RESIDENT ROUNDS: PART II

Primary Immunodeficiencies

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INTRODUCTION

The primary immunodeficiencies (PIDs) can be classified by their effects on innate and adaptive immunity, and must be distinguished from secondary immunodeficiencies, which are commonly caused by medications, infections, and malnutrition. PIDs commonly present with recurrent infections and cutaneous manifestations, but can also result in autoimmune disease, allergy, and malignancy due to immune dysregulation.[1,2]

Cutaneous Manifestations of Primary Immunodeficiencies

Primary Immunodeficiency	Most Common Inheritance	Affected Gene	Functional Defect	Distinct Cutaneous Manifestations	Distinct Associations	Select Laboratory Findings
Innate Immunity						
Neutrophils, Macrophages						
Chédiak-Higashi syndrome[3]	AR	LYST	Lysosomal trafficking in neutrophils, melanocytes, platelets	Pigmentary dilution of skin, hair, eyes; silvery/metallic hair	Bleeding diathesis; cytopenias; neurologic deterioration	Giant granules within neutrophils; small clumps of melanin in hairs
Chronic granulomatous disease[3]	XR	CYBB	NADPH oxidase enzyme complex, respiratory burst to kill phagocytosed organisms	Granulomas; DLE-like skin lesions; Sweet's syndrome; oral ulcers	Suppurative adenitis	<10% normal nitroblue tetrazolium reduction
Complement						
C2 complement deficiency[7]	AR	C2	Classical pathway component	Encapsulated bacterial infections; leukocytoclastic vasculitis, urticaria, atrophoderma	Increased risk of SLE, SCLE, DLE, dermatomyositis	Decreased CH50

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Adaptive Immunity						
T-cells						
Hyperimmunoglobulin-E (HIES) syndrome (Job's syndrome)[4,5]	AD	STAT3	Th17 response	Cold abscesses; cephalic neonatal papulopustular eruption, followed by eczematous dermatitis	Craniofacial features (hypertelorism, broad nasal root, prognathism, retained primary teeth); scoliosis; joint hyperextensibility	Increased IgE
HIES[4,5]	AR	DOCK8	Actin cytoskeleton regulation in T-cells/NK cells	Viral infections (HSV, VZV, MCV, HPV); eczematous dermatitis	Asthma; allergies; cancer (SCC, lymphoma)	Increased IgE
Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX)[4,5]	XR	FOXP3	Regulatory T-cells	Eczematous dermatitis; psoriasiform dermatitis; cheilitis; onychodystrophy; alopecia	Autoimmune disease (thyroiditis, diabetes mellitus, enteropathy, hemolytic anemia); allergies	Increased IgE/IgA
Chronic mucocutaneous candidiasis (CMC)[6,8]	AD	STAT1	Th17 response	Candidiasis; disseminated coccidioimycosis; histoplasmosis	Autoimmune disease (thyroiditis, diabetes mellitus)	
CMC[6,8]	AR	Dectin-1, CARD9, IL17RA, ACT1	Th17 response	Vulvovaginal candidiasis (dectin-1, CARD9); invasive fungal infections (CARD9)		
Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED)[6,9]	AR	AIRE	Autoreactive T-cell deletion, thymic negative selection	Vitiligo; alopecia areata/universalis	Autoimmune disease (hypoparathyroidism, adrenal insufficiency, hypothyroidism)	
Wiskott-Aldrich syndrome[10]	XR	WASP	Actin filament assembly in platelets/T-cells	Encapsulated bacterial infections; flexural eczematous dermatitis; petechiae, ecchymoses; leukocytoclastic vasculitis	Thrombocytopenia; hemolytic anemia; inflammatory bowel disease; allergies; asthma; lymphoma	Small platelets
Severe combined immunodeficiency (SCID)[1,11]	XR	IL2RG	Cytokine receptors and signaling	Seborrheic-like dermatitis or morbilliform eruptions (materno-fetal GVHD)		Decreased T-cells

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T-cells (continued)						
SCID[1,11]	AR	ADA	Increased lymphocyte apoptosis	Same		No T/B-cells
Griscelli syndrome, type 2[12]	AR	RAB27A	Vesicle movement/ transfer in melanocytes and cytotoxic T-cells	Pigmentary dilution of skin and hair; silvery/ metallic hair	Cytopenias	Large clumps of melanin in hairs
B-cells						
Agammaglobulinemia[1,11]	XR	BTK	Pre-B-cell receptor signaling	Eczematous dermatitis; dermatomyositis-like eruption	Viral infections (hepatitis B, enterovirus); lymphoma	Decreased IgG
Common variable immunodeficiency (CVID)[1,11]	AD/AR	Many	B-cell Ig class switching, somatic hypermutation	Eczematous dermatitis; vitiligo; alopecia areata; vasculitis	Hemolytic anemia; increased overall cancer risk	Decreased IgG/IgA
Selective IgA deficiency[1,11]	AD	Unknown	B-cell Ig class switching	85-90% are asymptomatic		Decreased IgA
Hyper-IgM syndromes[1,11]	XR	CD40LG	B-cell Ig class switching	Oral and anogenital ulcers	Neutropenia; thrombocytopenia; hemolytic anemia	Increased IgM
Miscellaneous						
Ataxia-telangiectasia[13]	AR	ATM	Cell cycle checkpoint, DNA damage repair	Oculocutaneous telangiectasias; eczematous dermatitis; granulomas	Cerebellar ataxia; chromosomal instability; premature aging; cancer (BCC, leukemia/lymphoma)	Decreased IgA/IgE/IgG
Leukocyte adhesion deficiency (LAD)-I[14]	AR	ITGB2	β-2 integrin subunit (CD18), leukocyte migration	Gingivitis; chronic ulcers; atrophic scarring	Delayed umbilical cord separation	Neutrophilia
LAD-II[14]	AR	FUCT1	Leukocyte tethering/ rolling	Same	Mild LAD-I features; mental retardation; short stature	Neutrophilia
LAD-III[14]	AR	KIND3	Integrin activation	Same	LAD-I features; bleeding diathesis	Neutrophilia
Cartilage-hair hypoplasia syndrome[15]	AR	RMRP	mDNA, rRNA processing	Viral infections (varicella, herpes); fine, sparse, hypopigmented hair	Short-limbed dwarfism; cancer (lymphoma, BCC)	

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Miscellaneous (continued)						
Phosphoglucomutase 3 deficiency[5]	AR	PGM3	Glycosylation pathway	Cold abscesses; viral infections (HSV, MCV); eczematous dermatitis; leukocytoclastic vasculitis	Allergies; asthma; neurological symptoms	Eosinophilia

DISCLOSURES

The authors have no relevant conflicts of interest to disclose.

REFERENCES

1. Al-Herz W, Bousfiha A, Casanova JL, et al. Primary immunodeficiency diseases: an update on the classification from the international union of immunological societies expert committee for primary immunodeficiency. *Front Imunol.* 2014;5:162.
2. Relan M, Lehman HK. Common dermatologic manifestations of primary immune deficiencies. *Curr Allergy Asthma Rep.* 2014;14(12):480.
3. Dinauer MC. Disorders of neutrophil function: an overview. *Meth Mol Biol.* 2014;1124:501-515.
4. Farmand S, Sundin M. Hyper-IgE syndromes: recent advances in pathogenesis, diagnostics and clinical care. *Curr Opin Hematol.* 2015;22(1):12-22.
5. Pichard DC, Freeman AF, Cowen EW. Primary immunodeficiency update: Part I. Syndromes associated with eczematous dermatitis. *J Am Acad Dermatol.* 2015;73(3):355-364.
6. Pichard DC, Freeman AF, Cowen EW. Primary immunodeficiency update: Part II. Syndromes associated with mucocutaneous candidiasis and noninfectiouus cutaneous manifestations. *J Am Acad Dermatol.* 2015;73(3):367-381.
7. Truedsson L. Classical pathway deficiencies - A short analytical review. *Mol Immunol.* 2015. [Epub ahead of print]
8. Kisand K, Peterson P. Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy and other primary immunodeficiency diseases help to resolve the nature of protective immunity against chronic mucocutaneous candidiasis. *Curr Opin Pediatr.* 2013;25(6):715-721.
9. De Martino L, Capalbo D, Improda N, et al. APECED: A paradigm of complex interactions between genetic background and susceptibility factors. *Front Immunol.* 2013;4:331.
10. Kallikourdis M, Viola A, Benvenuti F. Human immunodeficiencies related to defective APC/T cell interaction. *Front Immunol.* 2015;6:433.
11. Ochs HD, Hagin D. Primary immunodeficiency disorders: general classification, new molecular insights, and practical approach to diagnosis and treatment. *Ann Allergy Asthma Immunol.* 2014;112(6):489-495.
12. Van Gele M, Dynoodt P, Lambert J. Griscelli syndrome: a model system to study vesicular trafficking. *Pigment Cell Melanoma Res.* 2009;22(3):268-282.
13. Ambrose M, Gatti RA. Pathogenesis of ataxia-telangiectasia: the next generation of ATM functions. *Blood.* 2013;121(20):4036-4045.
14. Badolato R. Defects of leukocyte migration in primary immunodeficiencies. *Eur J Immunol.* 2013;43(6):1436-1440.
15. Polmar SH, Pierce GF. Cartilage hair hypoplasia: immunological aspects and their clinical implications. *Clin Immmunol Immunopathol.* 1986;40(1):87-93.

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