Genetic syndromes with immunological disturbances

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Generally speaking, immunodeficiency conditions express a genetic component. In some of these cases, patients may request medical advice due to immune disturbance rather than due to genetic abnormality. Sometimes, the immune defect is not encountered in all cases. Yet, in certain cases, it is realized after diagnosis, while in others the immune defect is not the main clinical problem at all. However, immune defects maybe fatal in some syndromes and require urgent intervention. This review presents a brief overview on the immune response and then delineate the genetic syndromes manifesting immunological abnormalities.

Keywords:
genetic syndromes, immunodeficiency, primary immunodeficiency, syndromic immunodeficiencies

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Introduction

Immune deficiency disorders usually express a genetic component; in fact the patients may seek medical advice due to a defective immune system, which is the case in primary immune deficiencies. These cases mostly show no phenotypic abnormality except the immune deficiency.

On the other hand, some well-defined genetic syndromes may be associated with immune defects and hence are termed 'syndromic immune deficiencies'.

In these cases, the immune defect is usually identified after diagnosis of the syndrome. In some cases, the immune defect is not the major clinical problem, in others, it may be fatal.

Some genetic disorders might fit into two categories: primary and syndromic immune deficiency. Such cases have a well-noted organ dysfunction and/or dysmorphology associated with the syndrome itself in addition to a well-defined immune defect (Geha *et al.*, 2007).

Syndromic immunodeficiencies often present combined with vast diverse processes such as chromosomal anomalies, defective embryogenesis, and metabolic as well as teratogenic disorders. Moreover, information of causative gene defects specific for the development of the involved systems helps in deciphering the syndrome, hence managing its sequelae (Ming *et al.*, 2003).

Recognition of a syndromic immunodeficiency is an important issue when the patient seeks medical advice as it drives the clinician's attention to abnormalities in other organ systems. This allows proper management which is sometimes lifesaving. In addition, establishing a correct diagnosis helps in prenatal counseling to avoid the possible risk in future pregnancies of the patient, his family, or relatives (*http://www.uptodate.com/contents/syndromic-immunodeficiencies*).

According to the hallmark of the disorder, that is, according to the main organ affected, syndromic immunodeficiencies may be categorized into syndromes with growth defects, syndromes with hematologic, skin, gastrointestinal, or neurologic manifestations in addition to syndromes with inborn errors of metabolism, chromosomal abnormalities, and other miscellaneous groups. Immune defect may affect cellular, humoral, or both arms of the immune system and thus the resulting symptoms vary in severity from mild to fatal recurrent infections and autoimmunity, as classified and tabulated by Ming *et al.* (2003) and Ming and Graham (2014).

Collectively, syndromic immune deficiencies may occur as a result of different mechanisms which affect the immune system and other organ/systems involved in the syndrome, namely, affection of one or more genes (mutation or deletion) responsible for the function, regulation, or change in either structure and/or activity of crucial proteins leading to the dysfunction. In addition, defect in thymic or bone development may lead to a hostile environment incapable of hosting proper development and maturation of immune cells. In the same context, perinatal insults and toxic metabolites exposure (as in some inborn

errors of metabolism) may well affect some functions of the immune system as well as other organs and/or systems (Ming and Graham, 2014).

An overview of the immune response

The host is threatened by a great spectrum of pathologic mechanisms. Accordingly, the immune response manages to eliminate these organisms through a multifarious array of protective mechanisms. Such mechanisms depend on the detection of pathogens' structural features which distinguish them as different from host cells (Chaplin, 2010).

Fortunately, our immune system consists of three lines of defense. The first line is provided by a group of mechanical, chemical, and biologic barriers that guard the body.

If these barriers are breached, then second and third lines of protective mechanisms are activated and taken over through a group of cells and organs: first the innate, and then the adaptive immune system.

The innate immune response

This represents the second line of defense against infection, responses of which occur much faster than responses of the adaptive immune system. To provide this, innate immune system components are genetically programmed to distinguish molecules associated with a wide-ranging classes of pathogens. Cells of the innate immune system are either agranular leukocytes which comprise lymphoid lineage cells (B lymphocytes, T lymphocytes, and natural killer cells) or monocytic lineage cells (monocytes/macrophages and dendritic cells) or granular leukocytes (neutrophils, basophils/mast cells, and eosinophils).

The adaptive immune response

The adaptive immune system is one of the most remarkable organ systems. It is the third line of defense and has the capacity to recognize essentially an infinite number of autologous and foreign antigens and maintain immune memory throughout life. To do so, adaptive immunity requires intricate developmental mechanisms that support the generation of immune diversity (via T-cell receptors, and B-cell receptors, lymphocyte development; from naïve to clonal expansion of mature specific T cells and functioning molecules of cellular interaction; cytokines, chemokines, adhesion molecules, cluster of differentiation and signal transduction molecules) (Alberts *et al.*, 2002).

Adaptive immune system plays its role through a vast number of cells and organs:

(1) Lymphocytes:
   (a) Thymus derived (CD4+ and Cd8+ T cells)
   (b) Bone marrow-derived cells (B cells/plasma cells)
   (c) Natural killer cells
(2) Lymphoid tissues and organs:
   (a) Primary organs (thymus and bone marrow)
   (b) Secondary tissue and organs (spleen, lymph nodes, and mucosa-associated lymphoid tissue, *MALT*)
   (c) Lymphatic circulatory system.

Genetic syndromes with immune disturbances

This term refers to some well-defined genetic syndromes coupled with immune defects. In these cases, the immune defect is frequently recognized after diagnosis of the syndrome. Patients can present with disturbances in neurologic, skeletal, hematologic, dermatologic, and gastrointestinal function or development. Such conditions might be due to the developmental abnormalities, metabolic disorders chromosomal aberrations, or due to teratogens (Ming *et al.*, 2003).

Syndromes of growth defects with immunologic disturbances

Regarding syndromic immune deficiencies associated with growth defects, some of these conditions may result from skeletal dysplasia which is a clinically diverse and genetically heterogeneous group. These disorders are early diagnosed reporting short stature either disproportionate or proportionate, the latter of which is associated with a hormonal cause as growth hormone deficiency (Ming *et al.*, 2003).

On the other hand, skeletal dysplasias with disproportionate short stature were coupled with immune defects often affecting the limbs rather than the trunk. These are often reported with combined immunodeficiency, namely cellular, or perhaps a primary humoral defect (Table 1) (Ming and Stiehm, 2008).

Hematologic syndromes with immunologic disturbances

Patients with hereditary blood disorders have been reported to have a markedly altered immune profile (Table 2), some of which are rather common and are considered a genetic cause of secondary immune deficiency such as β-thalasemia major and sickle cell disease, whereas others are rather rare and in addition to being multiorgan syndromes are also considered primary immune deficiency.

Table 1 Syndromic immunodeficiency with growth defects

Syndromes	Mode of inheritance	Clinical features	ID	References
Short-limb skeletal dysplasia with combined immune deficiency (#200900)	AR	Skeletal dysplasia, severe and recurrent infections, diarrhea, failure to thrive, short stature and other skeletal anomalies	T, B	*https://www.ncbi.nlm.nih.gov/omim* Gennery (2013)
Short-limb skeletal dysplasia with humoral immunodeficiency	AR?	Skeletal dysplasia, with repeated infections.	B	Ammann *et al*. (1974)
SPENCDI (#607944)	AR (ACP5) 19p13	Spondyloenchondrodysplasia, short stature immunodeficiency and autoimmunity, +/-neurological findings	B	*https://www.ncbi.nlm.nih.gov/omim* Roifman and Melamed (2003), Briggs *et al*. (2016)
Roifman syndrome (# 616651)	XL? (RNU4ATAC) 2q14.	Spondyloepiphyseal dysplasia, growth retardation, cognitive delay dysmorphology, antibody deficiency	B	*https://www.ncbi.nlm.nih.gov/omim* Merico *et al*. (2015)
Cartilage hair hypoplasia (# 250250)	AR (RMRP) 9p13	Skeletal dysplasia, short-limbed dwarfism, fine/sparse hair, susceptibility to infection+/− GIT, +/− ↑ risk of cancer	T, B, phagocytes	*https://www.ncbi.nlm.nih.gov/omim* Makitie *et al*. (1998)
Spondyl-o-mesomelic-acrodysplasia	Unknown	Mild short-limb dwarfism, brachydactyly, SCID	T, B	Castriota-Scanderbeg *et al*. (1997)
McDermot syndrome (#200900)	AR?	Short limbs, bowed femora	T, B, Phagocytes	MacDermot *et al*. (1991)
Schimke immuno-osseus dysplasia (# 242900)	AR (SMARCAL1) 2q35	Spondyloepiphyseal dysplasia, peculiar phenotype, progressive nephropathy, defective cellular immunity, skin changes	T	*https://www.ncbi.nlm.nih.gov/omim* Boerkoel *et al*. (2002)
[a]Kenny-Caffey (Type 1 and 2) (# 244460) (# 127000)	AR, AD (TBCE) (11q12,1q42)	Cortical thickening of long bones with bone medullary stenosis, myopia, hypocalcemia; growth retardation, eye Symptoms, craniofacial anomalies, small hands and feet, hypocalcemia hypoparathyroidism	T, Phagocytes	*https://www.ncbi.nlm.nih.gov/omim* Bergada *et al*. (1988)
X-linked agammaglobulinemia with growth hormone deficiency (#300300)	XLR (BTK)	Recurrent infections, short stature, retarded bone age, delayed onset of puberty	B	*https://www.ncbi.nlm.nih.gov/omim* Fleisher *et al*. (1980)
Mulvihill Smith syndrome (#176690)	AR	Premature aging, microcephaly, short stature, multiple pigmented nevi, mental retardation, decreased facial subcutaneous fat, in addition to repeated infections	T, B	Bartsch *et al*. (1994); Ferri *et al*. (2005)
Sutor syndrome	Unknown	Short stature, impaired post natal growth and sexual development, immunodeficiency	T, B & NK	Sutor *et al*. (1998)
Shokeir syndrome (#274190)	AR	Short stature, absent thumbs, anosmia, immunodeficiency	T & B,↓ IgA	Shokeir (1978)
BILU syndrome[b] (#609296)	AD	Humoral immunodeficiency, limb abnormalities, urogenital malformations,	B	Hoffman *et al*. (2001); Tischkowitz *et al*. (2004)
Toriello syndrome (#251190)	AR	Prenatal growth deficiency, mental retardation, cataract, microcephaly and recurrent infections	B phagocytes	Toriello *et al*. (1986)
Bernard syndrome (#609981)[c]	AR (MCM4) 8q11	Prenatal and postnatal growth retardation, adrenal insufficiency, selective NK deficiency	T, NK	Bernard *et al*. (2004); Gineau *et al*. (2012)
Stoll syndrome (#601347)	AR	Developmental delay, dysmorphology, congenital heart, recurrent infections	Phagocytes	Stoll *et al*. (1994)
FILS syndrome (#615139)	AR (POLE1) 12q24	Immunodeficiency, facial dysmorphism, short stature and Livedo	T and B	Pachlopnik Schmid *et al*. (2012)
Kabuki syndrome (#147920)[a]	AD (KMT2D) 12q13	Mental retardation, postnatal dwarfism, pPeculiar facies, congenital heart	B	McGaughran *et al*. (2001); Adam and Hudgins (2004)
CHARGE (# 214800)[a]	AD (CHD7) 8q12	Coloboma, heart defect, Choanal atresia, retarded growth, hypogonadism, ear anomalies/deafness	T	Van Meter and Weaver (1996); Vervloed *et al*. (2006); Blake *et al*. (2008)
Mulibrey nanism (#253250)[a]	AR (TRIM37) (17q22)	Prenatal growth disorder, hepatomegaly, muscle weakness, eye lesions, +/− nevi	B	Hamalainen *et al*. (2006)

Contd...

Table 1 Contd...

Syndromes	Mode of inheritance	Clinical features	ID	References
Rubinstein-Taybi syndrome (#180849)[a]	AD (CREBBP) 16p13	Mental retardation, postnatal growth disorder, microcephaly, dysmorphic facial features, broad thumbs and halluces, abnormal smile	T, Ph	Rubinstein (1969); Bartsch *et al.* (2010)

Adapted from Ming *et al.* (2003); Ming and Graham (2014). AD, autosomal dominant; AR, autosomal recessive; B-cell defect; B, NK, natural killer cell defect; CHARGE, choanal atresia, retardation, genital and ear anomalies, mulibrey, muscle-liver-brain-eye nanism; FILS, facial dysmorphism, immunodeficiency, Livedo and short stature; ID, immunologic defect; T, T-cell defect; XL, X-linked; XLR, X-linked recessive. [a]Syndromes in which ID is less frequently reported. [b]Also referred to as Hoffman syndrome. [c]Also referred to as natural killer cell and glucocorticoid deficiency with DNA repair defect (NKGCD).

Table 2 Syndromic immune deficiencies with hematologic manifestations

Syndromes	Mode of inheritance	Clinical features	ID	References
Wiskott-Aldrich syndrome (# 301000)	XLR (WAS) Xp11.23	Thrombocytopenia, eczema, recurrent infections, bloody diarrhea	T, B, NK	*https://www.ncbi.nlm.nih.gov/omim* Lanzi *et al.* (2012)
Chediak-Higashi syndrome (#214500)	AR (LYST) 1q42.3	Partial albinism, photophobia, nystagmus, recurrent infections, giant cytoplasmic granules in leukocytes, malignant lymphoma, +/– neuropathy	T, B, NK, phagocytes	*https://www.ncbi.nlm.nih.gov/omim* Tardieu *et al.* (2005)
Shwachman syndrome (# 260400)	AR (SBDS) 7q11	Exocrine pancreatic insufficiency, hematologic abnormalities, skeletal abnormalities, recurrent infections, increased risk of malignant transformation	T, B, phagocytes	*https://www.ncbi.nlm.nih.gov/omim* Toiviainen-Salo *et al.* (2008)
IPEX syndrome (# 304790)	XLR (FOXP3) Xp11.23	Severe diarrhea, autoimmune enteropathy, infantile diabetes mellitus, polyendocrinopathy, +/– hemolytic anemia	T, B	*https://www.ncbi.nlm.nih.gov/omim* Gambineri *et al.* (2008)
Omenn syndrome (# 603554)	AR (RAG1, RAG2, DCLRE1C) 11p12 10p13	Characteristic erythematous scaly rash, eosinophilia, lymphadenopathy, recurrent infections	T, B, NK	*https://www.ncbi.nlm.nih.gov/omim* Marrella *et al.* (2011)
MTHFD1 mutations (172460)[a]	AR (14q23.3)	Neural tube defect, megalobalstic anemia, hemolytic uremic syndrome	T, B	*https://www.ncbi.nlm.nih.gov/omim* De Marco *et al.* (2006); Keller *et al.* (2013)
Pearson syndrome (#557000)	Mitochondrial disease	Exocrine pancreatic dysfunction, pancytopenia, sideroblastic anemia, failure to thrive, neurologic symptoms	T, B, phagocytes	Pearson *et al.* (1979); Williams *et al.* (2012)
β-Thalassemia major #613985[a]	AR (HBB) 11p15.4	Severe anemia, failure to thrive, splenomegaly, ↑risk of infections	T, B, phagocytes	https://www.ncbi.nlm.nih.gov/omim Vento *et al.* (2006); Cavazzana-Calvo *et al.* (2010)
Sickle cell disease (#603903)[a]	AR (11p15)	Sickling crisis, ↑risk of infections	T, B, phagocytes	*https://www.ncbi.nlm.nih.gov/omim*

Adapted from Ming *et al.* (2003), Ming and Graham (2014). AD, autosomal dominant; AR, autosomal recessive; B, B-cell defect; ID, immunologic defect; IPEX, immune dysregulation polyendocrinopathy enteropathy X-linked syndrome; MTHFD1 methylenetetrahydrofolate dehydrogenase 1; NK, natural killer cell defect; T, T-cell defect; WHIM, warts, hypogammaglobulinemia, infections and myelokathexis; XL, X-linked; XLR, X-linked recessive. [a]Referred to as diseases and not syndromes.

Dermatologic syndromes with immunologic disturbances

Patients suffering from immune defects usually experience skin problems. However, syndromic immunodeficiencies with skin manifestations primarily present with skin problems, yet immune deficiency symptoms are reported in the majority of cases as Griscelli syndrome type 2, Pignata, ectodermal dysplasia, anhidrotic, with immunodeficiency, osteopetrosis and lymphedema (OLEDAID), PLCG2-associated autoinflammation antibody deficiency and immune dysregulation (APLAID), PLAID and some other rarely encountered syndromes as Jung, Davennport, Ipp-Gelfand, whereas, immune symptoms are less encountered in Papillon–Lefevre, xeroderma pigmentosum, dyskeratosis congenita, and incontinentia pigmenti (Table 3).

Neurological syndromes with immunologic disturbances

Many neurological abnormalities have been reported with immune deficiency manifestations in more than 65% of the diagnosed cases as in the first six syndromes in Table 4, whereas others express immunologic symptoms in less than 30% of the diagnosed cases such as myotonic dystrophy type 1, Cohen, Mousa, Arts and MECP2 duplication Syndrome (Trisomy X28). Moreover, other disorders also exhibit immunologic symptoms in the majority of cases, yet, little is known about these syndromes due to their rarity

Table 3 Syndromic immunodeficiency with skin manifestations

Syndromes	Mode of inheritance	Clinical features	ID	References
Griscelli type 2 (#607624)	AR (RAB27A) 15q21	Hypomelanosis neutropenia, thrombocytopenia +/– neurologic symptoms	T, B, NK and phagocytes	*https://www.ncbi.nlm.nih.gov/omim* Ménasché *et al*. (2000)
WHIM syndrome (#193670)	AD (CXCR4) 2q22.1	Warts, hypogammaglobulinemia, recurrent infection, myelokathexis	T, B, phagocytes	*https://www.ncbi.nlm.nih.gov/omim* Hernandez *et al*. (2003)
APLAID (#614878)	AD (PLCG2) 16q23	Recurrent skin lesions inflammation of joints, eye, and GIT, recurrent pulmonary infection	T and B	*https://www.ncbi.nlm.nih.gov/omim* Zhou *et al*. (2012)
*Familial cold autoinflammatory Syndrome (FCAS3) (#614468)	AD (PLCG2) 16q23	Cutaneous urticaria, erythema, and pruritus on exposure to cold, susceptibility to infection, autoimmunity	B cells	*https://www.ncbi.nlm.nih.gov/omim* Ombrello *et al*. (2012)
OLEDAID (#300301)	XL (IKBKG) Xq28	Osteopetrosis, lymphedema, anhidrotic ectodermal dysplasia, immune defects	T and B	*https://www.ncbi.nlm.nih.gov/omim* Doffinger *et al*. (2001)
Hermansky -Pudluck syndrome 2 (#608233)	AR (AP3B1) 5q14.1	Oculocutaneous albinism platelet defects, +/-dysmorphology, microcephaly, mental retardation +/– oro-dental	NK and phagocytes	*https://www.ncbi.nlm.nih.gov/omim* Jung *et al*. (2006)
Pignata syndrome (#601705)	AR (FOXN1) 17q11-q12	Congenital alopecia, ridging and pitting of all nails	T	*https://www.ncbi.nlm.nih.gov/omim* Vigliano *et al*. (2011)
Jung syndrome (146840)	AD/XL?	Skin manifestations; i.e., pyoderma, folliculitis, atopic dermatitis	T, B and phagocytes	Jung *et al*. (1983)
Onychotrichodysplasia (%258360)	AR	Hypoplastic fingernails, trichorrhexis, neutropenia, recurrent infections, +/– psychomotor symptoms	Phagocytes	*https://www.ncbi.nlm.nih.gov/omim* Dallapiccola *et al*. (1994)
Neutrophil chemotactic defect (%162820)	AD?	Recurrent skin infection, ichthyosis	Phagocytes	Van Scoy *et al*. (1975)
p14 deficiency (#610798)	AR (MAPBPIP) 2p23	Hypopigmentation, neutropenia, recurrent respiratory infections	T, B and phagocytes	Bohn *et al*. (2007)
Davenport syndrome	AR?	Hypopigmentation, sensory hearing loss	Phagocytes	Davenport *et al*. (1979)
Ipp-Gelfand syndrome	AR?	Alopecia, recurrent infections	B	Ipp and Gelfand (1976)
Xeroderma pigmentosum (#278700)	AR (XPA-XPG)	Sensitivity to sunlight, skin lesions/tumors, central, and peripheral nervous systems	T, NK	*https://www.ncbi.nlm.nih.gov/omim* Mariani *et al*. (1992)

Adapted from Ming *et al*. (2003), Ming and Graham (2014). AD, autosomal dominant; APLAID, autoinflammation antibody deficiency and immune dysregulation PLCG2-associated; AR, autosomal recessive; B, B-cell defect; ID, immunologic defect; NK, natural killer cell defect; OLEDAID, ectodermal dysplasia, anhidrotic, with immunodeficiency, osteopetrosis and lymphedema; T, T-cell defect; XL, X-linked. *Also referred to as PLCG2-associated antibody deficiency and immune dysregulation (PLAID).

such as Aguilar, Aderson, and Krawinkel syndrome (Ming and Graham, 2014).

Chromosomal abnormalities associated with immunologic disturbances

Syndromes with chromosome abnormality usually have immune symptoms and increased risk for malignancy. This may be a result of either chromosome breakage or defective DNA repair (Table 5) or abnormalities in number or structure.

Nevertheless, syndromes with known abnormalities in number or structure also report immune disturbances (Table 6), some of which immune symptoms are reported in nearly half of the diagnosed cases, as DiGeorge and Wolf–Hirschhorn Syndrome. Some well-recognized cases as Trisomy 21 and Turner report immune disturbances, but in less than 30% of cases, while others rarely complain of immune symptoms as in the deletion of long/short arm of chromosome 18, ring chromosome 21, and others (Chen *et al*., 2010).

Syndromes of inborn errors of metabolism with immune disturbances

Many cases with inborn errors of metabolism show some symptoms of immune deficiency (Table 7). However, immunological defects are due to obstruction of a metabolic process crucial for immune function, accumulation of toxic metabolites resulting from the metabolic disorder and adversely affecting immune cells or a nonspecific damaging effect on immune cell proliferation. Usually, the immunological abnormalities are secondary to the metabolic disorder which when properly managed corrects the immune function (Ming and Graham, 2014).

Syndromic immune deficiencies with gastrointestinal manifestations

Abnormalities of the gastrointestinal tract (GIT) can lead to immunodeficiency as a result of malnutrition. However, in syndromic immune deficiencies, the immune defects precede malnutrition and hence are likely to be intrinsic to each syndrome. Moreover, GIT manifestations are considered the second

Table 4 Syndromic immune deficiencies with neurological manifestations

Syndromes	Mode of inheritance	Clinical features	ID	References
Rambam-Hasharon syndrome (LADII, CDGIIc) (#266265)	AR (SLC35C1) 11p11.2	Mild dysmorphism, moderate to severe psychomotor retardation, recurrent infections, impaired neutrophil motility	Phagocytes	*https://www.ncbi.nlm.nih.gov/omim* Dauber *et al.* (2014)
Microcephaly with immune defects (251240)	XL Xp22.2p21.2	Microcephaly, dysmorphic facies, developmental delay, and hypoglobulinemia, defective chemotaxis, recurrent infections, +/− eye symptoms	B, phagocytes	*https://www.ncbi.nlm.nih.gov/omim* Say *et al.* (1986); Carpenter *et al.* (2000)
Høyeraal-Hreidarsson syndrome (DKCX) (# 305000)	XLR (DKC1) (Xq28)	Microcephaly, intrauterine growth retardation, absent corpus callosum, delayed development, immunodeficiency, bone marrow failure, cerebellar hypoplasia+dyskeratosis congenital	T, B, phagocytes	*https://www.ncbi.nlm.nih.gov/omim* Walne *et al.* (2013)
Vici syndrome (# 242840)	AR (EPG5) 18q12.3-q21.1	Agenesis of the corpus callosum, hypopigmentation, bilateral cataracts, progressive cardiomyopathy, immunodeficiency, recurrent infections, profound psychomotor retardation and hypotonia	T, B	*https://www.ncbi.nlm.nih.gov/omim* Del Campo *et al.* (1999); Said *et al.* (2012)
Roifman-Chitayat syndrome (613328)	AR 15q11-q21.1	Facial dysmorphism, skeletal anomalies, optic atrophy, developmental delay, myoclonic seizures, combined immunodeficiency, recurrent infections	T, B	*https://www.ncbi.nlm.nih.gov/omim* Roifman and Chitayat (2009)
Calcium entry defect syndromes (# 612783) (# 612782)	AR (STIM1) 11p15	Hypotonia, hepatosplenomegaly, defective enamel, thrombocytopenia, hemolytic anemia, lymphadenopathy recurrent infections	T	*https://www.ncbi.nlm.nih.gov/omim* Picard *et al.* (2009); Byun *et al.* (2010)
Mousa syndrome (271320)[a]	AR	Congenital cataracts, myopia spastic ataxia, macular corneal dystrophy.	B	*https://www.ncbi.nlm.nih.gov/omim* Mousa *et al.* (1986)
Myotonic dystrophy, type 1 (# 160900)	AD (DMPK) 19q13.32	Myotonic, muscle dystrophy, cataract, hypogonadism, frontal balding, widespread nervous system dysfunction	T, B	*https://www.ncbi.nlm.nih.gov/omim* Donahue *et al.* (2009); Kaminsky *et al.* (2011)
Cohen syndrome (# 216550)	AR (VPS13B) 8q22.2	Facial dysmorphism, intellectual disability, microcephaly, truncal obesity, progressive retinopathy, and intermittent congenital neutropenia	Phagocytes	*https://www.ncbi.nlm.nih.gov/omim* Waite *et al.* (2010)

Adapted from Ming *et al.* (2003), Ming and Graham (2014). AD, autosomal dominant; AR, autosomal recessive; B, B-cell defect; CDGII, congenital disorder of gycolysation type II; ID, immunologic defect; NK, natural killer cell defect; T, T-cell defect; XL, X-linked; XLR, X-linked recessive; LAD II, leukocyte adhesion deficiency type II, DKCX, X-linked dyskeratosis congenita. [a]Also referred to as Bedouin spastic ataxia syndrome and spinocerebellar degeneration with macular corneal dystrophy, congenital cataract and myopia.

Table 5 Syndromic immune deficiencies with chromosomal abnormalities instability and/or DNA repair

Name	Chromosome	Associated features	ID
Bloom syndrome (# 210900)	AR (15q26.1) RECQL3	Sensitivity to sunlight, telangiectatic erythema of the face, short stature	T, B
Fanconi pancytopenia (# 227650)	AR (16q24) FANCA	Short stature, hyperpigmentation, radial hypoplasia, pancytopenia	Ph, NK
Ataxia-telangiectasia (# 208900)	AR (11q22.3) ATM	Progressive cerebellar ataxia, choreoathetosis telangiectasias (conjunctival)	T, B
Nijmegen breakage syndrome (# 251260)	AR (8q21.3) NBN	Prenatal-onset short stature, mental retardation, microcephaly, bird-like facies, malignancy, cafe×au lait spots	T, B, NK
ICF syndrome (immunodeficiency-centromeric instability, facial anomalies) (# 242860)	AR (20q11.21) DNMT3B	Mental retardation, facial dysmorphism, variable immune deficiency, chromosome instability	T, B, NK
DNA ligase I deficiency (*126391)	(19q13.33)	Sensitivity to sunlight and short stature	T, B
DNA ligase IV deficiency (*601837)	(13q33.3)	Short stature, photosensitivity, developmental delay, microcephaly, hypothyroidism, diabetes	Ph
RIDDLE syndrome (# 611943)	AR (3q29) RNF168	Characteristic facies, short stature, ataxia, radiosensitivity learning difficulties	B
NHEJ1 deficiency (# 611291)	AR (2q35)	Microcephaly, SCID, radiosensitivity, and short stature	T, B

Adapted from Ming *et al.* (2003), Ming and Graham (2014). *https://www.ncbi.nlm.nih.gov/omim*. AR, autosomal recessive; B, B-cell defect; ID, immunodeficiency; NHEJ1, Nonhomologous end=joining factor 1; NK, NK cell defect; Ph, phagocytic defect; SCID, severe combined immune deficiency; T, T-cell defect.

(after pulmonary disease) most common complication of primary immunodeficiency diseases (PID) and symptoms have been reported in up to 50% of cases of immune deficiency whether primary or syndromic. Symptoms include diarrhea, malabsorption, failure to thrive as well as inflammatory bowel

Table 6 Syndromic immunodeficiencies with chromosomal abnormalities (number or structure)

Names	Chromosome	Associated features	ID
Deletion of long arm of chromosome 22 (DiGeorge/velo-cardio-facial syndrome) (# 188400)	(22q11.2) TBX1	Facial dysmorphism, aortic arch anomalies, hypocalcemia, thymic hypoplasia, and cleft palate	T
Deletion of short arm of chromosome 4 (Wolf-Hirschhorn syndrome) (# 194190)	(4p16.3)	Developmental and growth deficiency, 'Greek helmet'-like facies, coloboma, microcephaly.	B
Trisomy 21 (Down syndrome) (# 190685)	21	Mental retardation, flat facies, hypotonia, upslanting palpebral fissures.	T, B, Ph, NK
Missing or abnormal X chromosome (Turner syndrome)	XO, isoX, ring X;	Short stature, broad chest, webbed neck, congenital lymphedema ovarian dysgenesis	T, B
Deletion of short arm of chromosome 10% 601362))	(10p13-p14)	DiGeorge anomaly, renal anomaly. hypoparathyroidism, +/– deafness.	T
Deletion of long arm of chromosome 18	18	Mental retardation, midface hypoplasia, microcephaly, nystagmus	B

Adapted from Ming *et al.* (2003). Deletion of short arm of chromosome 18, deletion of long arm of chromosome 22 (22q13), deletion of long arm of chromosome 2 (2q37) and ring chromosome 21 are anomalies with <5% cases reporting immune disturbances, all of which report B-cell defects except for deletion of long arm of chromosome 22 which has both T and NK defects. B, B-cell defect; ID, immunodeficiency; NK, NK cell defect; Ph, phagocytic defect; T, T-cell defect.

Table 7 Inborn errors of metabolism with immune disturbances

Syndromes	Inheritance	Clinical features	ID
Adenosine deaminase (ADA) deficiency(# 102700)	AR (ADA) 20q13.12	Cupping and flaring of costochondral junctions, severe combined immunodeficiency	T, B
Purine nucleoside phosphorylase deficiency (# 613179)	AR (PNP) 14q11.2	Neurological findings, severe immunodeficiency, and hemolytic anemia	T
5×-nucleotidase elevation	?	Aggressive behavior, increased nucleotide catabolism, megaloblastic anemia, developmental delay, seizures	B
Glycogen storage disease Ib/Ic (# 232220) (# 232240)	AR (G6PT1) 17q21.31	Hypoglycemia, lactic acidosis, hyperlipidemia, hepatomegaly	Ph
Barth syndrome (# 302060)	XL (TAZ) Xq28	Cardiomyopathy, myopathy, growth retardation	Ph
Chondroitin-6-sulfaturia (215250)	?	Bone demineralization, short stature, nephritic syndrome, corneal opacities	T
Methylmalonic aciduria (# 251000)	AR (MUT) 6p12.3	Acidosis, recurrent severe infection	T, B, Ph
Propionic acidemia (# 606054)	AR(PCCB-PCCA) 3q22.3/13q32.3	Acidosis, vomiting, ketosis	B, Ph
Isovaleric acidemia (# 243500)	AR (IVD) 15q15.1	Acidosis, vomiting, urinary odor of sweaty socks	Ph

Adapted from Ming and Graham (2014). AR, autosomal recessive; ID, immunodeficiency; NK, NK cell defect; Ph, phagocytic defect; T-cell defect; T, B, B-cell defect; XL, X-linked.

disease, unresponsive to conventional therapies (Agarwal and Mayer, 2013).

Syndromes associated with GIT dysfunction include:

(1) Trichohepatoenteric syndrome 1 (Girault syndrome): this condition is an autosomal recessive disorder due to mutation of the TTC37 gene on chromosome 5q15 and characterized by diarrhea, dysmorphic features, wooly hair, developmental delay, and immune deficiency. Immune defects are reported in more than 65% of diagnosed cases and involve both T and B lymphocytes (Hartley *et al.*, 2010)
(2) Trichohepatoenteric syndrome 2: it is very much like trichohepatoenteric syndrome 1, as it is characterized by trichorrhexis nodosa of the hair, infantile diarrhea, and immunodeficiency in more than half of the cases mainly affecting B cells
The condition results from mutation in the SKIV2L gene on chromosome 6p21 (Fabre *et al.*, 2012)
(3) Dawson syndrome: mode of inheritance is yet questionable. Cases suffer from severe diarrhea as well as malabsorption of fat, vitamin B12, bile acids, and xylose. Immune symptoms mainly involve B cells and were reported in more than half of the recognized cases (Dawson *et al.*, 1979)
(4) Familial intestinal polyatresia: this is an autosomal recessive disorder resulting from mutation in the TTC7A gene on chromosome 2p21 characterized by multiple intestinal atresia at different levels along the small and large intestines. The outcome is poor and usually fatal. In some cases, intestinal features are associated with either mild or severe combined immunodeficiency (SCID), starting early when the patient still has a good nutritional status. Defects include hypogammaglobulinemia, T-cell lymphopenia, and NK cell dysfunction in addition to lymphoid depletion in the thymus and peripheral lymphoid tissues (Samuels *et al.*, 2013; Avitzur *et al.*, 2014; Lemoine *et al.*, 2014)
(5) Sclerosing cholangitis with immunodeficiency: this disorder is characterized by intrahepatic sclerosing cholangitis. Around 5–30% of the reported cases have documented immune

deficiency, involving both cellular and humoral immunity (Record *et al.*, 1973).

Other genetic syndromes with immune disturbances (according to the frequency of reporting immune deficiency symptoms)

(1) TIIAC syndrome: this is an autosomal recessive disorder characterized by T-cell immunodeficiency, recurrent infections, autoimmunity, and cardiac malformations caused by mutation in the STK4 gene on chromosome 20q13.12 (Abdollahpour *et al.*, 2012)
(2) Somech's syndrome: this syndrome presents with ovarian dysgenesis, pulmonary fibrosis, and combined immunodeficiency. Mode of inheritance is questioned (Somech *et al.*, 2008)
(3) Thymic-renal-anal-lung dysplasia: this disorder is characterized by hypoplastic thymus, growth failure, renal dysgenesis, unilobed lung, and an imperforate anus (Rudd *et al.*, 1990)
(4) Hisama syndrome: this syndrome presents with renal dysgenesis, absent nipples, nail anomalies and other organ defects. Mode of inheritance is questionable (Horvathand Armstrong, 2007)
(5) Frenkel-Russe syndrome: it is also referred to as retinal telangiectasia and hypogammaglobulinemia: Inheritance of this syndrome is in a way questionable. In addition to the syndrome clinical findings, cases suffered recurrent infections due to defective immunity involving both T and B cells (Frenkel and Russe, 1967)
(6) Lichtenstein syndrome: this disorder of unrevealed mode of inheritance is characterized by bone anomalies, osteoporosis in addition to hypogammaglobulinemia and neutropenia (Lichtenstein, 1972)
(7) Hypercatabolic hypoproteinemia: this condition is also titled β-2-microglogulinemia and is caused by homozygous mutation in the B2M gene on chromosome 15q21.1. It was described as a syndrome with bowed radii, shortened ulnae and hypogammaglobulinemia and chemical diabetes (Wani *et al.*, 2006)
(8) Schaller syndrome: this is a disease of questionable mode of inheritance. It is referred to as lymphopenic hypergammaglobulinemia, antibody deficient, autoimmune hemolytic anemia, glomerulonephritis, and lymph node hypoplasia (Schaller *et al.*, 1966)
(9) Turner-like phenotype with immunodeficiency: this case was reported in 1976 by Feldmen and colleagues as a case with Turner phenotype, normal karyotype, and immunodeficiency
(10) Timothy syndrome: timothy syndrome is defined as an autosomal dominant disorder resulting from the mutation in the CACNA1C gene on chromosome 12p13.33. It is characterized by webbing of the fingers and toes, arrhythmias, multiorgan dysfunction, and in addition to congenital heart disease and intermittent hypoglycemia. Immune deficiency as well as cognitive abnormalities and autism have been also reported (Splawski *et al.*, 2004)
(11) Asplenia syndrome: this is an autosomal recessive condition which can be caused by mutation in the GDF1 gene on chromosome 19p12 and is also referred to as asplenia with cardiovascular anomalies. Immunologic defects concern T cells (Wang and Hsieh, 1991).

Well-established genetic syndromes with occasional immune disturbances

In some well-known genetic syndromes, immune disturbances have been reported in some patients. It is not clear if reports of immunologic disturbances are coincidental co-occurrences of two rare conditions, or do they just occur with some frequency in these cases (Table 8).

Primary immune deficiencies

As redundancy is built in, malfunction of one part of the immune system may be covered by another part with a similar or overlapping function. In some cases, failures in immune function become explicit and may have a brutal clinical impact. Immune deficiencies or 'immunodeficiencies' caused by defects in different components of the immune system are rare, although not irrelevant, and occur in two different ways: primary or secondary.

PIDs are a group of disorders that are caused by genetic abnormalities that manifest in immune dysfunction. The most common among these are defects that affect the adaptive immune system. They span defects in cytokines or cytokine receptor genes, V-D-J recombination and nonhomologous end-joining, and telomere dysfunction, among others. Since 1999 the International Union of Immunological Societies (IUIS) PID expert committee proposed a PID classification that facilitates clinical research and comparative studies all over the world; it is revised every other year to comprise new disorders or disease-causing genes (Bousfiha *et al.*, 2018).

They met in London on 14 and 15 March 2015 to update the classification of PIDs to provide the latest updates where 34 new gene defects have been updated (Picard *et al.*, 2015).

Moreover, in total, as of 2016, it is estimated that there are 280 genetic disorders that cause PIDs (*http://www.ipopi.org/uploads/WEB-IPOPI-Classification.pdf*).

Table 8 Well-established syndromes with occasional immune disturbances

Immune defect	Syndrome	References
Decreased T-cell and B-cell number	Schwartz-Jampel syndrome(# 255800)	Mollica *et al.* (1979)
Thymic hypoplasia and defective T-cell function	Beckwith-Wiedemann syndrome Zellweger syndrome (# 130650)	Hong *et al.* (1981)
Hypoplastic thymus and reduced T cells in secondary lymphatic origin	Ectrodactyly- ectodermal dysplasia, cleft lip/palate syndrome with urinary tract anomalies (EECUT) (% 129900)	Frick *et al.* (1997)
Impaired T-cell function	Menkes syndrome (# 309400) Pseudoachondroplasia (# 177170)	Pedroni *et al.* (1975), Kultursay *et al.* (1988)
Hypogammaglobulinemia	Hallermann-Streiff syndrome (% 234100) Ritscher-Schinzel syndrome(# 220210)	Lauener *et al.* (1989)
Monocyte dysfunction	Smith-Lemli-Opitz syndrome (# 270400)	Ostergaard *et al.* (1992)
Combined immunodeficiency	Hutchinson-Gilford syndrome (# 176670)	Harjacek *et al.* (1990)
Leukopenia	Progressive diaphyseal dysplasia (Camurati- Engelmann syndrome) (# 131300)	Crisp and Brenton (1982)
Neutropenia	Wolfram syndrome (# 222300)	Borgna-Pignatti *et al.* (1989)
Hypogammaglobulinemia and lymphopenia	Proteus syndrome (# 176920)	Hodge *et al.* (2000)
Abnormal T-cell number and function and decreased NK activity	Cowden syndrome (# 158350)	Guerin *et al.* (1989)

Nevertheless, the latest meeting updated the classification of human PID to include 330 distinct disorders with 320 diverse gene defects (Picard *et al.*, 2017).

Advances in sequencing technologies will undoubtedly lead to even more advances in this area. PIDs that manifest in newborns and in infancy are the most severe of the PIDs, and given new efforts in some parts of the world to implement newborn screening, understanding their underlying biology is critical for diagnostic, treatment, and prognostic decisions. Most PIDs become noticeable at about 6 months of age. This is when maternally derived antibodies begin to disappear. Several features characterize PIDs such as recurrent infections, inability to clear infectious agents after antibiotic therapy, failure to thrive, hepatosplenomegaly, skin rashes, diarrhea, and others (Notarangelo, 2010).

According to the latest report of the IUIS-PID EC, primary immune deficiencies have been classified into nine major groups according to the immunologic defect. However, in this classification there is an obvious overlap between syndromic immune deficiencies and PIDs, where the expert committee considers all immune deficiencies of genetic origin as PIDs whether syndromic or otherwise and accordingly classifies them with respect to the immunologic defect rather than the genetic syndrome. This report represents the most current and complete catalog of known PIDs (Picard *et al.*, 2015).

The nine groups were addressed as follows:

(1) Immunodeficiencies affecting cellular and humoral immunity: this comprises nearly 50 different syndromes caused by 49 genes of which five new genes have been recently added to the pathogenesis
Conditions are classified as SCID syndromes [such as Jak3 deficiency, RAG deficiency, adenosine deaminase (ADA) deficiency, and many others] and as combined immune deficiencies less profound than SCID (as CD40 ligand deficiency, MHC class II deficiency, Omenn syndrome, and many others)

(2) Combined immune deficiencies with associated or syndromic features: this category comprises more than 40 syndromes caused by 45 genes of which six new genes have been recently added to the pathogenesis. It is further subclassified into 11 subgroups:
   (a) Congenital thrombocytopenia (Wiskott-Aldrich syndrome and WIP deficiency)
   (b) DNA repair defects (e.g., Ataxia-telangiectasia, Nijmegen breakage, Bloom syndrome, and many others)
   (c) Thymic defects with additional congenital anomalies (e.g., DiGeorge, CHARGE syndrome, and others)
   (d) Immuno-osseus dysplasia (cartilage hair hypoplasia and Schimke dysplasia)
   (e) Hyper immunoglobulin (Ig) E syndromes (Job, Cornel-Netherton)
   (f) Dyskeratosis congenita with bone marrow failure, including the whole group whether AR or AD and caused by a vast number of gene mutations
   (g) Defects of vitamin B12 and folate metabolism (e.g., MTHFD1 deficiency)
   (h) Anhidrotic ectodermoplasia with immune deficiency (EDA-ID)
   (i) Calcium channel defects

(j) Other defects (e.g., VODI, FILS)
(k) Immunodeficiency with multiple intestinal atresia (e.g., VICI, PNP deficiency and others)

(3) Predominantly antibody deficiencies: this comprises more than 30 different syndromes caused by 28 genes of which six new genes have been recently added to the pathogenesis. They are further subdivided into four subgroups:
   (a) Severe reduction in all serum immunoglobulin isotypes with profoundly decreased or absent B cells
   (b) Severe reduction in at least two serum immunoglobulin isotypes with normal or low number of B cells
   (c) Severe reduction in serum IgG and IgA with generally normal number of B cells
   (d) Isotype or light chain deficiencies with generally normal number of B cells
(4) Diseases of immune dysregulation: this comprises more than 35 different syndromes caused by 37 genes of which eight new genes have been recently added to the pathogenesis. They are further subdivided into five subgroups:
   (a) Familial hemophagocytic lymphohistiocytosis syndromes (e.g., Chediak-Higashi, Griscelli type 2, Hermansky Pudlak type 2 and type 9)
   (b) T-regulatory cells genetic defects (e.g., IPEX)
   (c) Autoimmunity ± lymphoproliferation (e.g., APECED)
   (d) Immune dysregulation with colitis (e.g., IL-10 deficiency)
   (e) Type I interferonopathies (e.g., Aicradi Goutieres, SPENCDI)
(5) Congenital defects of phagocyte number, function, or both: three new genes have been recently added to the pathogenesis of this group which comprises ~30 different syndromes caused by 31 genes. They are further subdivided into four subgroups (Appendix Table A1):
   (a) Congenital neutropenia (e.g., Cosman, Bath, and glycogen storage disease type 1b)
   (b) Defects of motility (e.g., LAD 1/2/3, Papillon-Lefèvre, Shwachman-Diamond)
   (c) Defects of respiratory burst (e.g., X-linked granulomatous disease)
   (d) Others
(6) Defects in intrinsic innate immunity: this comprises more than 30 different syndromes caused by 32 genes of which four new genes have been recently added to the pathogenesis. They are further subdivided into nine subgroups (Appendix Table A2)
   (a) Mendelian susceptibility to mycobacterial disease
   (b) Epidermodysplasia verruciformis (EVER), for example, EVER 1, 2, WHIM
   (c) Predisposition to severe viral infections
   (d) Herpes simplex encephalitis
   (e) Predisposition to invasive fungal diseases
   (f) Chronic mucocutaneous candidiasis
   (g) TLR signaling pathway deficiency
   (h) Isolated congenital asplenia
   (i) Trypanosomiasis
(7) Autoinflammatory disorders: this comprises around 20 different syndromes caused by 17 genes of which three new genes have been recently added to the pathogenesis. They are further subdivided into two subgroups
   (a) Defects affecting the inflammasome (e.g., FMF, Muckle-Wells, PLAID, APLAID)
   (b) Noninflammatory-related conditions (e.g., Blau, CANDLE, Majeed, Cherubism)
(8) Complement deficiencies: this comprises around 30 different syndromes caused by 30 genes. No new genes have been added to the pathogenesis in the 2015 classification. They are further subdivided into two subgroups: integral complement cascade component deficiencies and complement regulatory defects
(9) Phenocopies of PID: this group comprises about 10 syndromes associated with either somatic mutations or with antibodies (e.g., autoimmune lymphoproliferative syndrome, Muckle-Wells, atypical hemolytic uremic syndrome).

Management of genetic syndromes with immunologic disturbances

Early detection of PID is essential for intervention before severe infections compromise the patient's general condition. In an attempt to assist clinical interpretation concerning when to suspect PID in clinical practice, the 'National Primary Immunodeficiency Resource Center' adopted a list of '10 warning signs of PID' (Appendix). Physicians should think about PID if a patient encounters one or more of these 'warning signs'. Nevertheless, Cunningham-Rundles *et al.* (2004) adopted an 'immunodeficiency-related (IDR) score' to identify the probability of finding immunodeficiency among patients undergoing immune assessment. The score includes numerous medical conditions linked with PID (Appendix). An IDR score of greater than or equal to 6 was considered as a threshold indicating the probability of PID (Yarmohammadi *et al.*, 2006).

(1) Clinical presentation: whom to evaluate: in 2009, Notarangelo and colleagues considered a few warning criteria as most important: 'infections in multiple anatomic sites, increasing frequency and severity of infections with age, recurrent serious infections with common pathogens

and serious infections with unusual pathogens'. Moreover, three of the 10 warning signs were considered most helpful for suspecting PIDs, namely, 'a positive family history; a diagnosis of sepsis treated with intravenous antibiotics; and failure to thrive'. In addition to this, a child with frequent serious infections with a positive family history of these diseases or who is from an ethnicity related with higher parental consanguinity must be screened for an immunodeficiency disease (Reust, 2013)

Nevertheless, physical examination can also provide important hints guiding to particular syndromic immunodeficiencies (Notarangelo, 2010)

(2) Initial evaluation: a basic laboratory workup includes testing for HIV antibody in children greater than 18 months (viral testing is required if <18 months), complete blood count with differential count. Assessment of serum immunoglobulins and complement levels can spot children who need further investigations and referral to a subspecialist for an assumed immunodeficiency disease (Subbarayan *et al.*, 2011)

(a) Complete blood count:

A complete blood count with differential must be obtained to screen for a T-cell or phagocytic defect. T-cell defects are characterized by lymphocytopenia, while newborns usually have lymphocytosis. When the absolute lymphocyte count is less than 3000/mm^3 in a newborn, this can be used as the cutoff for assumption of a T-cell disorder with respect to age-dependent reference intervals

T-cell disorders may be further confirmed by lack of a 'delayed hypersensitivity skin test response to Candida, mumps, or tetanus' in children older than 1 year, and by 'lymphocyte subset analysis' at any age. Lymphocyte subset analysis using the basic panel will screen for the number and percentage of 'T cells (CD3, CD4, CD8), B cells (CD19, CD20), and NK (CD16, CD56)'

Phagocytic defects are characterized by neutropenia. PID should be assumed if the neutrophil count is less than 1500 per mm^3. However, if the count is normal then there is still suspicion of PID, granulocyte function tests can be considered (Reda *et al.*, 2013)

(b) Serum immunoglobulins:

Patients with B-cell defects have low serum immunoglobulins and decreased production or response of immunoglobulins to vaccination with respect to age-specific cutoffs (Kim, 2012). In case of low immunoglobulin levels, serum albumin must be checked. IgG antibody titers to vaccine antigens may be checked to determine reaction to vaccination to indicate responsiveness of B cells (Reust, 2013)

(c) Complement testing:

Complement defects are screened by assessing the components of the classic and alternative pathways. The 'classic pathway', which involves C1 through C9, is checked by a CH50 assay. In case of normal results, the child does not have a clinically considerable complement deficiency. On the other hand, abnormal results mandate checking the alternative pathway using an AH50 or CH100 assay. By combining the results of the two tests, specific disorders can be diagnosed (Abbott and Hauk 2016)

(3) Newborn screening for immunological disorders: the idea of newborn screening is for early detection of inborn conditions where timely treatments diminish mortality or irreversible damage. Provided that SCID is diagnosed before infections become threatening, the affected infants can be saved with 'hematopoietic stem-cell transplantation (HSCT); gene therapy; or, for ADA deficiency, enzyme replacement therapy' (Pai *et al.*, 2014). Population-based screening is the only way to detect SCID prior to the onset of infections in nearly all cases, as more than 80% do not have a positive family history (Chan *et al.* 2011)

'T-cell receptor excision circles (TRECs)' is a biomarker for T lymphopoiesis. It is measured by 'PCR' using DNA isolated from an infant's dried blood spots which is collected for newborn screening (Chan and Puck, 2005). Using a cutoff less than 30 copies/μl, screening for TRECs is considered 100% sensitive for the detection of T-cell disorders (Reust, 2013). Number of cases of SCID are missed by TREC screening and overdiagnosis of SCID when not clinically present is avoided by having flow cytometric evaluation of T-cell numbers, a perfect test, mandated for infants with very low or unnoticeable TRECs. The TREC assay has proven outstanding for detecting syndromes with poor T-cell production or insufficient numbers of circulating T cells. A few more entities may be diagnosed by screening for the circular by-products of 'B-cell immunoglobulin gene rearrangement'. Mild or severe cases of 'ADA deficiency' can be recognized by a modification of the present mass spectrometry assay already used for newborn screening. However; infants with T-cell defects beyond the developmental stage of 'recombination of T-cell receptors (e.g., major histocompatibility complex class II deficiency)' have normal TRECs, but altered T-cell function. Genomic sequencing may be necessary to detect

deleterious mutations in PIDs, of which nearly 200 are identified (Al-Herz *et al.*, 2014)
Newborn screening for SCID by means of assays to detect TRECs started in Wisconsin in 2008, and SCID was added to 'the National Recommended Uniform Panel for Newborn Screened Disorders' in 2010. Currently 23 states conduct population-wide newborn screening for SCID. The incidence of SCID in the USA is estimated at 1 in 100 000 births. However, this differs from one country to another; PIDs are not infrequent in Egyptian children and the observed frequency of combined 'T-cell and B-cell immunodeficiencies' in Egyptian studies was found quite higher than other countries (Reda *et al.*, 2013)
Moreover, there are advances in the screening for the circular by-products of 'B-cell immunoglobulin gene rearrangement' (KRECs)
Nevertheless, mild or severe cases of ADA deficiency can be recognized by a modification of the present mass spectrometry assay

(4) Treatment of PIDs: immediate measures should be put in place for all cases of PIDs: prophylactic antibodies, immunoglobulin replacement therapy, in addition to avoidance of live vaccines and protection from exposure to infections (*http://primaryimmune.org/treatment-information/newborn-screening/*).

However, definitive treatment of SCID and other forms of PIDs needs reconstitution of T-cell immunity; this can be accomplished by HSCT or enzyme substitution or gene therapy for certain monogenic disorders (Ghosh *et al.*, 2015). However, active viral infections have proved to negatively influence survival during HSCT and patients with PIDs stay particularly vulnerable to viral infections during and after HSCT. For this reason, viral-specific T-lymphocytes (VSTs) represent a novel therapy for the prevention and treatment of viral infections for patients with PIDs before and after HSCT and the overall survival of treated patients is estimated as 80% at 6 months after VST infusion. In time, both 'HSCT donor-derived and off-the-shelf VST therapy' might become the standard of care along with antiviral pharmacotherapy for patients with PIDs (Naik *et al.*, 2015).

Due to the genetic complexity, genetic counseling is necessary for the patients and their families. Genetic counseling helps families in understanding the genetic contributions to disease incidence and recurrence risks. It is important in facilitating decision-making and arranging genetic testing. Geneticists should be an essential part of the healthcare team (Krause and Wessels, 2012).

Summary and conclusion

This review modestly presented a brief overview on the immune response and delineated genetic syndromes manifesting immunologic abnormalities and primary immune deficiencies.

The term 'syndromic immunodeficiencies' refers to a number of conditions featuring immunodeficiency with clinical problems that are not directly due to the immunologic deficit.

Several genetic disorders may be considered as both primary and syndromic immunodeficiencies since they both have characteristic organ dysfunction and/or dysmorphology unrelated to the immune system, as well as a consistent, well-defined immunodeficiency such as Wiskott-Aldrich syndrome and ataxia-telangiectasia.

Recognition of a syndromic immunodeficiency is important, as it may be diagnostic for a specific syndrome and if a child presents with one of these syndromes, it is important to establish if an immune defect is present so that appropriate intervention can be undertaken.

According to the hallmark of the disorder, syndromic immunodeficiencies may be categorized into syndromes with growth defects, syndromes with hematologic, skin, gastrointestinal, or neurologic manifestations in addition to syndromes with inborn errors of metabolism, chromosomal abnormalities, and other miscellaneous groups.

Immune defects may affect cellular, humoral, or both arms of the immune system and thus the resulting symptoms vary in severity from mild to fatal recurrent infections and autoimmunity.

PID are a group of disorders that are caused by genetic abnormalities that manifest in immune dysfunction. The most common among these are defects that affect the adaptive immune system.

The International Union of Immunological Societies (IUIS) Expert Committee on Primary Immunodeficiency (PID EC) updated the classification of human primary immunodeficiencies in 2015 into nine major groups according to the immunologic defect rather than the genetic syndrome. Thirty-four new gene defects have been added in this update.

Newborn screening is early detection of inborn conditions for which prompt treatments diminish mortality or irreversible damage. This is currently implemented by measurement of T-cell receptor excision circles (TRECs) in peripheral blood

coupled with basic and +/– specific flow cytometric measurements.

Advances in sequencing technologies will undoubtedly lead to even more advances in this area.

In addition to emergency measures, definitive treatment of SCID and other forms of PIDs is by HSCT coupled with viral-specific T lymphocytes (VST) or enzyme substitution or gene therapy.

Genetics professionals play a fundamental role in the management of patients with PIDs and form a vital part of the management team to guarantee that the best possible care is provided for the patient and his family.

Appendix

Table A1 The 10 warning signs of primary immunodeficiency in children

1	Four or more new ear infections within 1 year
2	Two or more serious sinus infections within 1 year
3	Two or more months on antibiotics with little effect
4	Two or more pneumonias within 1 year
5	Failure of an infant to gain weight or grow normally
6	Recurrent, deep skin or organ abscesses
7	Persistent thrush in mouth or fungal infection on skin
8	Need for intravenous antibiotics to clear infections
9	Two or more deep-seated infections including septicemia
10	A family history of primary immunodeficiency

Adapted from National Primary Immunodeficiency Resource Center (*http://www.info4pi.org*).

Table A2 Immunodeficiency diseases-related score

Diagnosis or condition	Score	Diagnosis or condition	Score
Pneumonia, organism unknown	3	Malabsorption	2
Bacterial pneumonia	3	Giardiasis	2
Septicemia	3	Autoimmune hemolytic anemia	2
Empyema	3	Chronic bronchitis[a]	1
Bronchiectasis	3	Chronic sinusitis[a]	1
Osteomyelitis	3	Chronic otitis media	1
Other abscess	3	Chronic diarrhea[a]	1
Aseptic meningitis	3	Acute bronchitis	1
Splenic abscess	3	Acute sinusitis	1
Chronic mastoiditis[a]	3	Fever of unknown origin	1
Bacterial meningitis	3	Cutaneous candidiasis	1
Liver abscesses	3	Suppurative otitis media	1
Lung Abscess	2	Failure to thrive	1
Lymphopenia	2	Thrush	1
Cellulitis	2	Lymphadenitis	1
Neutropenia	2	Gastroenteritis	1
Splenomegaly	2	Mycosis	1
Lymphadenopathy	2	Acute otitis media	1
Immune thrombocytopenia	2	Abnormal weight loss	1

Adapted from Yarmohammadi *et al.* (2006). [a]Chronic condition counting only once in 12 months.

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