特別講演

16:25～17:25

座長 宮崎大学
布井　博幸

Progress in gene therapy for primary immunodeficiencies

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17:25～17:30

閉会挨拶
代表幹事　防衛医科大学校
野々山　恵章

17:30～17:35

次回当番幹事挨拶

※学術集会終了後、情報交換会を予定しています。

Ⅲ　研究成果の刊行に関する一覧

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Ⅳ　研究成果の刊行に関する一覧　別冊

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ORIGINAL RESEARCH

The 2015 IUIS Phenotypic Classification for Primary Immunodeficiencies

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Abstract There are now nearly 300 single-gene inborn errors of immunity underlying phenotypes as diverse as infection, malignancy, allergy, auto-immunity, and auto-inflammation. For each of these five categories, a growing variety of phenotypes are ascribed to Primary Immunodeficiency Diseases (PID), making PIDs a rapidly expanding field of medicine. The International Union of Immunological Societies (IUIS) PID expert committee (EC) has published every

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other year a classification of these disorders into tables, defined by shared pathogenesis and/or clinical consequences. In 2013, the IUIS committee also proposed a more user-friendly, phenotypic classification, based on the selection of key phenotypes at the bedside. We herein propose the revised figures, based on the accompanying 2015 IUIS PID EC classification.

Keywords Primary immunodeficiencies · classification · IUIS PID expert committee

Abbreviations

αFP	Alpha- fetoprotein
Ab	Antibody
AD	Autosomal dominant inheritance
ADA	Adenosine deaminase
Adp	Adenopathy
ALPS	Autoimmune lymphoproliferative syndrome
AML	Acute myeloid leukemia
Anti PPS	Anti- pneumococcus antibody
AR	Autosomal recessive inheritance
BCG	Bacilli Calmette-Guerin
BL	B lymphocyte
CAMPS	CARD14 mediated psoriasis
CANDLE	Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome
CAPS	Cryopyrin-associated periodic syndromes
CBC	Complete blood count
CD	Cluster of differentiation
CDG-IIb	Congenital disorder of glycosylation, type IIb
CGD	Chronic granulomatous disease
CID	Combined immunodeficiency
CINCA	Chronic infantile neurologic cutaneous and articular syndrome
CMC	Chronic mucocutaneous candidiasis
CMF	Flow cytometry available
CMV	Cytomegalovirus
CMML	Chronic myelomonocytic leukemia
CNS	Central nervous system
CSF	Cerebrospinal fluid
CT	Computed tomography
CTL	Cytotoxic T-lymphocyte
DA	Duration of attacks
Def	Deficiency
DHR	DiHydroRhodamine
Dip	Diphtheria
DITRA	Deficiency of interleukin 36 receptor antagonist
EBV	Epstein-Barr virus
EDA	Anhidrotic ectodermal dysplasia
EDA-ID	Anhidrotic ectodermal dysplasia with immunodeficiency
EO	Eosinophils
FA	Frequency of attacks
FCAS	Familial cold autoinflammatory syndrome
FILS	Facial dysmorphism, immunodeficiency, livedo, and short stature
FISH	Fluorescence in situ hybridization
GI	Gastrointestinal
GOF	Gain-of-function
HHV8	Human herpes virus type 8
Hib	*Haemophilus influenzae* serotype b
HIDS	Hyper IgD syndrome
HIES	Hyper IgE syndrome
HIGM	Hyper Ig M syndrome
HLA	Human leukocyte antigen
HLH	Hemophagocytic lymphohistiocytosis
HPV	Human papilloma virus
HSM	Hepatosplenomegaly
HSV	Herpes simplex virus
HUS	Hemolytic uremic syndrome
Hx	Medical history
IBD	Inflammatory bowel disease
IFNγ	Interferon gamma
Ig	Immunoglobulin
IL	Interleukin
IUGR	Intrauterine growth retard
LAD	Leukocyte adhesion deficiency
LOF	Loss-of-function
MC	Molluscum contagiosum
MKD	Mevalonate kinase deficiency
MSMD	Mendelian susceptibility to mycobacterial disease
MWS	Muckle-wells syndrome
N	Normal, not low
NK	Natural killer
NKT	Natural killer T cell
NN	Neonatal
NOMID	Neonatal onset multisystem inflammatory disease
NP	Neutropenia
PAPA	Pyogenic sterile arthritis, pyoderma gangrenosum, acne syndrome
PMN	Neutrophils
SCID	Severe combined immuno deficiency
Sd	Syndrome
SLE	Systemic lupus erythematosus
SPM	Splenomegaly
Staph	*Staphylococcus sp.*

subcl	Subclass
TCR	T-cell receptor
Tet	Tetanus
T	T lymphocyte
TNF	Tumor necrosis factor
TRAPS	TNF receptor-associated periodic syndrome
VZV	Varicella zoster virus
WBC	White blood cells
XL	X-linked

Introduction

Human Primary Immunodeficiency Diseases (PID) comprise at least 300 genetically-defined single-gene inborn errors of immunity [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]. They may be even more common, if we consider the emerging monogenic determinants leading to common infectious diseases, such as severe influenza [3]; autoimmune diseases, such as systemic lupus erythematosus [4], and auto-inflammatory diseases, such as Crohn's disease [5]. The International Union of Immunological Societies (IUIS) PID expert committee has

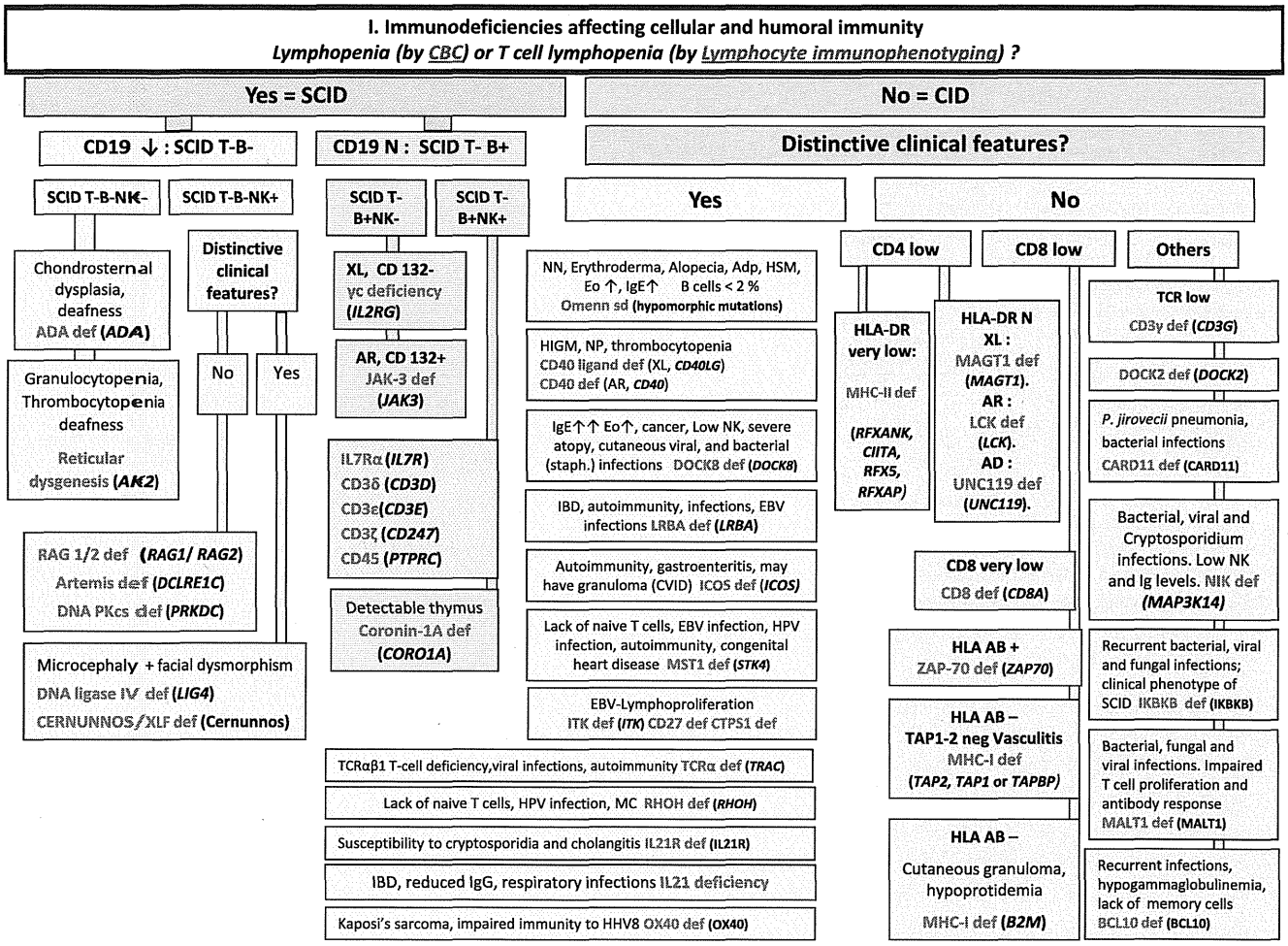

Fig. 1 Immunodeficiencies affecting cellular and humoral immunity. *ADA* Adenosine Deaminase, *Adp* adenopathy, *AR* Autosomal Recessive inheritance, *CBC* Complete Blood Count, *CD* Cluster of Differentiation, *CID* Combined Immunodeficiency, *EBV* Epstein-Barr Virus, *EO* Eosinophils, *HHV8* Human Herpes virus type 8, *HIGM* Hyper IgM syndrome, *HLA* Human Leukocyte Antigen, *HSM* Hepatosplenomegaly, *HPV* Human papilloma virus, *IBD* Inflammatory bowel disease, *Ig* Immunoglobulin, *MC* Molluscum contagiosum, *N* Normal, not low, *NK* Natural Killer, *NN* Neonatal, *NP* Neutropenia, *SCID* Severe Combined ImmunoDeficiency, *Staph Staphylococcus sp.*, *TCR* T-Cell Receptor, *XL* X-Linked

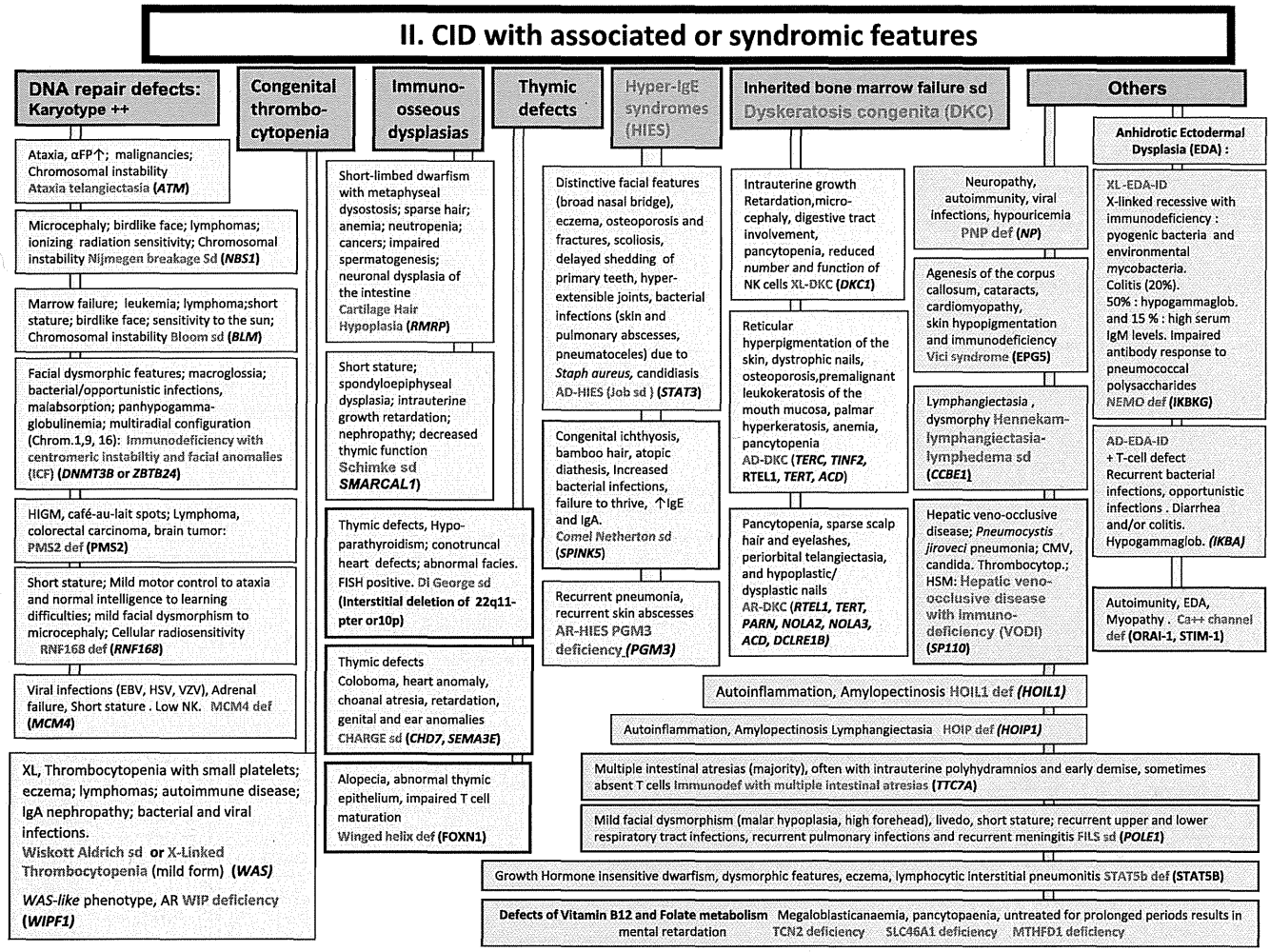

Fig. 2 CID with associated or syndromic features. These syndromes are generally associated with T-cell immunodeficiency. *αFP* alpha-fetoprotein, *AD* Autosomal Dominant inheritance, *AR* Autosomal Recessive inheritance, *CMF* Flow cytometry available, *EDA* Anhidrotic ectodermal dysplasia, *EDA-ID* Anhidrotic Ectodermal Dysplasia with Immunodeficiency, *FILS* Facial dysmorphism, immunodeficiency, livedo, and short stature, *FISH* Fluorescence in situ Hybridization, *HSM* Hepatosplenomegaly, *HSV* Herpes simplex virus, *Ig* Immunoglobulin, *VZV* Varicella Zoster virus, *WAS* Wiskott-Aldrich syndrome, *XL* X-Linked inheritance

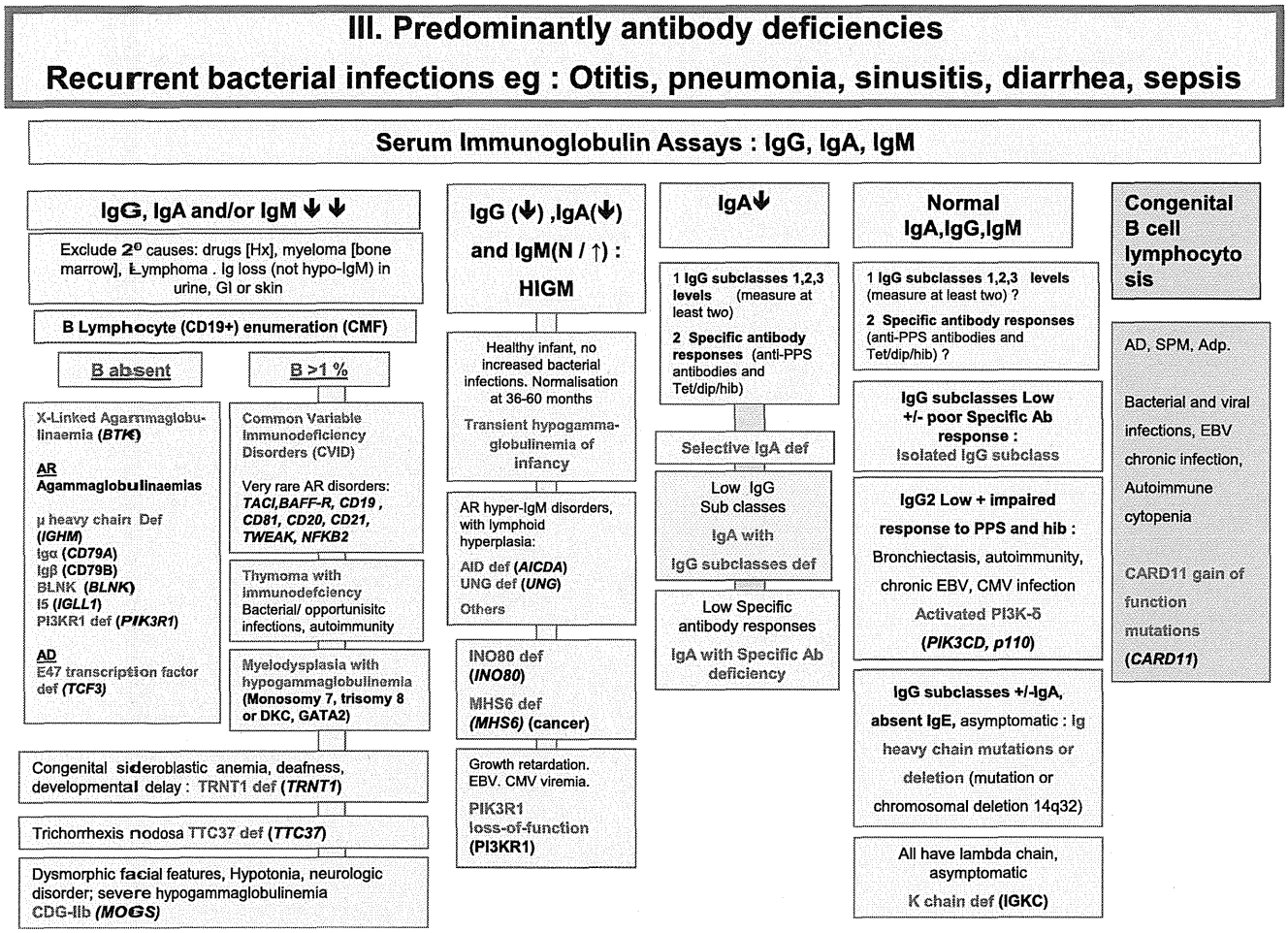

Fig. 3 Predominantly Antibody deficiencies. *Ab* Antibody, *Adp* adenopathy, *Anti PPS* Anti- pneumococcus Antibody, *AR* Autosomal Recessive inheritance, *CD* Cluster of Differentiation, *CDG-IIb* Congenital disorder of glycosylation, type IIb, *CMV* Cytomegalovirus, *CT* Computed Tomography, *EBV* Epstein-Barr Virus, *Dip* Diphtheria, *GI* Gastrointestinal, *Hib Haemophilus influenzae* serotype b, *Hx* medical history, *Ig* Immunoglobulin, *SPM* Splenomegaly, *subcl* subclass, *Tet* Tetanus, *XL* X-Linked inheritance

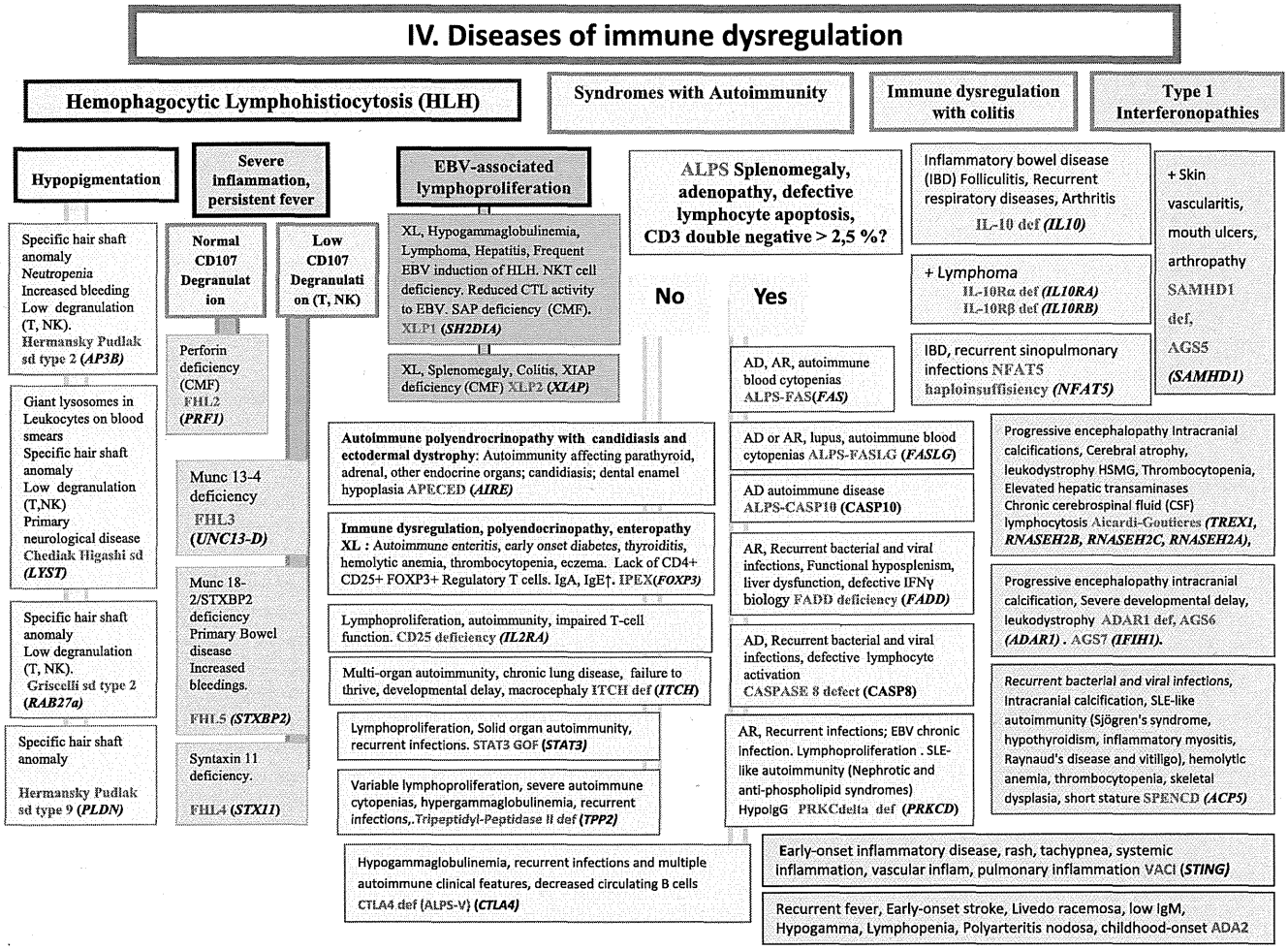

Fig. 4 Diseases of Immune Dysregulation. *AD* Autosomal Dominant inheritance, *ALPS* Autoimmune lymphoproliferative syndrome, *AR* Autosomal Recessive inheritance, *CD* Cluster of Differentiation, *CMF* Flow cytometry available, *CSF* Cerebrospinal fluid, *CTL* Cytotoxic T-Lymphocyte, *EBV* Epstein-Barr Virus, *GOF* Gain-of-function, *HLH* Hemophagocytic lymphohistiocytosis, *HSM* Hepatosplenomegaly, *IBD* Inflammatory bowel disease, *IFNγ* Interferon gamma, *Ig* Immunoglobulin, *IL* interleukin, *Inflam* Inflammation, *NK* Natural Killer, *NKT* Natural Killer T cell, *T* T lymphocyte, *XL* X-Linked inheritance

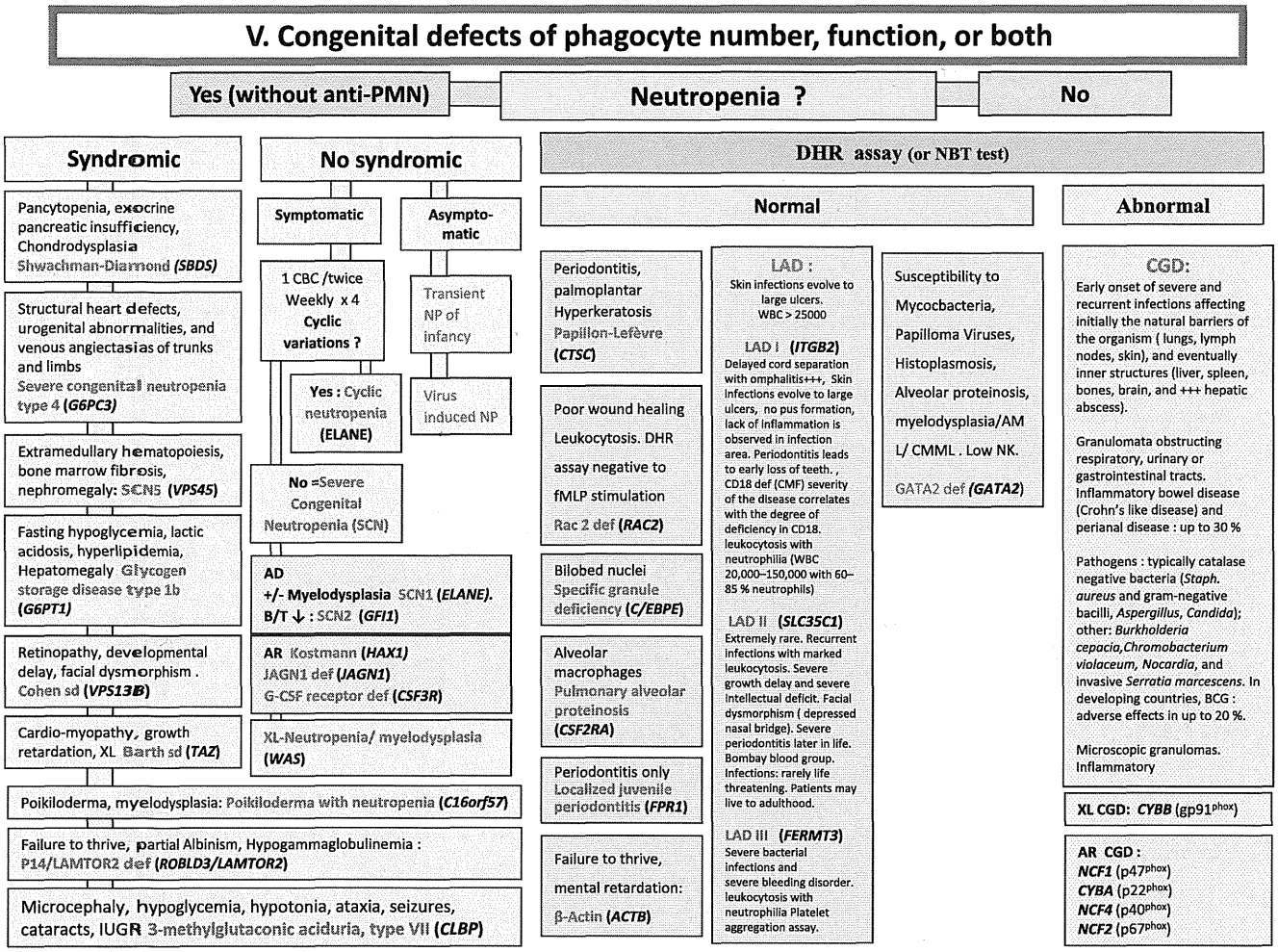

Fig. 5 Congenital defects of phagocyte number, function, or both. For DHR assay, the results can distinct XL-CGD from AR-CGD, and gp40phox defect from others AR forms. *AD* Autosomal Dominant inheritance, *AML* Acute Myeloid Leukemia, *AR* Autosomal Recessive inheritance, *BCG* Bacilli Calmette-Guérin, *CBC* Complete Blood Count, *CD* Cluster of Differentiation, *CGD* Chronic Granulomatous Disease, *CMML* Chronic MyeloMonocytic Leukemia, *DHR* DiHydroRhodamine, *IUGR* Intrauterine growth retard, *LAD* Leukocyte Adhesion Deficiency, *NP* Neutropenia, *PNN* Neutrophils, *SCN* Severe congenital neutropenia, *WBC* White Blood Cells, *XL* X-Linked inheritance

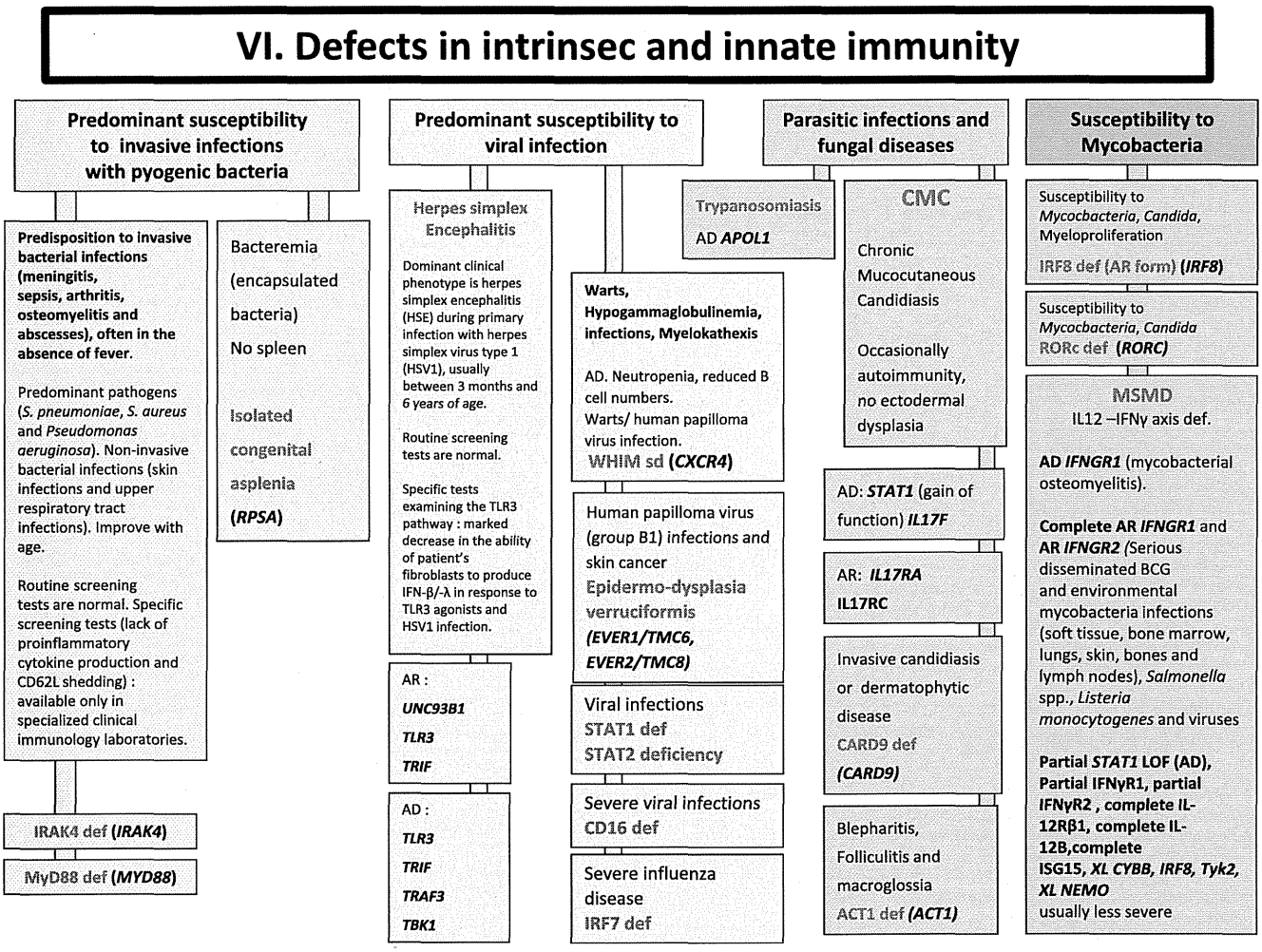

Fig. 6 Defects in Intrinsec and Innate Immunity. *AD* Autosomal Dominant inheritance, *AR* Autosomal Recessive inheritance, *BCG* Bacilli Calmette-Guérin, *BL* B lymphocyte, *CMC* Chronic mucocutaneous candidiasis, *HSV* Herpes simplex virus, *IFNγ* Interferon gamma, *Ig* Immunoglobulin, *IL* interleukin, *LOF* Loss-of-function, *MSMD* Mendelian Susceptibility to Mycobacterial Disease, *PMN* Neutrophils, *XL* X-Linked inheritance

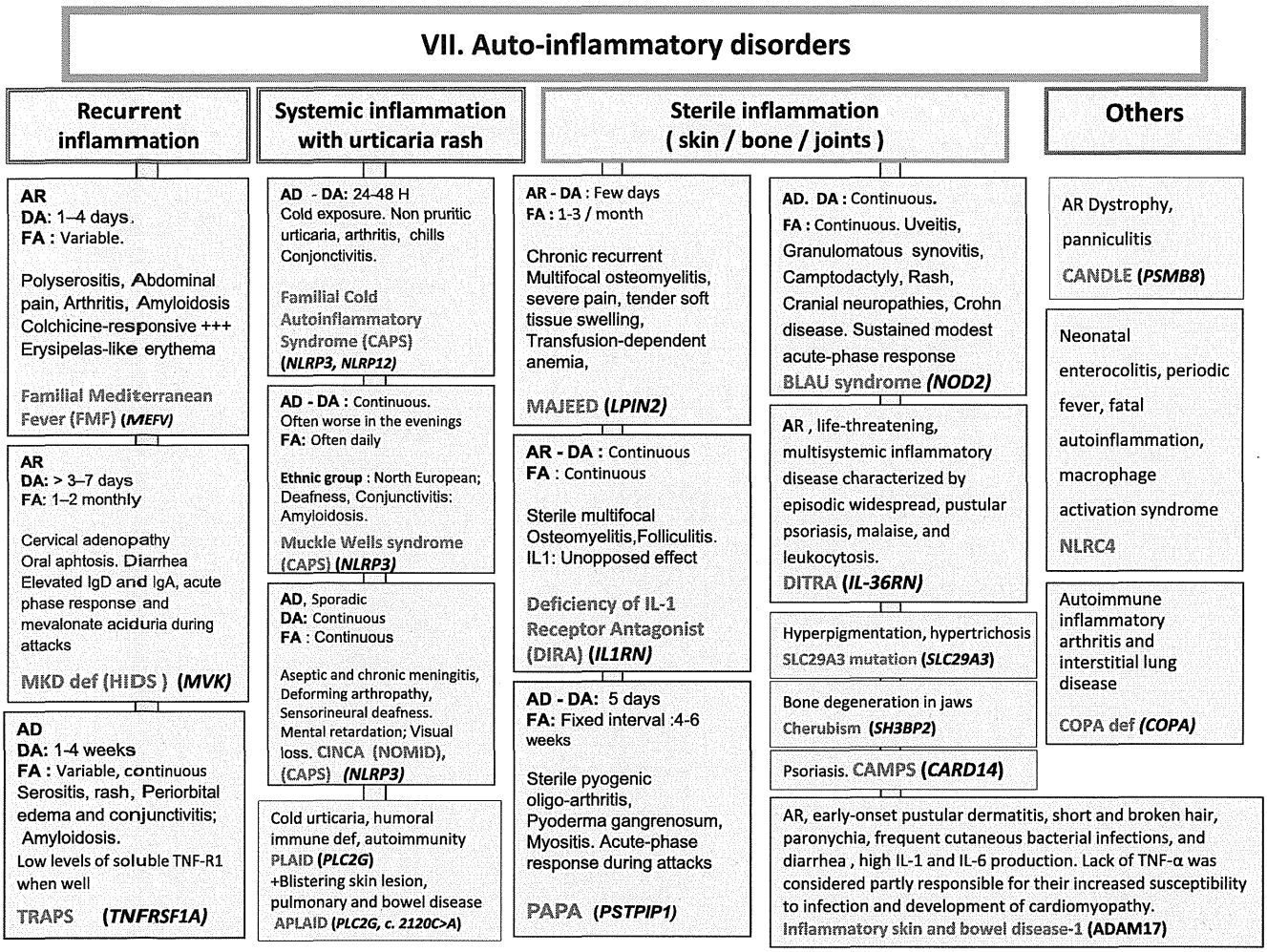

Fig. 7 Autoinflammatory Disorders. *AD* Autosomal Dominant inheritance, *AR* Autosomal Recessive inheritance, *CAMPS* CARD14 mediated psoriasis, *CANDLE* Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome, *CAPS* Cryopyrin-Associated Periodic syndromes, *CINCA* Chronic Infantile Neurologic Cutaneous and Articular syndrome, *DA* Duration of Attacks, *DITRA* deficiency of interleukin 36 Receptor antagonist, *FA* Frequency of Attacks, *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

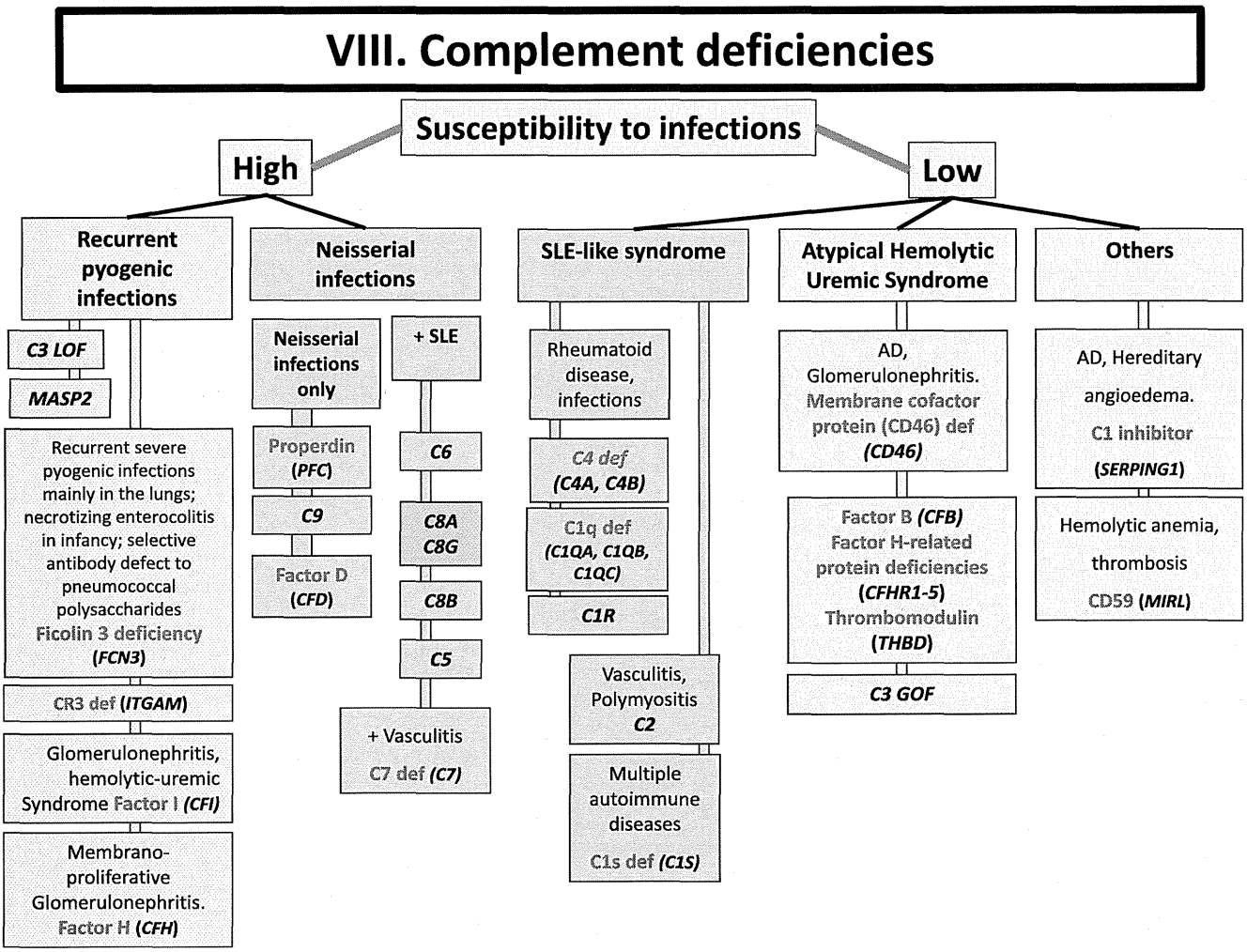

Fig. 8 Complement deficiencies. *AD* Autosomal Dominant inheritance, *GOF* Gain-of-function, *LOF* Loss-of-function, *LAD* Leukocyte Adhesion Deficiency, *SLE* Systemic Lupus Erythematosus

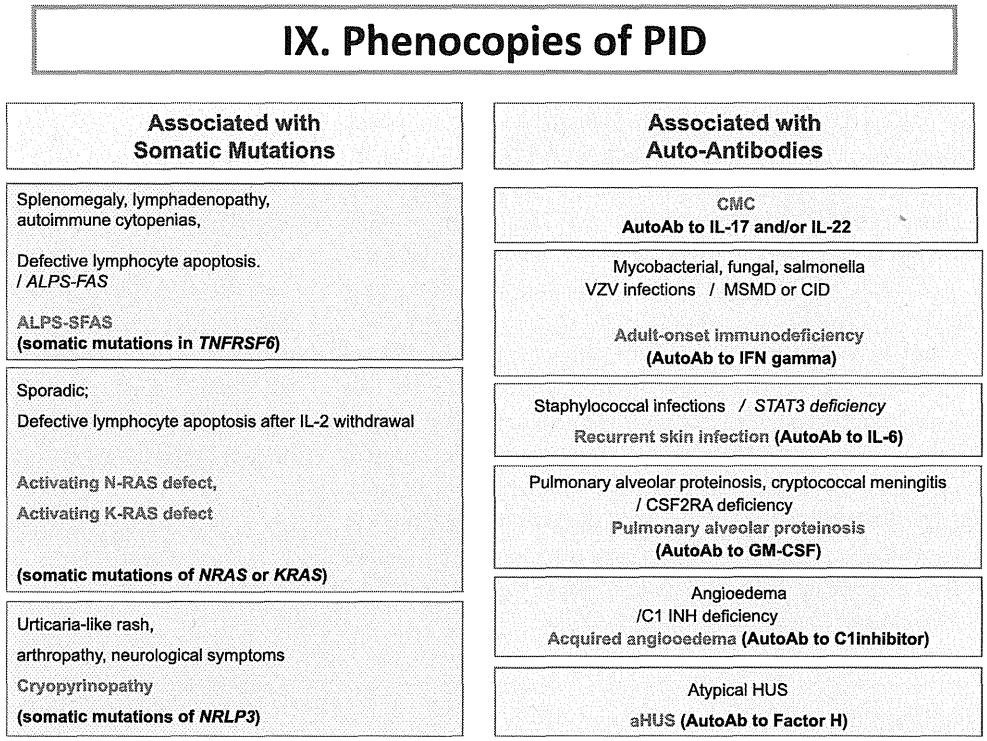

Fig. 9 Phenocopies of primary immunodeficiencies. *Ab* Antibody, *ALPS* Autoimmune lymphoproliferative syndrome, *CMC* Chronic mucocutaneous candidiasis, *CID* Combined Immunodeficiency, *HUS* Hemolytic uremic syndrome, *IFNγ* Interferon gamma, *IL* Interleukin, *MSMD* Mendelian Susceptibility to Mycobacteria Disease, *VZV* Varicella Zoster virus

proposed a PID classification [1], which facilitates clinical research and comparative studies world-wide; 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 classification may be cumbersome for use by the clinician at the bedside, the IUIS PID expert committee recently proposed a phenotypic complement to its classification [6]. As the number of PIDs is quickly increasing, and at an even faster pace since the advent of next-generation sequencing, the phenotypic classification from 2013 became outdated and requires revision at the same pace as the classical IUIS classification. Our original phenotypic classification proved successful, which placed it in the 96th percentile for citation rank in Springer journals [7]. Given the success of our user-friendly classification of PIDs, providing a tree-based decision-making process based on the observation of clinical and biological phenotypes, we present here an update of these figures, based on the accompanying 2015 PID classification.

Methodology

We included all diseases included in the 2015 update of the IUIS PID classification [1], keeping the nine major categories unchanged. In addition, we considered other articles proposing a PID classification published recently [8, 9]. 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. In addition, we classed diseases or genes from most common to less common, at the best of our knowledge [10, 11]. These algorithms were first established by a small committee; then validated by one or two experts for each figure.

Results

An update of our classification, validated by the IUIS PID expert committee, is presented in Figs. 1, 2, 3, 4, 5, 6, 7, 8 and 9.

Discussion

Since our 2013 study, 70 new diseases have been included in the 2015 classification. Four disorders have been removed, as the reports concerning associated immunodeficiency or genetic base were not confirmed. We also eliminated duplication of a disease in more than one figure and profoundly revised some figures, following the 2015 IUIS classification.

Conclusion

The IUIS PID expert committee developed this phenotypic classification in order to help clinicians at the bedside to diagnose PIDs but also to promote collaboration with national and international research centers. Needless to say, the expert committee encourages the development of other types of PID classification. Indeed, given the success encountered by the two current IUIS classifications, others classifications are likely to be useful and complementary.

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on by climate changes and allowed them to coalesce, potentially leading to the eventual regime shifts and collapses observed in megafaunal ecosystems. The lack of evidence for larger-scale ecological regime shifts during earlier periods of the Glacial (i.e., >45 ka) when interstadial events were common, but modern humans were not, supports a synergistic role for humans in exacerbating the impacts of climate change and extinction in the terminal Pleistocene events.

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SUPPLEMENTARY MATERIALS

www.sciencemag.org/content/349/6248/602/suppl/DC1
Materials and Methods
Supplementary Text
Figs. S1 to S8
Tables S1 to S4
References (*43*–*54*)

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IMMUNODEFICIENCIES

Impairment of immunity to *Candida* and *Mycobacterium* in humans with bi-allelic *RORC* mutations

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Human inborn errors of immunity mediated by the cytokines interleukin-17A and interleukin-17F (IL-17A/F) underlie mucocutaneous candidiasis, whereas inborn errors of interferon-γ (IFN-γ) immunity underlie mycobacterial disease. We report the discovery of bi-allelic *RORC* loss-of-function mutations in seven individuals from three kindreds of different ethnic origins with both candidiasis and mycobacteriosis. The lack of functional RORγ and RORγT isoforms resulted in the absence of IL-17A/F–producing T cells in these individuals, probably accounting for their chronic candidiasis. Unexpectedly, leukocytes from RORγ- and RORγT-deficient individuals also displayed an impaired IFN-γ response to *Mycobacterium*. This principally reflected profoundly defective IFN-γ production by circulating γδ T cells and $CD4^+CCR6^+CXCR3^+$ αβ T cells. In humans, both mucocutaneous immunity to *Candida* and systemic immunity to *Mycobacterium* require RORγ, RORγT, or both.

Inborn errors of human interleukin-17A and interleukin-17F (IL-17A/F) or interferon-γ (IFN-γ) immunity are each associated with a specific set of infections. Inborn errors of IL-17A/F underlie chronic mucocutaneous candidiasis (CMC), which is characterized by infections of the skin, nails, and oral and genital mucosae with *Candida albicans*, typically in the absence of other infections. Five genetic etiologies of CMC have been reported, with mutations in five genes (*1*, *2*). Inborn errors of IFN-γ underlie Mendelian susceptibility to mycobacterial disease (MSMD), which is characterized by selective susceptibility to weakly pathogenic mycobacteria, such as *Mycobacterium bovis* Bacille Calmette-Guérin (BCG) vaccines and environmental mycobacteria. Eighteen genetic etiologies of MSMD have been reported, involving mutations of nine genes (*3*, *4*). Only a few patients display both candidiasis and mycobacteriosis, including some