

A Phenotypic Approach for IUIS PID Classification and Diagnosis: Guidelines for Clinicians at the Bedside

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Received: 11 December 2012 / Accepted: 9 April 2013 / Published online: 9 May 2013
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Abstract The number of genetically defined Primary Immunodeficiency Diseases (PID) has increased exponentially, especially in the past decade. The biennial classification published by the IUIS PID expert committee is therefore quickly expanding, providing valuable information regarding the disease-causing genotypes, the immunological anomalies, and the associated clinical features of PIDs. These are grouped in eight, somewhat overlapping, categories of immune dysfunction. However, based on this immunological classification, the diagnosis of a specific PID from the clinician's observation of an individual clinical and/or immunological phenotype remains difficult,

especially for non-PID specialists. The purpose of this work is to suggest a phenotypic classification that forms the basis for diagnostic trees, leading the physician to particular groups of PIDs, starting from clinical features and combining routine immunological investigations along the way. We present 8 colored diagnostic figures that correspond to the 8 PID groups in the IUIS Classification, including all the PIDs cited in the 2011 update of the IUIS classification and most of those reported since.

Keywords Primary immunodeficiency · classification · IUIS · diagnosis tool

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Abbreviations

α FP	Alpha- fetoprotein	EDA-ID	Anhidrotic ectodermal dysplasia with immunodeficiency
Ab	Antibody	EO	Eosinophils
AD	Autosomal dominant inheritance	FA	Frequency of attacks
ADA	Adenosine deaminase	FCAS	Familial cold autoinflammatory syndrome
Adp	Adenopathy	FISH	Fluorescence in situ hybridization
AIHA	Auto-immune hemolytic anemia	GI	Gastrointestinal
AML	Acute myeloid leukemia	Hib	<i>Haemophilus influenzae</i> serotype b
Anti PSS	Anti- pneumococcus polysaccharide antibodies	HIDS	Hyper IgD syndrome
AR	Autosomal recessive inheritance	HIES	Hyper IgE syndrome
BL	B lymphocyte	HIGM	Hyper Ig M syndrome
CAPS	Cryopyrin-associated periodic syndromes	HLA	Human leukocyte antigen
CBC	Complete blood count	HSM	Hepatosplenomegaly
CD	Cluster of differentiation	Hx	Medical history
CGD	Chronic granulomatous disease	Ig	Immunoglobulin
CID	Combined immunodeficiency	IL	Interleukin
CINCA	Chronic infantile neurologic cutaneous and articular syndrome	LAD	Leukocyte adhesion deficiency
FCM*	Flow cytometry available	MKD	Mevalonate kinase deficiency
CMML	Chronic myelo-monocytic leukemia	MSMD	Mendelian susceptibility to mycobacteria disease
CNS	Central nervous system	MWS	Muckle-Wells syndrome
CVID	Common variable immunodeficiency disorders	N	Normal, not low
CT	Computed tomography	NK	Natural killer
CTL	Cytotoxic T-lymphocyte	NKT	Natural killer T cell
DA	Duration of attacks	NN	Neonate
Def	Deficiency	NOMID	Neonatal onset multisystem inflammatory disease
DHR	DiHydroRhodamine	NP	Neutropenia
Dip	Diphtheria	PAPA	Pyogenic sterile arthritis pyoderma gangrenosum, Acne syndrome
EBV	Epstein-barr virus	PMN	Neutrophils
EDA	Anhidrotic ectodermal dysplasia	PT	Platelet
		SCID	Severe combined immune deficiencies

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Sd	Syndrome
SLE	Systemic lupus erythematosus
SPM	Splenomegaly
Subcl	IgG subclass
TCR	T-cell receptor
Tet	Tetanus
TL	T lymphocyte
TNF	Tumor necrosis factor
TRAPS	TNF receptor-associated periodic syndrome
WBC	White blood cells
XL	X-linked

Introduction

Primary Immunodeficiency Diseases (PID) comprise at least 200 genetically-defined inborn errors of immunity

[1–3]. The International Union of Immunological Societies (IUIS) PID expert committee has proposed a PID classification [1], which facilitates clinical care and clinical research studies world-wide; it is updated every other year to include new information. The PIDs are grouped into eight categories based on the principal mechanism in each disease, though if more than one mechanism is involved, there are diseases that could appear in more than one category. For each individual PID, the genotype, immunological and clinical phenotypes are briefly described. Since the number of disorders is quickly increasing every year [4–6], at an even faster pace since the advent of next-generation sequencing, the classification and these tables are therefore cumbersome. They offer limited assistance to most physicians at the bedside, especially those outside the field of PIDs and those in training; clinicians in regions

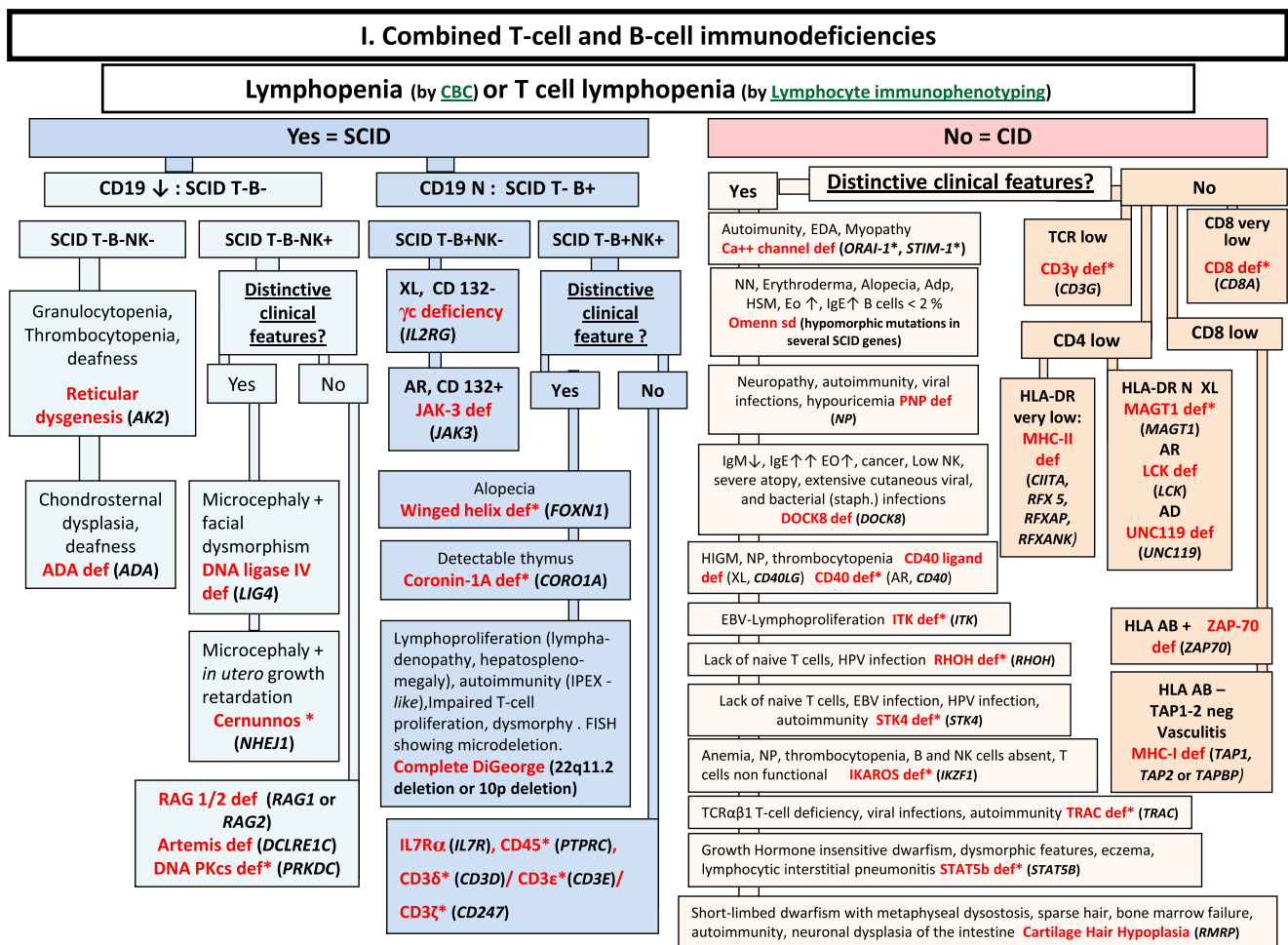


Fig. 1 Combined T- and B- cell immunodeficiencies. ADA: Adenosine Deaminase; Adp: adenopathy; AIHA: Auto-Immune Hemolytic Anemia; AR: Autosomal Recessive inheritance; CBC: Complete Blood Count; CD: Cluster of Differentiation; CID: Combined Immunodeficiency; EBV: Epstein-Barr Virus; EDA: Anhidrotic ectodermal dysplasia; EO: Eosinophils;

FISH: Fluorescence in situ Hybridization; HIGM: Hyper IgM syndrome; HLA: Human Leukocyte Antigen; HSM: Hepatosplenomegaly; Ig: Immunoglobulin; N: Normal, not low; NK: Natural Killer; NN: Neonate; NP: Neutropenia; PT: Platelet; SCID: Severe Combined ImmunoDeficiency; TCR: T-Cell Receptor; XL: X-Linked

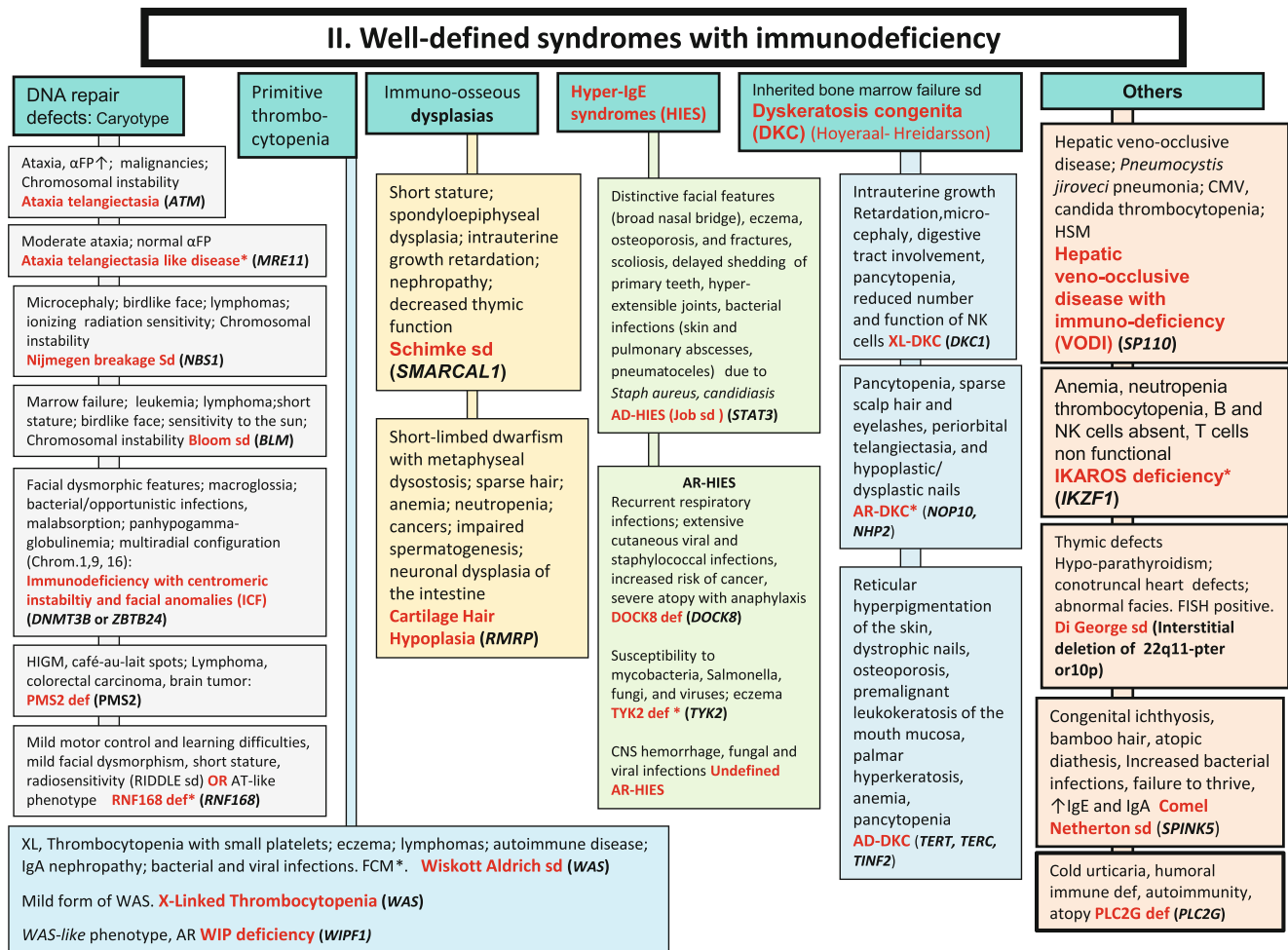


Fig. 2 Well-defined syndromes with immunodeficiencies. These syndromes are generally associated with T-cell immunodeficiency. αFP: alpha- fetoprotein; AD: Autosomal Dominant inheritance; AR: Autosomal Recessive inheritance; CNS: Central Nervous

System; FCM*: Flow cytometry available; FISH: Fluorescence in situ Hybridization; HSM: Hepatosplenomegaly; Ig: Immunoglobulin; NK: Natural Killer; XL: X-Linked inheritance

of the world where awareness for PIDs is limited may also find the tables tricky.

Patients with a PID may first present to many types of medical and surgical disciplines and this is likely to be increasingly common given the growing number of patients with known or suspected PIDs [7]. Such physicians, who may lack familiarity with PIDs, need a classification that is based on a clinical and/or biological phenotype that they observe. This prompted IUIS PID experts to work on a simplified classification, based on simple clinical and immunological phenotypes, in order to provide some easy-to-follow algorithms to diagnose a particular PID or group of PIDs. This will optimize collaboration between primary centers and specialized centers, particularly for genetic

studies, and will lead to faster and more precise molecular diagnosis and genetic counseling, paving the way to more appropriate management of affected patients and families. This work presents a user-friendly classification of PIDs, providing a tree-based decision-making process based on the observation of clinical and biological phenotypes.

Methodology

We included all diseases from the 2011 update of IUIS PID classification [1]. To stay up-to-date, we also included new diseases described in the last 2 years [2]. However, there may be other genes associated with

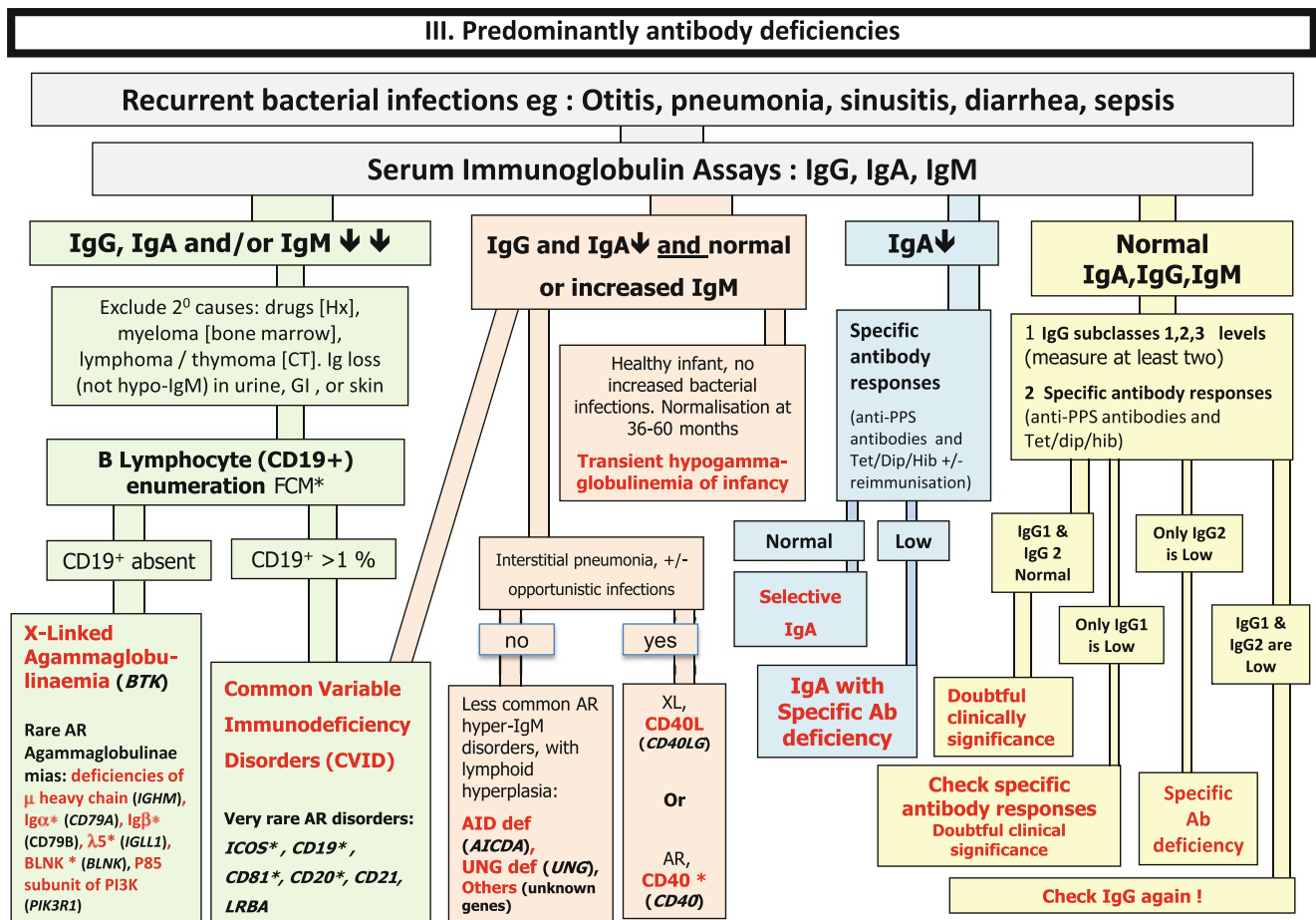


Fig. 3 Predominantly antibody deficiencies. Ab: Antibody; Anti PPS: Anti- pneumococcal polysaccharide antibodies; AR: Autosomal Recessive inheritance; CD: Cluster of Differentiation; CVID: Common Variable Immunodeficiency Disorders; CT:

Computed Tomography; Dip: Diphtheria; FCM*: Flow cytometry available; GI: Gastrointestinal; Hib: *Haemophilus influenzae* serotype b; Hx: medical history; Ig: Immunoglobulin; subcl: IgG subclass; Tet; Tetanus; XL: X-Linked inheritance

PIDs that are not included here to be faithful to our inclusion criteria. An algorithm was assigned to each of the eight main groups of the classification. We used the same color for each group of similar conditions. Disease names are written in red. As in the IUIS Classification, an asterisk is added to highlight extremely rare disorders (less than 10 cases reported in the medical literature). These algorithms were first established by a small committee; then validated by one or two experts for each figure.

Results

A classification validated by the IUIS PID expert committee is presented in Figs. 1, 2, 3, 4, 5, 6, 7 and 8.

Discussion

These figures are diagnostic tools that represent a modified and simplified version of the 2011 IUIS classification [1]. They are based on patients' clinical and biological phenotypes and are mostly presented as decision trees for diagnostic orientation. These figures serve as diagnostic orientation tools for the typical forms of PID; the more atypical presentations of PIDs are not covered in these figures. These figures do not therefore aim to replace decisional trees or diagnostic protocols proposed by other teams or scientific societies [8–11]. Rather they aim at being a user-friendly first approach to the IUIS classification [1]. These figures enable non-PID specialists to select the most appropriate diagnostic tree and to undertake some preliminary

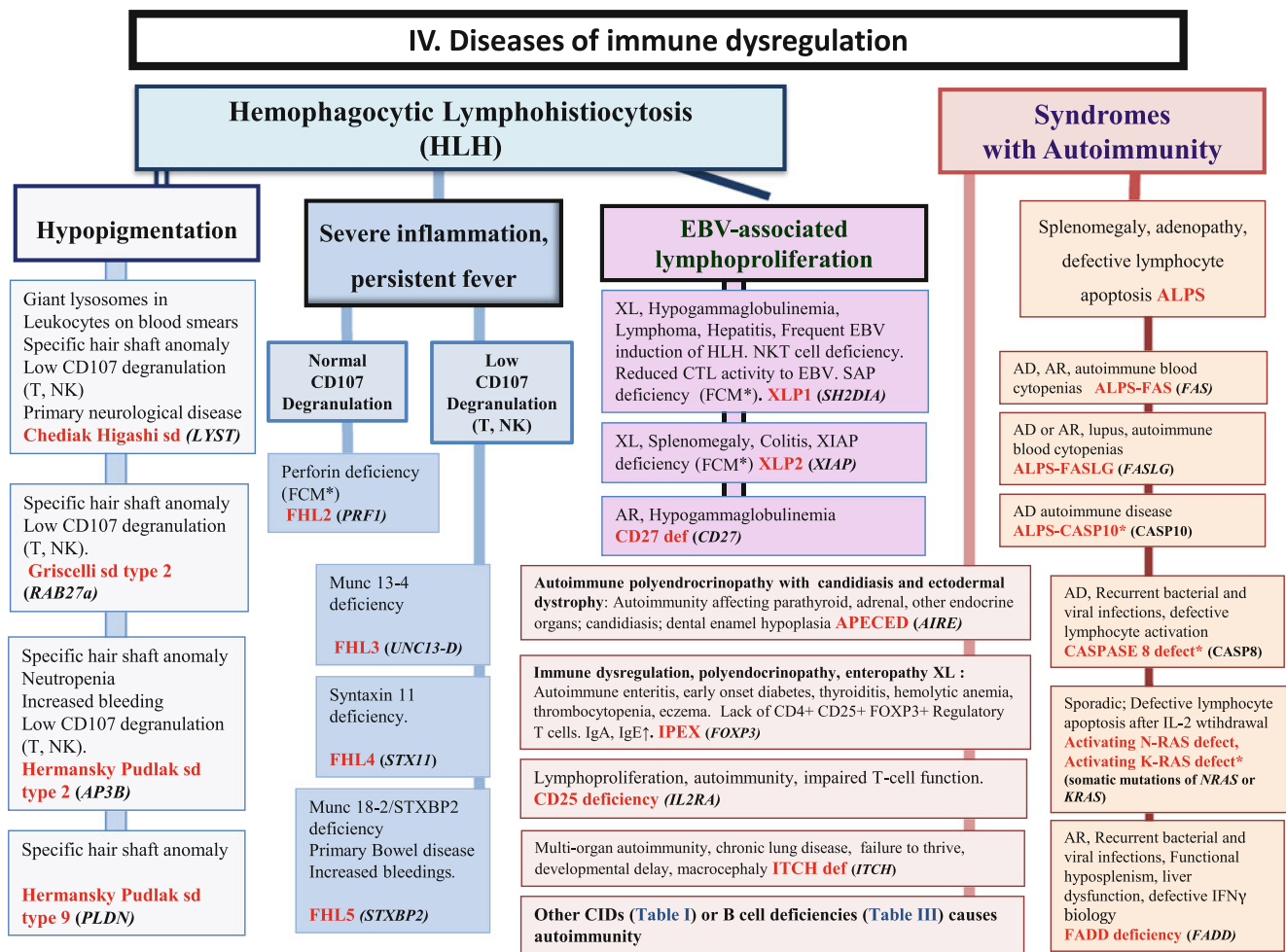


Fig. 4 Diseases of immune dysregulation. AD: Autosomal Dominant inheritance; AR: Autosomal Recessive inheritance; CD: Cluster of Differentiation; CTL: Cytotoxic T-Lymphocyte; EBV: Epstein-Barr Virus; FCM*: Flow cytometry available; HSM:

Hepatosplenomegaly; Ig: Immunoglobulin; IL: interleukin; NK: Natural Killer; NKT: Natural Killer T cell; TL: T lymphocyte; XL: X-Linked inheritance

investigations, whilst contacting an expert in PIDs. They may also help in the selection of the center or expert to whom the patient should be referred, given the patient’s particular phenotype. In all cases, whether a tentative diagnosis can be made based on these figures or not, we recommend that the practitioner outside the field who sees a patient with a possible PID seeks specialist advice.

To simplify our figures, we did not systematically include all data from the IUIS classification (OMIM number, presumed pathogenesis, affected cells or function...) [1]. In order to present the 24 pages from the IUIS classification in only 8 figures, we used common abbreviations familiar to most physicians (explained in footnotes). The use of a color code makes these figures

easy to follow, so that they could be hung, in larger format, in clinical wards. This is also suitable for informing young clinicians and students.

To make these figures easier to use by clinicians and biologists, we highlighted the clinical and biological features, adding to the data from the IUIS classification some other features typical of the PID in question. This allows an initial orientation towards a particular disease or group of diseases. Whenever it was possible, we have focused on clinical or routine laboratory features that distinguish disorders that are closely related. Example: A female infant with an opportunistic infection in whom lymphocyte subpopulation investigation reveals profound CD3 and CD16/56 lymphopenia without CD19/20 lymphopenia

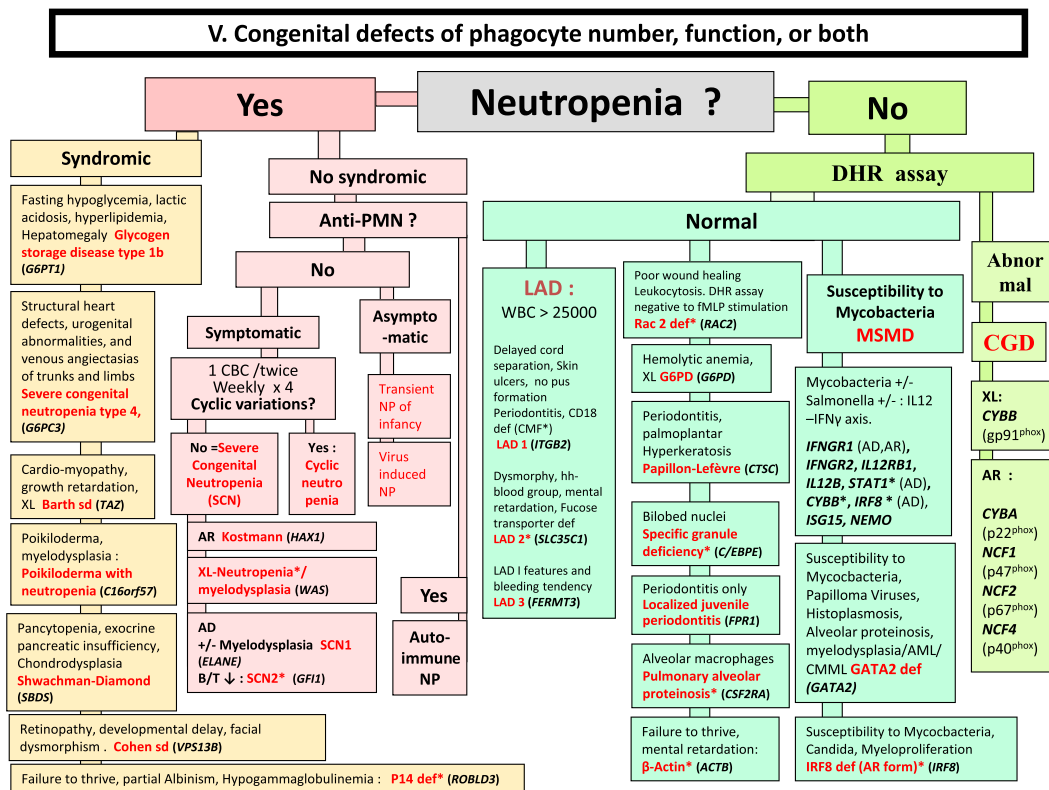


Fig. 5 Congenital defects of phagocyte number, function, or both. For DHR assay, the results can distinguish XL-CGD from AR-CGD, and gp40phox defect from others AR forms. AD: Autosomal Dominant inheritance; AML: Acute Myeloid Leukemia; AR: Autosomal Recessive inheritance; CBC: Complete Blood Count; CD: Cluster of

Differentiation; CGD: Chronic Granulomatous Disease; CMML: Chronic Myelo-monocytic Leukemia; DHR: DiHydroRhodamine; LAD: Leukocyte Adhesion Deficiency; MSMD: Mendelian Susceptibility to Mycobacteria Disease; NP: Neutropenia; PNN: Neutrophils; WBC: White Blood Cells; XL: X-Linked inheritance

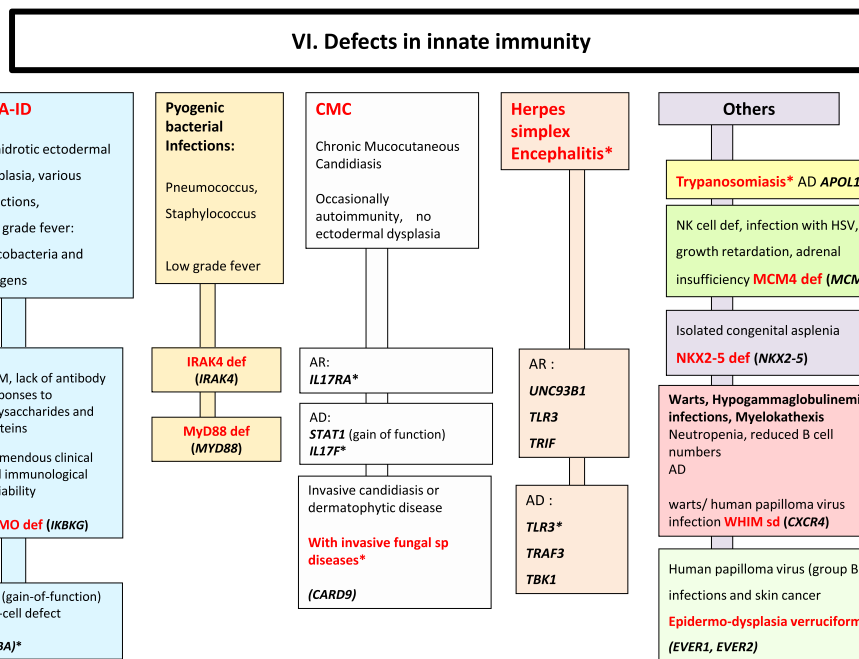


Fig. 6 Defects in innate immunity. AD: Autosomal Dominant inheritance; AR: Autosomal Recessive inheritance; BL: B lymphocyte; EDA-ID: Anhidrotic Ectodermal Dysplasia with Immunodeficiency; Ig: Immunoglobulin; PNN: Neutrophils; XL: X-Linked inheritance

VII. Auto-inflammatory disorders.

Usual age at onset

Neonatal		Infancy	Childhood / Early Adult	
<p>AR DA : Continuous FA : Continuous Sterile multifocal osteomyelitis, Folliculitis. IL1: Unopposed effect</p> <p>Deficiency of IL-1 Receptor Antagonist (DIRA)* (IL1RN)</p>	<p>AD DA : Continuous, often worse in the evenings FA: Often daily Ethnic group : North European Urticaria , Deafness, Conjunctivitis Amyloidosis. Muckle Wells syndrome (CAPS) (NLRP3)</p>	<p>AR DA: > 3–7 days FA: 1–2 monthly Cervical adenopathy Oral aphthosis. Diarrhea Elevated IgD and IgA, acute phase response and mevalonate aciduria during attacks</p> <p>MKD (HIDS) (MVK)</p>	<p>AR DA: 1–4 days. FA : Variable. Polyserositis, Abdominal pain, Arthritis, Amyloidosis Colchicine-responsive +++ Erysipelas-like erythema Marked acute-phase response during attacks Familial Mediterranean Fever (FMF) (MEFV)</p>	<p>AD DA: 1–4 weeks FA : Variable, continuous Serositis, rash, Periocular edema and conjunctivitis; Amyloidosis. Acute-phase response during attacks. Low levels of soluble TNF-R1 when well TRAPS (TNFRSF1A)</p>
<p>AR DA : Few days FA : 1-3 / month</p> <p>Chronic recurrent Multifocal osteomyelitis, severe pain, tender soft tissue swelling, Transfusion-dependent anemia,</p> <p>MAJEED* (LPIN2)</p>	<p>AR Early onset enterocolitis, Enteric fistulas, Perianal abscesses, Chronic folliculitis. ↑ TNFα</p> <p>EOIBD: Early onset inflammatory bowel disease (IL10 / IL10R)</p>	<p>AD, Sporadic DA: Continuous FA : Continuous Urticarial rash. Aseptic and chronic meningitis Deforming arthropathy Sensorineural deafness Mental retardation Visual loss. Acute-phase response most of the time CINCA (NOMID, CAPS) (NLRP3)</p>	<p>AD DA: 24–48 H Cold exposure. Non pruritic urticaria, arthritis, chills Conjunctivitis. Familial Cold Autoinflammatory Syndrome (CAPS) (NLRP3)</p>	<p>AD DA: 5 days FA: Fixed interval :4-6 weeks Sterile pyogenic oligo-arthritis, Pyoderma gangrenosum, Myositis. Acute-phase response during attacks PAPA (PSTPIP1)</p>
<p>AD. DA : Continuous. FA : Continuous. Uveitis, Granulomatous synovitis, Camptodactyly, Rash, Cranial neuropathies, Crohn disease. Sustained modest acute-phase response BLAU syndrome (NOD2)</p>				

Others :

- 1- AR**, early-onset pustular dermatitis, short and broken hair, paronychia, frequent cutaneous bacterial infections, and 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. **Inflammatory skin and bowel disease (ADAM17)**
- 2- AR** , life-threatening, multisystemic inflammatory disease characterized by episodic widespread, diffuse erythematous pustular rash associated with high fever, malaise, and leukocytosis. **Generalized pustular psoriasis (IL-36Ra)**

Fig. 7 Autoinflammatory disorders. AD: Autosomal Dominant inheritance; AR: Autosomal Recessive inheritance; CAPS: Cryopyrin-Associated Periodic syndromes; CINCA: Chronic Infantile Neurologic Cutaneous and Articular syndrome; DA: Duration of Attacks; FA: Frequency of Attacks; FCAS: Familial Cold Autoinflammatory Syndrome; HIDS: Hyper IgD syndrome;

Ig: Immunoglobulin; IL: interleukin; MKD: Mevalonate Kinase deficiency; MWS: Muckle-Wells syndrome; NOMID: Neonatal Onset Multisystem Inflammatory Disease; PAPA: Pyogenic sterile Arthritis, Pyoderma gangrenosum, Acne syndrome; SPM: Splenomegaly; TNF: Tumor Necrosis Factor; TRAPS: TNF Receptor-Associated Periodic Syndrome

has a SCID T-B+NK- phenotype, which strongly suggests Jak3 deficiency (Fig. 1). After discussion with a team specialized in the diagnosis and treatment of SCID patients, an analysis of the *JAK3* gene will be arranged as a priority, while expert advice will be given on the appropriate management for the infant.

Though atypical forms of PID are increasingly reported in the literature [12–15], typical presentations of these conditions remain predominant, permitting this classification to be useful in most of cases. Moreover, the genetic heterogeneity of most PIDs is high and patients with almost any PID may lack coding mutations in known disease-causing genes. This manuscript will therefore be up-dated

every other year along with the IUIS classification. Meanwhile, we hope that this phenotypic approach to diagnosis of PID can constitute a useful tool for physicians or biologists from various related specialties, especially in the setting of pediatric and adult medicine (internal medicine, pulmonology, hematology, oncology, immunology, infectious diseases, etc...) who may encounter the first presentation of PID patients.

Conclusion

The strengths of this algorithmic approach to the diagnosis of PID are its simplified format, reliance on phenotypic

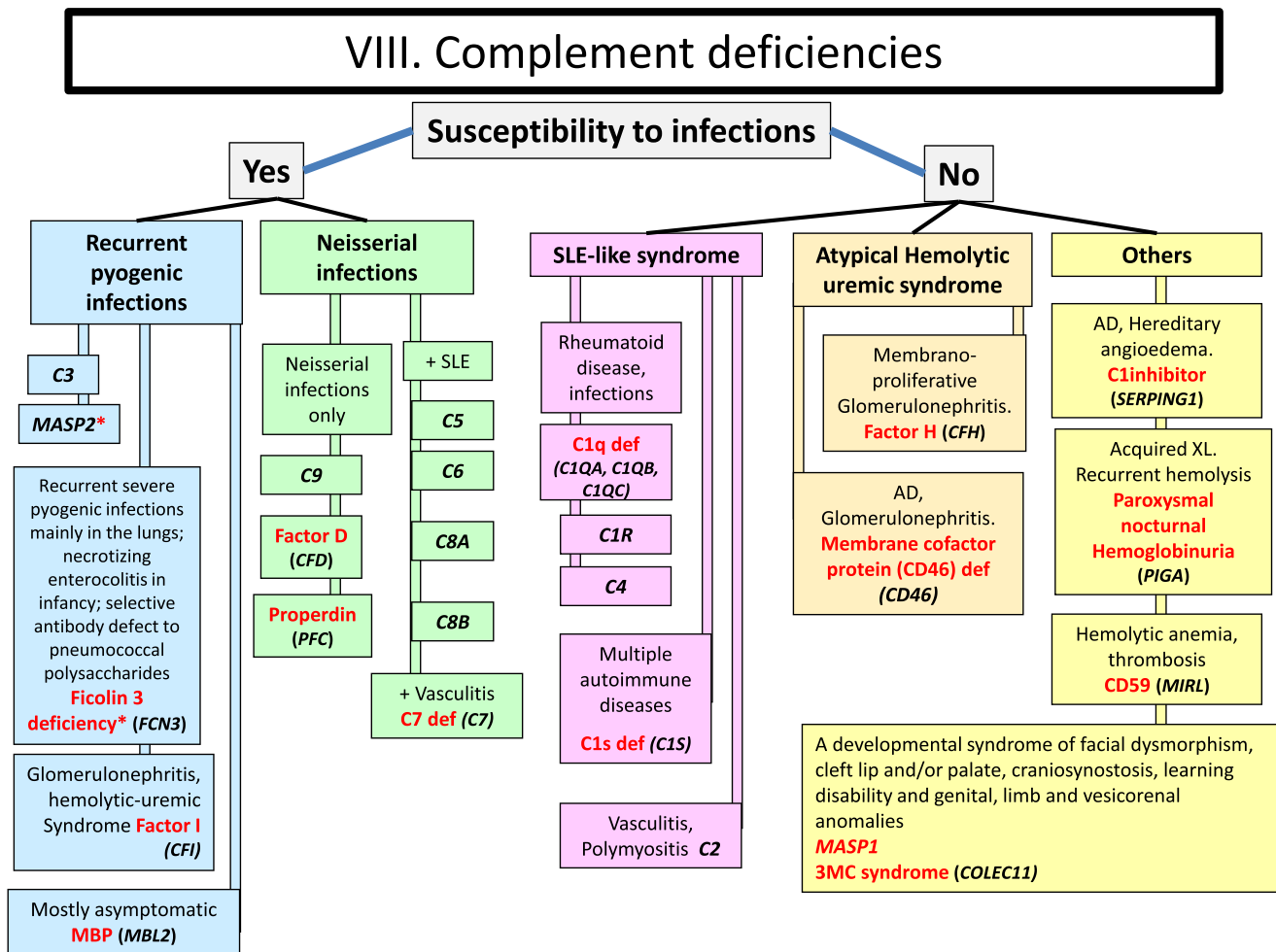


Fig. 8 Complement deficiencies. Def: deficiency; SLE: Systemic Lupus Erythematosus

features, presentation in user-friendly pathways, and validation by a group of PID experts. We hope they will be useful to physicians at the bedside in several areas of pediatrics, internal medicine, and surgery. While these algorithms cannot be comprehensive, due to the tremendous genetic and phenotypic heterogeneity of PIDs, they will be improved over time with progress in the field as well as by feed-back from users. They will also be expanded with the discovery of new PIDs and the refined description of known PIDs.

Acknowledgments We thank Dr Capucine Picard and Dr Claire Fieschi for their contribution to this work.

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