Immunodeficiency Disorders

By Melissa Pugliano-Mauro, MD, and Wendy Myers, MD. (Updated July 2015)*

DISEASE	INHERITANCE/GENE	INFECTIONS	KEY IMMUNOLOGIC FEATURES	MALIGNANCY	CLINICAL MANIFESTATIONS	TREATMENT
X-linked Agamma-globulinemia (Bruton Syndrome)	• X-linked recessive (90%) • AR (10%) • Bruton tyrosine kinase (Btk): maturation block in pre-B cell to B-cell differentiation	Gram-positive pyogenic infections	• Absent IgM, A, D, E • Small amount of IgG • B cells lacking • CMI intact	Lympho-reticular malignancies, especially leukemia	Atopic dermatitis, vasculitis, urticaria, no palpable lymph nodes (no geminal centers), diarrhea and growth failure	IVIG
Isolated IgA deficiency	• AD or AR: TNFRSF13B gene • Acquired (phenytoin or chemotherapy) • Defect in maturation of B-cell as it develops into IgA-producing plasma cell	One half have repeated infections	• Absent or low IgA • One half have Anti-IgA antibodies	Risk is increased	• 1 out of 600 white persons • Most common immunodeficiency disorder • Anaphylaxis to IVIG or transfusions • Asthma, autoimmunity (increase collagen vascular disease [SLE], celiac, UC, vitiligo) • Atopic dermatitis	
Common Variable Immuno-deficiency (CVID)	• Acquired • HLA B8 & DR3	Recurrent sinopul-monary infections	• Most Ig classes low with no antibodies to bacterial antigens • B cells are present but abnormal differentiation	• Lympho-reticular malignancies: lymphoma (400-fold) • Increase risk of cancer (10-fold overall)	• Second most common immunodeficiency disorder (after IgA deficiency) • Eczematous dermatitis, pyoderma, moniliasis , verruca, dermatophyte infections • Autoimmunity (vitiligo, alopecia areata, hemolytic anemia, ITP, vasculitis), GI abnormalities • Cutaneous and visceral non-infectious granulomas	
Immuno-deficiency with Hyper IgM	• X-linked: CD40LG (CD40 ligand on T cells) • AR: CD40 (on B cells)	Respiratory infections, otitis media	• Normal or elevated IgM, D • Low or absent IgG, A, E • Recurrent neutropenia		• Autoimmunity (thyroiditis and hemolytic anemia) • Painful oral and anogenital ulcers, diarrhea, widespread therapy-resistant warts	IVIG, allogenic BMT
Cartilage-hair Hypoplasia Syndrome	• AR: RMRP gene encodes RNA component of ribonucleoprotein endoribonuclease • Commonly in Amish and Finns	Severe varicella zoster and HSV infections	• Defective CMI • Minority of patients with defective humoral immunity • Hypoplastic anemia	Non-Hodgkin's lymphoma and BCC	• Short-limbed dwarfism, fine sparse hypopigmented hair, doughy skin with abnormal elastic tissue • Hirschsprung disease, impaired spermatogenesis	
Omenn Syndrome	• AR: RAG-1 and RAG-2 • Form of SCID	Recurrent infections	• Hypogamma-globulinemia with elevated IgE • Antibody production and CMI impaired • Eosinophilia • TcR rearrangements restricted with inefficient and/or abnormal generation of TcR		• Mimics GVHD • Exfoliative erythroderma (starting at a few weeks old) with alopecia • Diarrhea, HSM, LAD, early death	
Severe Combined Immuno-deficiency (SCID)	• X-linked Rec: deficiency of □ chain of IL-2 receptor (most common); IL2RG • AR: adenosine deaminase or JAK3	*Pseudomonas, Staph, Enterobac- teriaceae,* and *Candida* Viral infection; usual cause of death	• Impaired humoral and CMI • Deficiency or total absence of circulating lymphocytes • Mature T cells absent • B cells normal or decreased • Ig's low • Lack NK cells		• Thymus is small or absent • Triad: moniliasis of oropharynx and skin, intractable diarrhea and pneumonia • Recurrent infections, failure to thrive and intractable diarrhea apparent within first few months of life • Morbilliform eruption/ seborrheic dermatitis- like/LP-like/sclero-dermatous—GVHD secondary to in utero maternal lymphocytes, nonirradiated transfusions	BMT, antibiotics, irradiated blood products, gene therapy, recombinant IL-2 infusion

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Wiskott- Aldrich Syndrome	• X-linked recessive: WASP gene encodes WASP protein, which is important in lymphocyte and megakaryocyte signal trans- duction and actin filament assembly; • Impairs T cell activation and NK cell function. • Important in regulation of high affinity IgE receptor on mast cells	• Pyoderma, recurrent sinopulmonary infections (e.g. suppurative otitis media), infections with encapsulated organisms (e.g. pneumonia and meningitis) • Increased susceptibility to HSV (eczema herpeticum)	• Elevated IgA, D, E • Decreased IgM • Low or NL IgG • Impaired humoral and CMI	Lymphoreticular malignancy (up to ¼ of survivors develop lymphoma)	• Triad: chronic eczematous dermatitis, infections, thrombocytopenia with splenomegaly and purpura • Bloody diarrhea may distinguish this from SCID • Molluscum, HSV	Platelet transfusions, splenectomy, IVIG, BMT
Chronic Granuloma- tous Disease	X-linked recessive: gp91- phox (phagocyte oxidase) gene; CYBB gene which leads to absence of NADPH oxidase activity AR (24%): p47 and p67- phox genes; CYBA, NCF 1 and 2	*Staph aureus, Aspergillus fumigatus, Burkholderia cepacia, Candida* spp., atypical mycobacteria	• Deficiency of NADPH- oxidase complex with defective ability to generate hydro- gen peroxide and inability to kill intracellular organisms • Elevated IgG, M, A • Neutrophil leukocytosis		• Eczema of the scalp, backs of ears, face • Purulent and granulomatous infections of long bones, lym- phatic tissue, liver, skin and lungs • Ulcerative stomatitis, furunculosis, subcutaneous abscesses and suppurative LAD • Nitro-blue tetrazolium (NBT) is low/no blue color change • Female carriers: increased infections, arcuate dermal and DLE-like skin lesions, and aphthous stomatitis	• BMT/ stem cell transplantaion • Prophylaxis with trime- thoprim- sulfametho- xazole and itraconazole • IFN-γ to reduce frequency of infections
Chediak-Higashi Syndrome	AR: LYST (lysosomal trafficking regulator) gene which leads to defective vesicular transport to and from the lysosome, causing giant perinuclear vesicles in neutrophils (leukocytes with large azurophilic giant granules), melanocytes and neurons	Enteric bacterial organisms, bacterial sinusitis & pneumonia (*S. pyrogenes, S. pneumoniae*), superficial pyodermas	• Neutropenia • Neutrophils do not phagocytose normally and there is defective chemotaxis • Ig's normal • Melanocytes— pigmentary dilution • Neurons— progressive deterioration	• Lymphoma or other cancers usually cause early death • 85% with accelerated phase: lympho- histiocytic proliferation with infiltration of liver, spleen and LNs	• Light blond hair with silver sheen (small regularly spaced clumps of melanin on light microscopy), pigmented nevi, slate-gray skin color, bruises • Ocular albinism with nystagmus and photophobia • Pancytopenia • HSM • Platelet storage pool deficiency—petechiae, gingival bleeding, ecchymoses, epistaxis	BMT is treatment of choice and should be performed early (before accelerated phase)
Griscelli Syndrome	AR: Myosin-Va or RAB27A genes play a role in membrane transport and organelle trafficking, e.g. transfer of melanosomes	Pyogenic systemic infections		Accelerated phase as well	• Neutropenia, thrombocytopenia • Silver-gray hair, eyebrows and eyelashes (uneven clusters of melanin in the medulla on light microscopy) • Pigment dilution of the skin • HSM	BMT
Hyperimmuno- globulinemia E Syndrome (including Job Syndrome)	AD: STAT3 gene (signal transducer and activator of transcription 3) is critical to IL-6 pathway (acute phase response) AR: DOK8 gene	Furunculosis, sinopulmonary infections, cold abscesses *S. aureus, Candida* spp., Strep	• High IgE, D and IgE anti- staph antibodies • Eosinophilia • Chemotaxis of neutrophils and monocytes impaired		• Eczema, coarse facies, papular prurigo, keratoderma of palms and soles • Recurrent OM, bronchitis/ pneumonia, chronic mucocutaneous candidiasis, furuncles, carbuncles and abscesses • Osteopenia with fractures, scoliosis and dental abnormalities (retention of primary teeth) • Job Syndrome: females with red hair, freckles, blue eyes and hyper-extensible joints with cold abscesses	

Abbreviations:
AD: *autosomal dominant*
AR: *autosomal recessive*
BCC: *basal cell carcinoma*
BMT: *bone marrow transplant*
CM: *cell mediated immunity*
GVHD: *graft versus host disease*
HSM: *hepatosplenomegaly*
HSV: *herpes simplex virus*
Ig: *immunoglobulin*
ITP: *idiopathic thrombocytopenic purpura*
LAD: *lymphadenopathy*
LN: *lymph nodes*
NCF: *neutrophil cytosol factors*
NL: *normal*
OM: *otitis media*
TcR: *T cell receptor*

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