells; NKTc: NK T cells; Nl: normal; sd: syndrome; SLE: systemic lupus erythematous disease; T1D: type 1 diabetes; Tc: T cells; Tfh: follicular helper T cells; Treg: regulatory T cells; XL: X-linked inheritance. A searchable PDF file containing all figures in this article can be found under the "Supplements" tab.

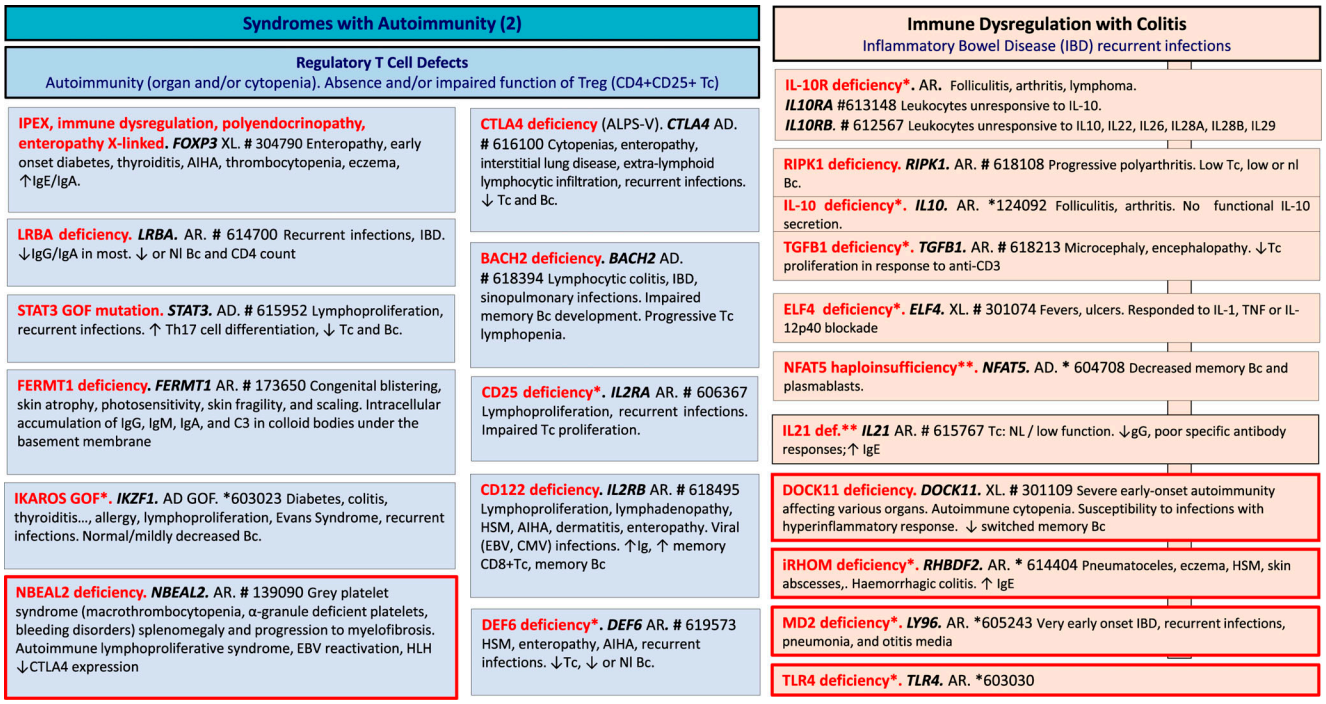

Figure 12. **Diseases of immune dysregulation** (4). Syndromes with autoimmunity and others. AD: autosomal dominant inheritance; AIHA: autoimmune hemolytic anemia; ALPS: autoimmune lymphoproliferative syndrome; AR: autosomal recessive inheritance; Bc: B cells; CD: cluster of differentiation; def: deficiency; EBV: Epstein-Barr virus; GOF: gain-of-function; HLH: hemophagocytic lymphohistiocytosis; (H)SM: (hepato)splenomegaly; IBD: inflammatory bowel disease; Ig: immunoglobulin; IL-10: interleukin-10; LOF: loss-of-function; NK: natural killer cells; Nl: normal; sd: syndrome; Tc: T cells; Treg: regulatory T cells; XL: X-linked inheritance. A searchable PDF file containing all figures in this article can be found under the "Supplements" tab.

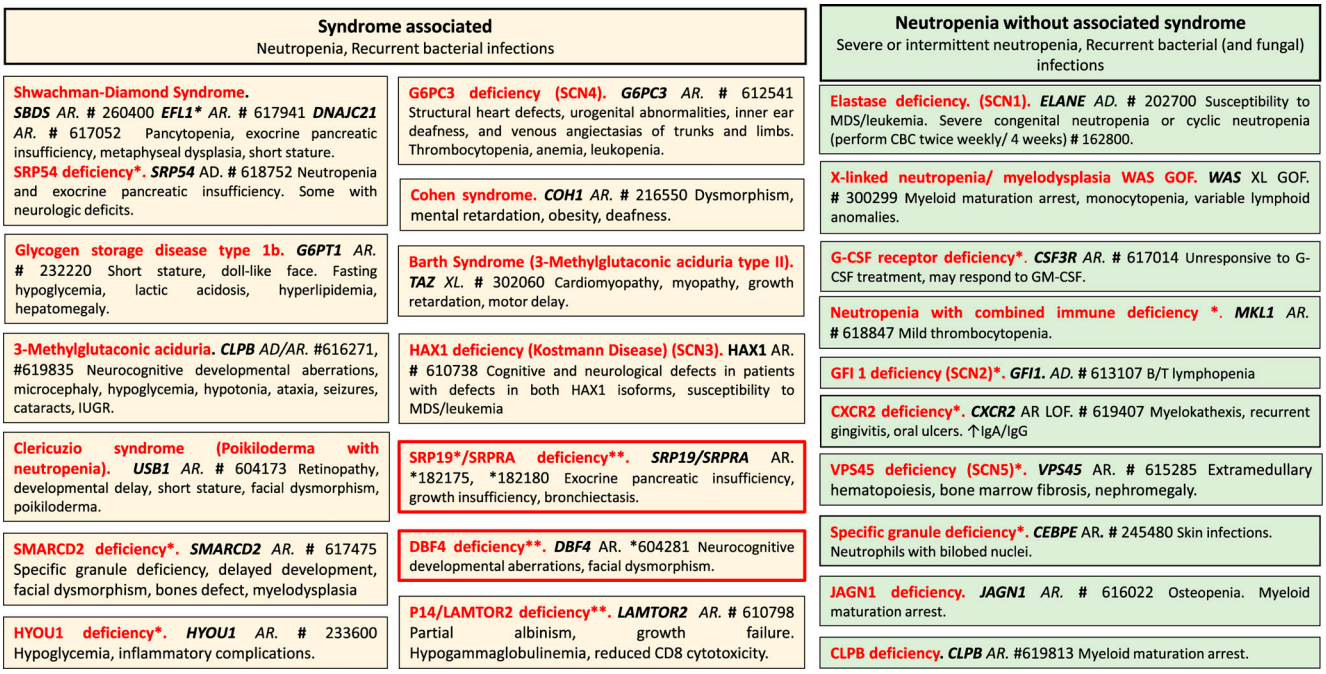

Figure 13. **Congenital defects of phagocyte number, function, or both. Neutropenia.** AD: autosomal dominant inheritance; AR: autosomal recessive inheritance; CBC: complete blood count; CD: cluster of differentiation; def: deficiency; GM-CSF: granulocyte/monocyte colony stimulation factor; GOF: gain-of-function; IUGR: intra uterine growth retardation; MDS: myelodysplasia; NK: natural killer cells; XL: X-linked inheritance. A searchable PDF file containing all figures in this article can be found under the "Supplements" tab.

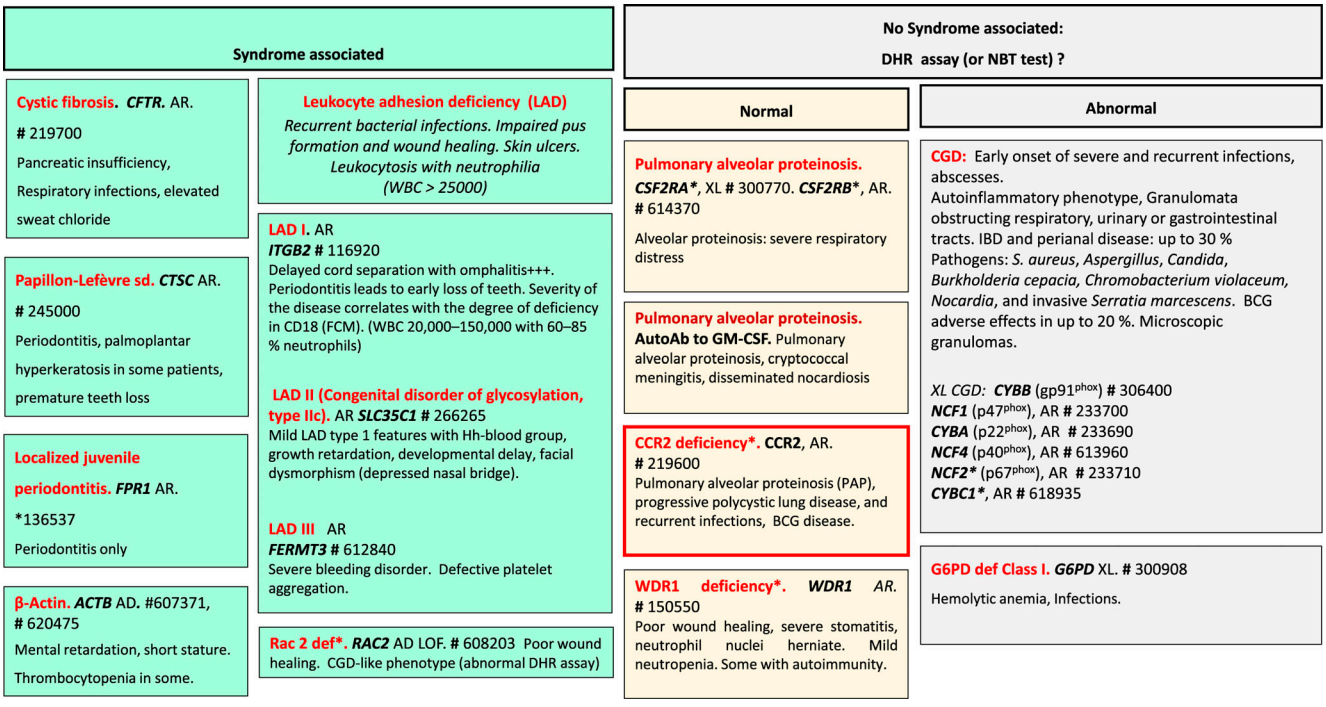

Figure 14. **Congenital defects of phagocyte number, function, or both. Functional defects of phagocytes.** AD: autosomal dominant inheritance; AR: autosomal recessive inheritance; BCG: Bacillus Calmette–Guerin; CD: cluster of differentiation; CGD: chronic granulomatous disease; FCM: flow cytometry; def: deficiency; DHR: dihydrorhodamine-1,2,3; GM-CSF: granulocyte/monocyte colony stimulation factor; IBD: inflammatory bowel disease; LAD: leukocyte adhesion deficiency; NBT: nitroblue tetrazolium; NK: natural killer cells; WBC: white blood cells; XL: X-linked inheritance. A searchable PDF file containing all figures in this article can be found under the "Supplements" tab.

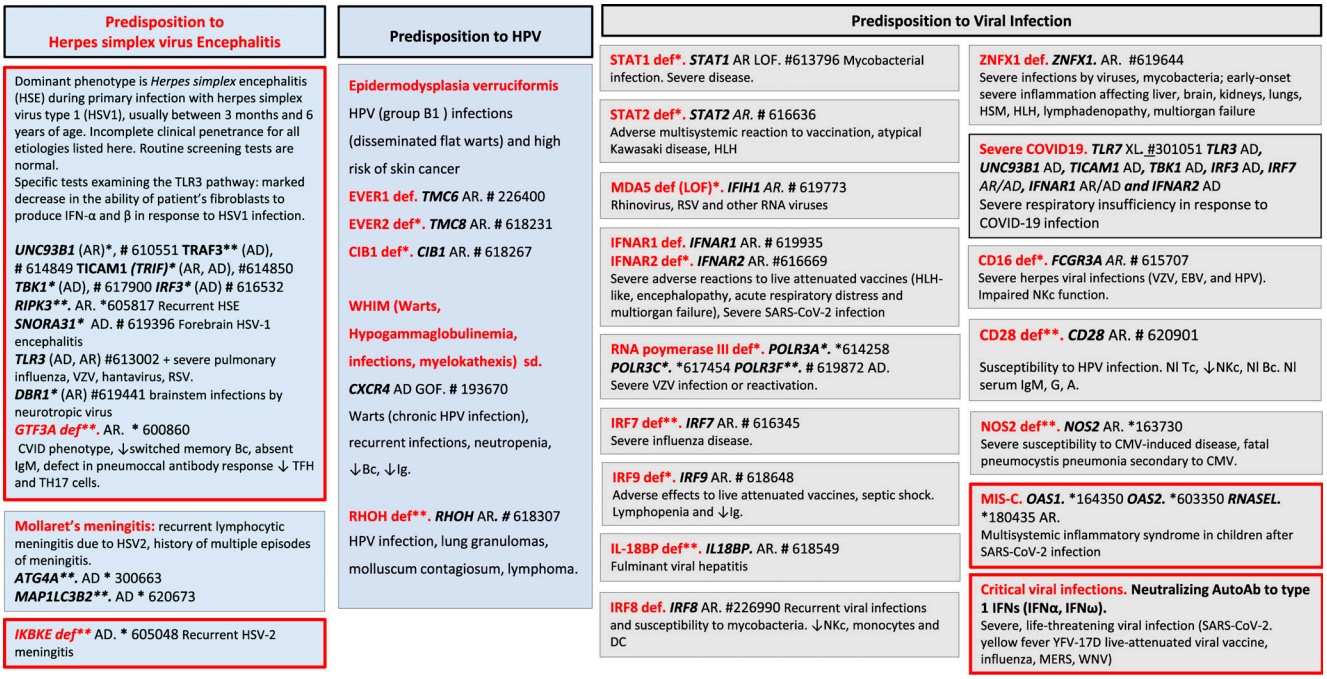

Figure 15. **Defects in intrinsic and innate immunity. Predisposition to viral infections**. AD: autosomal dominant inheritance; AR: autosomal recessive inheritance; CD: cluster of differentiation; CMV: cytomegalovirus; EBV: Epstein-Barr virus; GOF: gain-of-function; HLH: hemophagocytic lymphohistiocytosis; HPV: human papillomavirus; HSV: herpes simplex virus; LOF: loss-of-function; MIS-C: multisystem inflammatory syndrome in children; 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 inheritance. A searchable PDF file containing all figures in this article can be found under the "Supplements" tab.

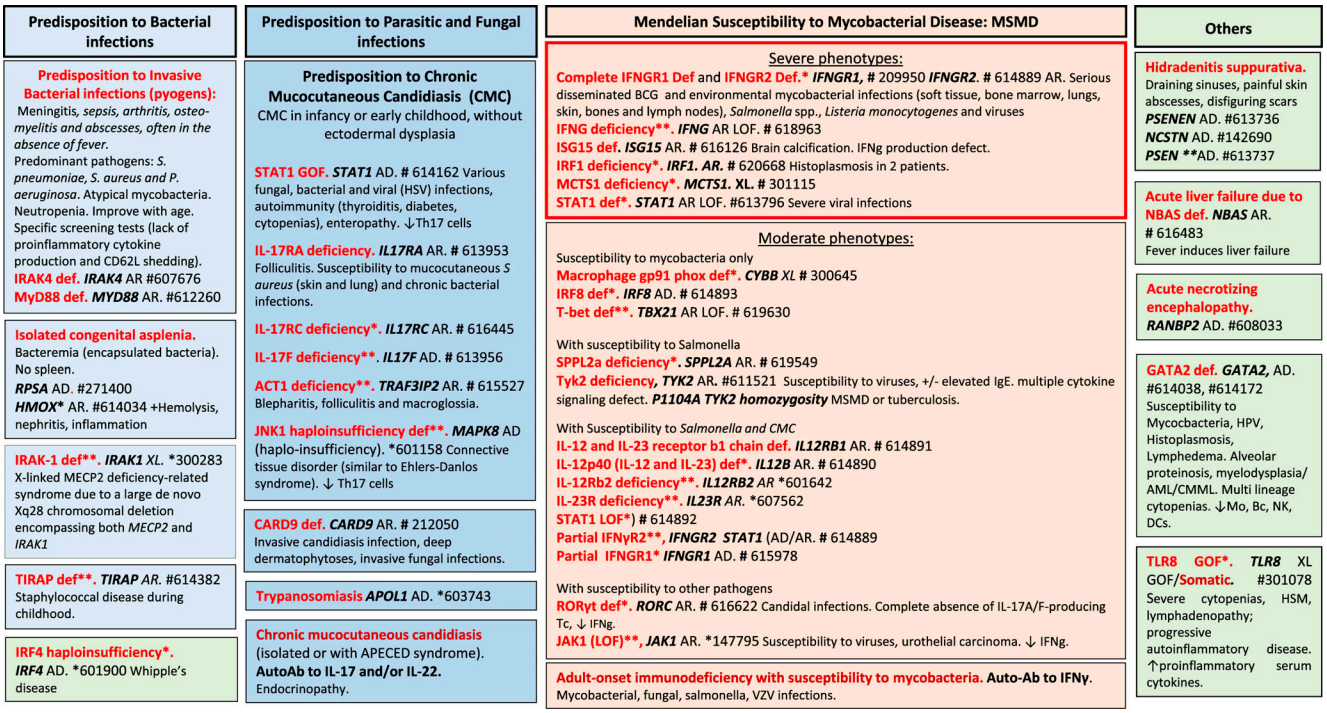

Figure 16. **Defects in intrinsic and innate immunity. Predisposition to bacterial, fungal, and parasitic infections and other defects.** AD: autosomal dominant inheritance; AML: acute myeloid leukemia; AR: autosomal recessive inheritance; BCG: Bacillus Calmette–Guerin; CD: cluster of differentiation; CMC: chronic mucocutaneous candidiasis; CMML: chronic myelomonocytic leukemia; GOF: gain-of-function; IFN-γ: interferon-γ; HPV: human papillomavirus; HSV: herpes simplex virus; LOF: loss-of-function; MSMD: Mendelian susceptibility to mycobacterial disease; NK: natural killer cells; Tc: T cells; VZV: varicella zoster virus; XL: X-linked inheritance. A searchable PDF file containing all figures in this article can be found under the "Supplements" tab.

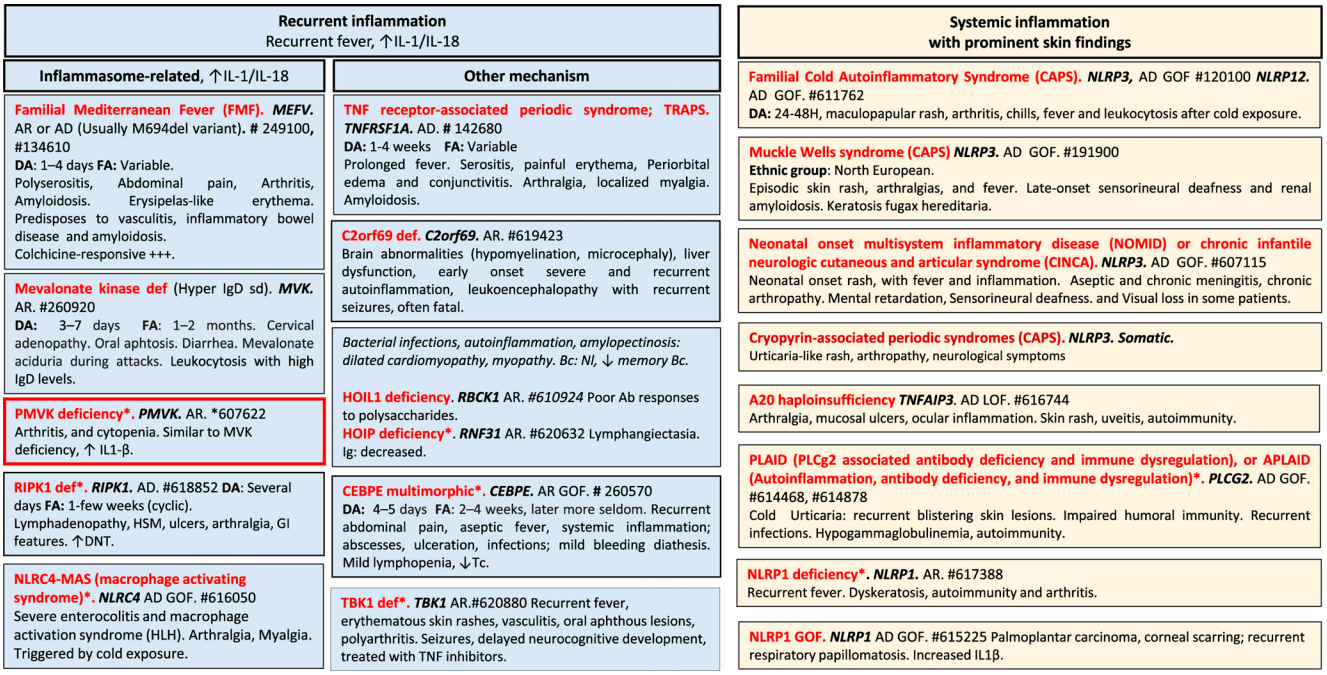

Figure 17. **Autoinflammatory disorders** (2). AD: autosomal dominant inheritance; AR: autosomal recessive inheritance; Bc: B cells; CAPS: cryopyrin-associated periodic syndrome; DA: duration of acute inflammation episode; def: deficiency; DNT: double-negative T cells; FA: frequency of acute inflammation episode; GI: gastrointestinal; GOF: gain-of-function; HLH: hemophagocytic lymphohistiocytosis; HSM: hepatosplenomegaly; IL: interleukin; Ig: immune serum globulin; LOF: loss-of-function; Nl: normal; sd: syndrome; Tc: T cells; TNF: tumor necrosis factor; XL: X-linked inheritance. A searchable PDF file containing all figures in this article can be found under the "Supplements" tab.

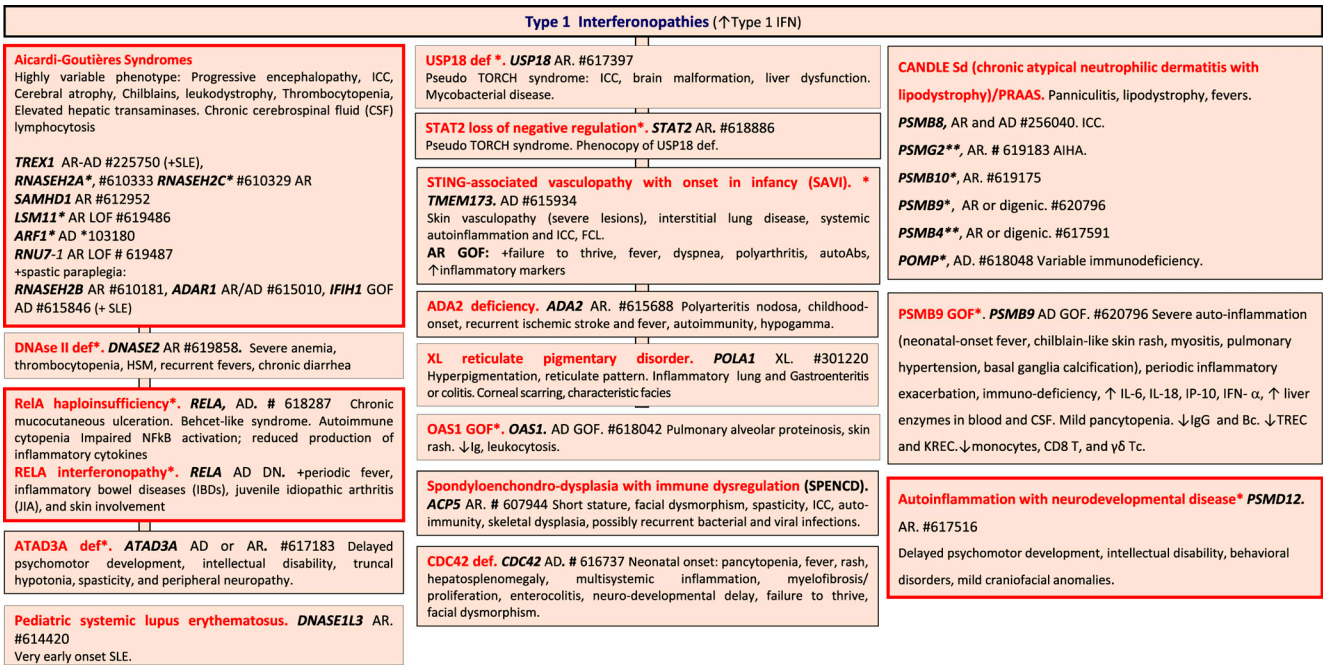

Figure 18. **Autoinflammatory disorders** (3). Ab: antibody; AD: autosomal dominant inheritance; AIHA: autoimmune hemolytic anemia; AR: autosomal recessive inheritance; Bc: B cells; CSF: cerebrospinal fluid; def: deficiency; DN: double-negative effect; FCL: familial chilblain lupus; GOF: gain-of-function; HSM: hepatosplenomegaly; ICC: intracranial calcifications; IFN: interferon; IL: interleukin; Ig: immune serum globulin; KREC: κ-deleting element recombination circle; LOF: loss-of-function; Nl: normal; sd: syndrome; SLE: systemic lupus erythematosus; Tc: T cells; TORCH: toxoplasmosis, other, rubella, cytomegalovirus, and herpes infection; TREC: T cell recombination excision circles; XL: X-linked inheritance. A searchable PDF file containing all figures in this article can be found under the "Supplements" tab.

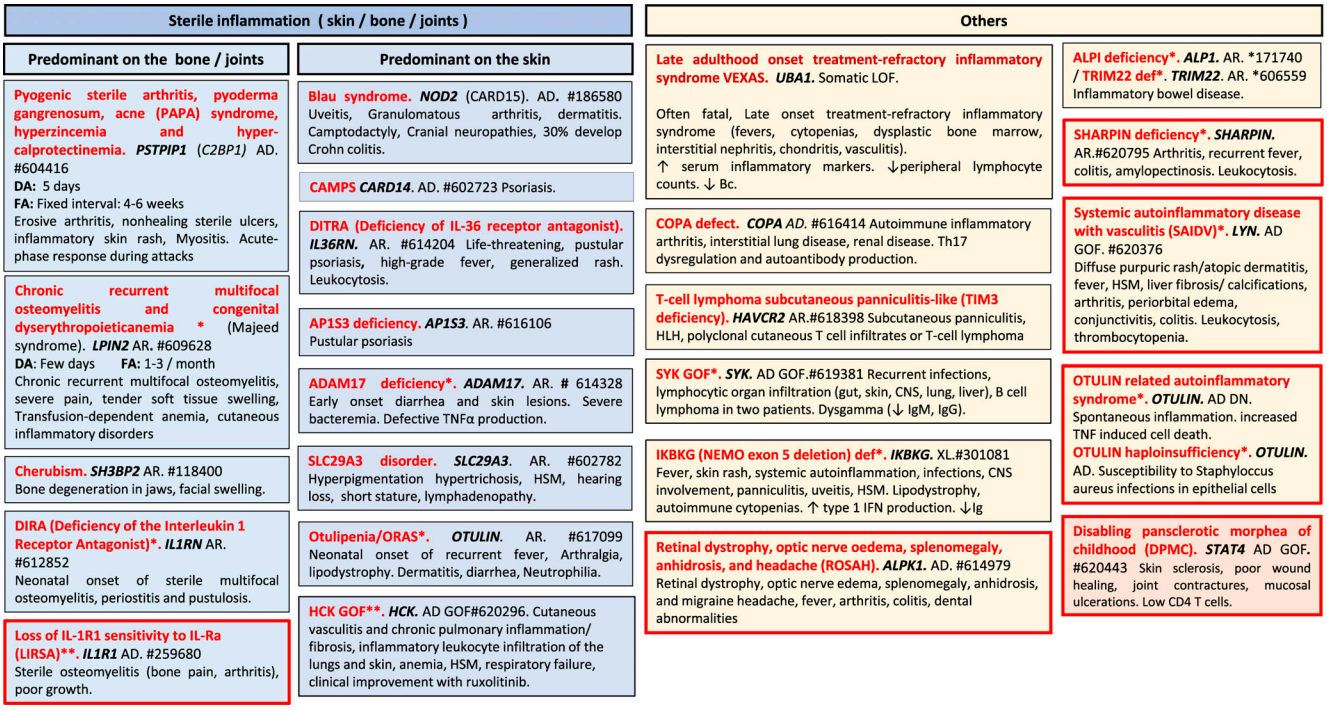

Figure 19. **Autoinflammatory disorders** (4). AD: autosomal dominant inheritance; AR: autosomal recessive inheritance; Bc: B cells; CNS: central nervous system; DA: duration of acute inflammation episode; def: deficiency; DN: double-negative effect; FA: frequency of acute inflammation episode; GOF: gain-of-function; HLH: hemophagocytic lymphohistiocytosis; HSM: hepatosplenomegaly; IFN: interferon; IL: interleukin; Ig: immune serum globulin; LOF: loss-of-function; Nl: normal; sd: syndrome; Tc: T cells; TNF: tumor necrosis factor; XL: X-linked inheritance. A searchable PDF file containing all figures in this article can be found under the "Supplements" tab.

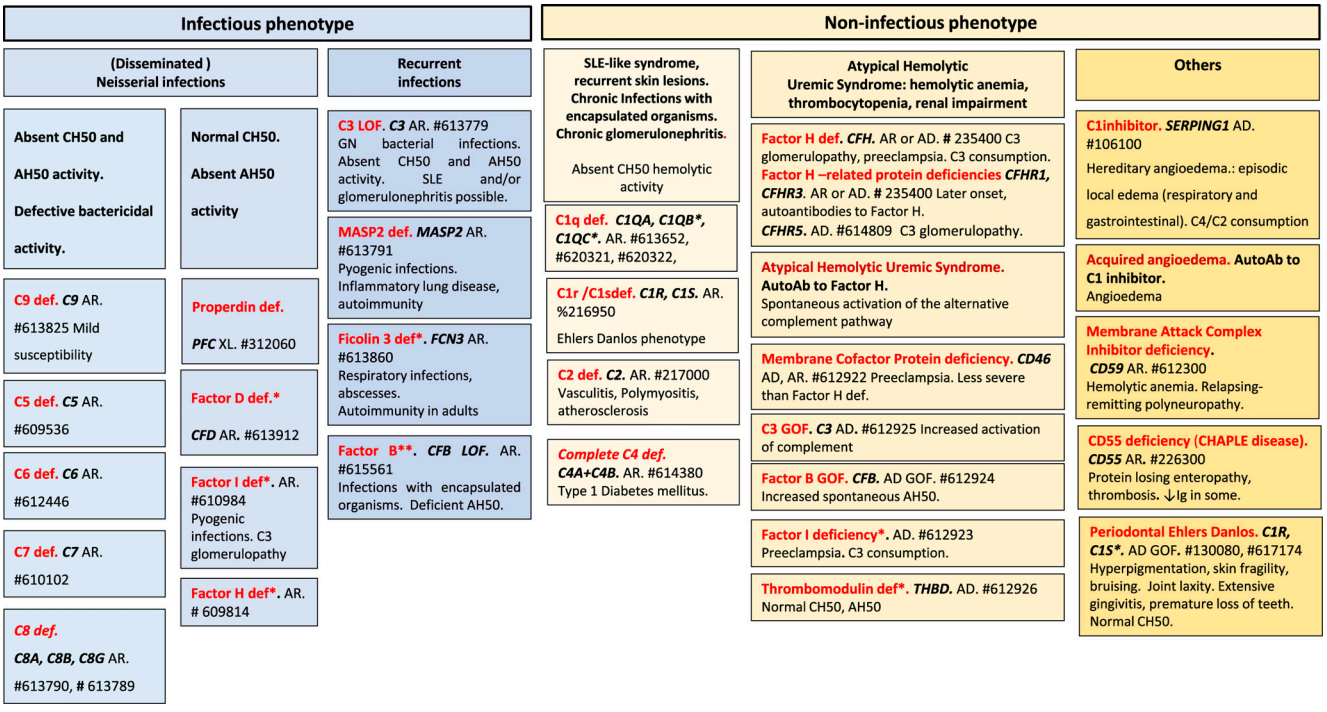

Figure 20. **Complement deficiencies.** AD: autosomal dominant inheritance; AH50: alternate pathway hemolytic activity; AutoAb: autoantibodies; AR: autosomal recessive inheritance; CHAPLE: complement hyperactivation, angiopathic thrombosis, and protein-losing enteropathy; CH50: complement hemolytic activity; def: deficiency; GOF: gain-of-function; LOF: loss-of-function; sd: syndrome; SLE: systemic lupus erythematosus; XL: X-linked inheritance. A searchable PDF file containing all figures in this article can be found under the "Supplements" tab.

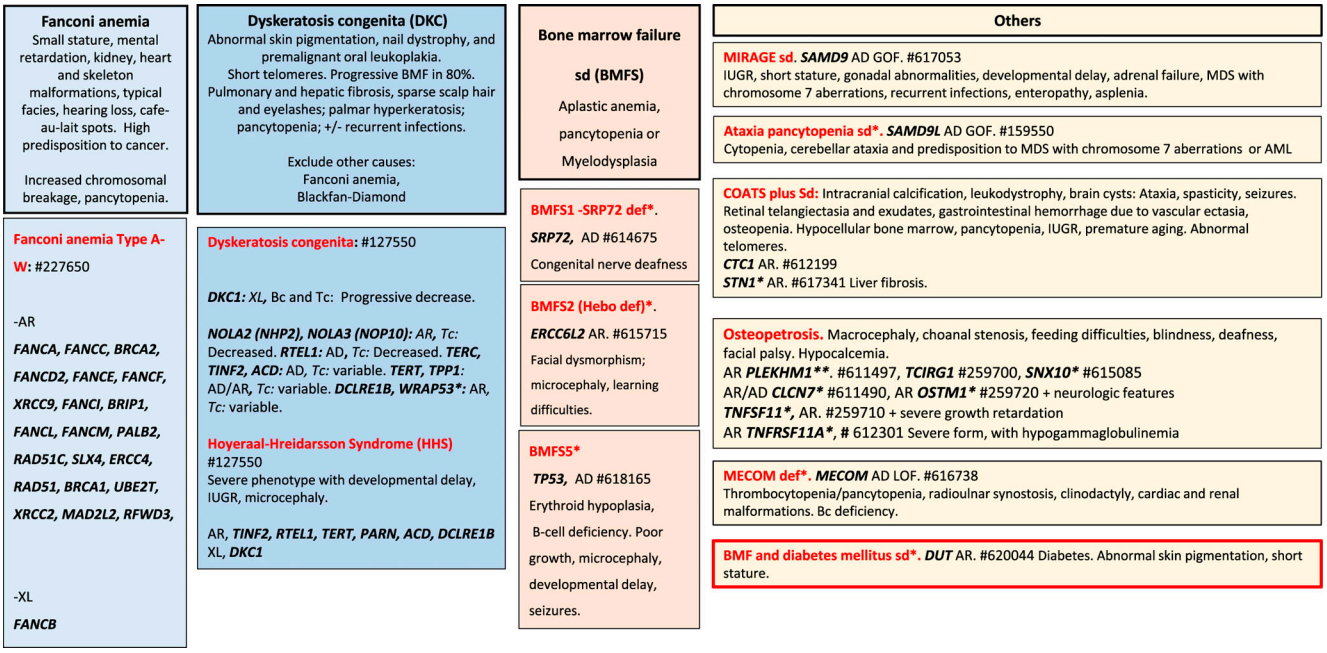

Figure 21. **Bone marrow failure disorders.** AD: autosomal dominant inheritance; AML: acute myeloid leukemia; AR: autosomal recessive inheritance; Bc: B cells; BMF: bone marrow failure; def: deficiency; DKC: Dyskeratosis congenita; GOF: gain-of-function; IUGR: intrauterine growth retardation; LOF: loss-of-function; MDS: myelodysplasia; sd: syndrome; Tc: T cells; XL: X-linked inheritance. A searchable PDF file containing all figures in this article can be found under the "Supplements" tab.

Discussion

These algorithms present the typical phenotype described for each disorder. However, clinicians should keep in mind the limitations of such an approach. First, the phenotypes of a given IEI are continuously expanding with the identification and clinical description of more patients. Moreover, hypomorphic or even neomorphic variants in a given IEI gene can present atypically. Second, there is the well-known incomplete penetrance and incomplete expressivity of the phenotype, due to autosomal random monoallelic expression (6). Moreover, from a practical point of view, the growing number of disorders to include in these tables makes them less and less readable. Here, we tried to reduce phenotypic complexity to the most relevant features and provided OMIM numbers to complete the clinical synopsis.

The clinical phenotype of patients with the same and different IEI may be quite variable and overlapping, respectively. This is related to pleiotropic effects and the genotype-phenotype relationship, which may not be fully appreciated with the first description of these novel genetic disease entities. Special caution is warranted when first publications report only one or a few cases.

We aimed to simplify as much as possible the classification, and this is probably our biggest limitation. Many disorders could have been included in several categories, and some secondary features (based on typical presentation) could have been present before the predominant features reported here. So users should be aware that the correct diagnosis is not always reached at the first try and consider the complete clinical and laboratory presentation when navigating through the decision tree–based process.

Based on these facts, our algorithms suggest the possible genotype and the lab tests useful for a more precise diagnosis to help in genetic diagnosis. However, with many overlapping phenotypes, the recommendation for genetic diagnostic testing would be the use of broad panels/exome, rather than targeted panels, except for a few specific diseases, such as X-linked agammaglobulinemia for which a logical rationale can be applied (7).

Conclusion

This phenotypic classification of IEI should be used as a diagnostic resource, aimed to complement the 2024 IUIS genotypic classification. This user-friendly diagnostic orientation tool provides a basic approach for physicians and biologists who are not necessarily experts in the field of IEI. This can 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.

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