e27 Primary Immunodeficiencies Associated with or Secondary to Other Diseases

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Immunodeficiency is seen as an associated feature in a wide variety of inherited disorders or may be acquired as a consequence of infection or drug treatments. Table e27-1 categorizes conditions in which the immunodeficiency is an integral component or a secondary consequence.

Gene mutations have now been identified as the cause of many primary immunodeficiencies. Table e27-2 categorizes currently recognized aberrant genes according to the predominant immunologic deficit or well-defined syndrome.

TABLE e27-1 IMMUNODEFICIENCIES ASSOCIATED WITH OR SECONDARY TO OTHER CONDITIONS[a]

Chromosomal Instability or Defective Repair

- Ataxia-telangiectasia (*ATM*)
- Bloom syndrome (*BLM* helicase)
- DNA ligase IV deficiency (*LIG4*)
- Fanconi anemia (multiple complementation groups)
- Immunodeficiency-centromeric instability-facial anomalies (ICF) syndrome (*DNMT3B* DNA methyltransferase, other)
- Nijmegen breakage syndrome (*Nibrin*)
- Seckel syndrome (*ATR*)
- Xeroderma pigmentosum (multiple complementation groups)

Chromosomal Defects

- Deletions or rings of chromosome 18 (18p– and 18q–)
- Down syndrome (trisomy 21)
- Monosomy 22
- Trisomy 8
- Turner syndrome (X chromosome monosomy)

Drug-Induced Hypogammaglobulinemia

- Antimalarial agents
- Captopril
- Carbamazepine
- Glucocorticoids
- Fenclofenac
- Gold salts
- Lamotrigine
- Penicillamine
- Phenytoin
- Sulfasalazine

Hereditary Defects of T Cell Regulation

- Autoimmune Lymphoproliferative Syndrome (ALPS)
  - ALPS 1A (*CD95*)
  - ALPS 1B (*CD95L*)
  - ALPS2A (*CASP10*)
  - ALPS2B (*CASP8*)
- Autoimmune polyendocrinopathy syndrome (APECED), type 1 (*AIRE*)
- Immunodysregulation, polyendocrinopathy, and enteropathy, X-linked (IPEX) (*FOXP3*)

Hereditary Metabolic Defects

- α-Mannosidosis (*MAN2B1*)
- Acrodermatitis enteropathica, zinc deficiency type (*SLC39A4*)
- Propionyl-CoA carboxylase, beta subunit, deficiency (*PCCB*)
- Chédiak-Higashi syndrome (*CHS1*)
- Glycogen storage disease, type 1b (*G6PT1*)
- Hyperzincemia with functional zinc depletion
- Orotic aciduria I (*UMPS*)
- Transcobalamin 2 deficiency (*TCN2*)

Hypercatabolism of Immunoglobulin

- Familial hypercatabolism
- Intestinal lymphangiectasia

Immunodeficiency with Dermatologic Defects

- Dyskeratosis congenita
  - Autosomal dominant (*TERC*)
  - Autosomal recessive
  - X-linked, Zinsser-Cole-Engman syndrome (*dyskerin*)
- Ectodermal dysplasia, anhidrotic, with T cell deficiency, autosomal dominant (*NFKBIA*)
- Ectrodactyly-ectodermal dysplasia-clefting syndrome
- Griscelli syndrome, partial albinism (*RAB27A*)
- Netherton syndrome (*SPINK5*)
- Trichothiodystrophy, congenital ichthyosis (*ERCC2/XPD* or *ERCC3/XPB*)

Immunodeficiency with Generalized Growth Retardation

- Schimke immuno-osseous dysplasia (*SMARCAL1*)
- Dubowitz syndrome
- Kyphomelic dysplasia with SCID
- Mulibrey nanism (*TRIM37*)
- Progeria (Hutchinson-Gilford syndrome) (*LMNA*)
- Thumb agenesis, short stature, and immunodeficiency
- X-linked agammaglobulinemia with growth hormone deficiency (*BTK*)

Infectious Diseases

- Congenital rubella
- Congenital infection with cytomegalovirus
- Congenital infection with *Toxoplasma gondii*
- Epstein-Barr virus
- Human immunodeficiency virus

Malignancy

- Chronic lymphocytic leukemia
- Immunodeficiency with thymoma

Other

- Cartilage-hair hypoplasia (endoribonuclease *RMRP*)
- Chronic mucocutaneous candidiasis
- Hereditary or congenital hyposplenia or asplenia (Ivemark syndrome)
- Liver transplantation
- Mannose binding lectin deficiency (MBL2)
- Omenn syndrome (AIRE, Artemis, IL7RA, RAG 1/2)

[a]Mutant genes are indicated in parentheses.

TABLE e27-2 GENES OR GENETIC LOCI ASSOCIATED WITH PRIMARY IMMUNODEFICIENCIES

Disorder	Gene or Locus	Chromosome
Severe Combined Immunodeficiency (SCID)		
Adenosine deaminase deficiency	*ADA*	20q13.11
Artemis deficiency (SCIDA)	*ARTEMIS*	10p
DNA ligase IV deficiency	*LIG4*	13q22-q34
CD45 deficiency	*CD45*	1q31-32
DNA-dependent protein kinase deficiency	*PRKDC*	8q11
Interleukin receptor γ chain deficiency	*IL2RG*	Xq13
Janus-associated kinase 3 deficiency	*JAK3*	19p13.1
Recombinase activating gene deficiency	*RAG1, RAG2*	11p13
Primary T Cell Immunodeficiency		
Antigen peptide transporter deficiency	*TAP1, TAP2*	6p21.3
CD8 deficiency	*CD8*	2p12
diGeorge syndrome	*DGCR1*	22q11
	DGCR2	10p13
Interleukin 7 receptor α deficiency	*IL7R*	5p13
LCK deficiency	*LCK*	1p34.3-1p35
Nude syndrome	*WHN*	17q11-q12
T cell receptor deficiency		
CD3γ	*CD3G*	7q35
CD3δ, CD3ε	*CD3D, CD3E*	11q23
CD3ζ	*CD3Z*	1q22-q23
MHC class II deficiency		
MHC class II transactivator (group A)	*CIITA*	16p13
Regulatory factor X, ankyrin repeat–containing (group B)	*RFXANK*	19p12
Regulatory factor X, 5 (group C)	*RFX5*	1q21.1-q21.3
Regulatory factor X–associated protein (group D)	*RFXAP*	13q14
Zeta chain–associated protein kinase deficiency	*ZAP70*	2q12
Purine nucleotide phosphorylase deficiency	*NP*	14q13.1

Disorder	Gene or Locus	Chromosome
Predominantly Antibody Deficiencies		
IgA deficiency/common variable immunodeficiency	*MHC*	6p21.3
TACI deficiency (autosomal dominant)	*TNFRSF13B*	17p11.2
Common variable immunodeficiency		
ICOS deficiency (autosomal recessive)	*ICOS*	2q33
BAFF-R	*TNFRSF13C*	22q13.1-q13.31
CD19 deficiency (autosomal recessive)	*CD19*	16p11.2
Hyper-IgM syndrome		
Activation-induced cytidine deaminase deficiency	*HIGM2*	12p13
CD40 deficiency	*HIGM3*	20q12-q13.2
Uracil-DNA glycosylase (UNG) deficiency	*HIGM5*	12q23-q24.1
X-linked hyper-IgM syndrome (XHM)	*HIGM1*	Xq26
XHM with ectodermal dysplasia (XHM-ED)	*IKBKG, NEMO*	Xq28
Immunoglobulin-associated beta (Igβ) deficiency	*CD79B*	17q23
Immunoglobulin heavy chain deficiencies	*IGHG1*	14q32.33
BLNK deficiency	*BLNK*	10q23.2
Surrogate light chain deficiency	*IGLL1*	22q11.21
LRRC8 truncation	*LRRC8*	9q34.13
X-linked agammaglobulinemia	*BTK*	Xq21.3-q22
Other Well-Defined Immunodeficiency Syndromes		
Atypical mycobacteriosis, familial		
Interferon γ receptor 1 deficiency	*IFNGR1*	6q23-q24
Interferon γ receptor 2 deficiency	*IFNGR2*	21q22.1-22.2
Interleukin 12 deficiency	*IL12B*	5q31-q33
Interleukin 12 receptor deficiency	*IL12RB1*	19p13.1
STAT1 deficiency	*STAT1*	2q32
Interleukin 1 receptor–associated kinase 4 deficiency	*IRAK4*	12q12
WHIM syndrome	*CXCR4*	2q21
Wiskott-Aldrich syndrome	*WAS*	Xp11.23-p11.22
X-linked lymphoproliferative syndrome	*SH2D1A/SAP*	Xq25