

Diploma thesis

**Diagnosis verification of inborn errors of immunity
applying clinical criteria using a standardized
human phenotype ontology terminology**

submitted by

Lukas Mathias Gasteiger

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Univ. Prof. Dr. Markus Seidel

Graz, August 24th, 2020

Affirmation in lieu of an Oath

I hereby formally declare, that I have written the submitted thesis independently and without any illegitimate assistance from third parties. I confirm, that I used no other than the declared sources for the preparation of this academic work. All used sources have been indicated as such and acknowledged by means of complete references in the text.

Graz, August 24th, 2020

Lukas Mathias Gasteiger eh.

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Abbreviations

IEI	Inborn Errors of Immunity
IUIS	International Union of Immunological Societies
SCID	Severe Combined Immunodeficiency
ATM	Ataxia telangiectasia
ALPS	Autoimmune lymphoproliferative syndrome
APECED	Autoimmune polyendocrinopathy – candidiasis – ectodermal dystrophy
APS1	Autoimmune polyendocrine syndrome type 1
CMC	Chronic mucocutaneous candidiasis
CHH	Cartilage hair hypoplasia
CGD	Chronic granulomatous disease
CVID	Common variable immunodeficiency disorders
FC3RN	Ficolin 3 Deficiency
FHLH	Familial hemophagocytic lymphohistiocytosis syndrome
IPEX	Immunodysregulation – polyendocrinopathy – enteropathy – X-linked syndrome
GS1b	Glykogen storage disease type 1b
HSE	Herpetic encephalitis
HLA	Human leukocyte antigen
MHC2	Major Histocompatibility complex class II
HIES	Hyper IgE syndrome
ICF	Immunodeficiency – centromeric instability – facial anomalies syndrome
PFC	Properdin P factor complement deficiency
SCID	Severe combined immunodeficiency
WHIM	Warts, hypogammaglobulinemia, infections and myelokathexis
XLP	X-linked lymphoproliferative syndrome
ESID	European Society for Immunodeficiencies
OMIM	Online Mendelian Inheritance in Man
HPO	Human Phenotype Ontology
DAG	Directed Acyclic Graph

OMIM	Online Mendelian Inheritance in Man
HOOM	HPO-ORDO Ontological Module
ORDO	Orphanet Rare Disease Ontology
OBAN	Open Biomedical Associations
OWL	Web Ontology Language
RDF	Resource Description Framework
ERN-RITA	European Reference Network – Rare Immunodeficiency, Autoinflammatory and Autoimmune Disease Network

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Zusammenfassung

Hintergrund: Seltene Erkrankungen wie primäre Immundefekte können durch charakteristische klinische Symptome und bestimmte Laborparameter diagnostiziert werden. Idealerweise wird diese Diagnose auch noch genetisch bestätigt. Da allerdings nicht bei allen Patientinnen und Patienten mit einem primären Immundefekt eine monogenetische Ursache für die Erkrankung bekannt ist, sind eine korrekte Diagnose und damit auch die Eingabe dieser in Patientenregister oftmals schwierig. Aus diesem Grund hat die ESID, die European Society for Immunodeficiencies, einen von Expertinnen und Experten erstellten und kreuzbegutachteten Katalog erstellt, welcher diagnostische Kriterien für insgesamt 75 primäre Immundefekte beinhaltet und damit die Diagnose von seltenen primären Immundefekten erleichtern soll und dadurch auch die Qualität der Daten im ESID Register erhöht werden soll. Jedoch wird in diesem Katalog kein standardisiertes Vokabular für die Beschreibung der auftretenden phänotypischen Veränderungen verwendet. Dieses standardisierte Vokabular wäre allerdings nicht nur für die Erstellung korrekter Diagnosen hilfreich, sondern würde auch die Vergleichbarkeit innerhalb verschiedener Datensätze erhöhen. Des Weiteren wäre eine solche standardisierte und exakte Beschreibung notwendig um Assoziationen zwischen bestimmten Phänotypen und neu entdeckten Genvarianten unklarer Signifikanz herstellen zu können. Zuletzt ist ein standardisiertes Vokabular nötig um die Verarbeitung der Daten mit KI-gestützten Algorithmen zu ermöglichen. Auf Grund dessen, wurde im Zuge dieses Projektes der Katalog der ESID zur klinischen Diagnose primärer Immundefekte geprüft und um Listen von standardisierten Beschreibungen der Phänotypen für alle im Katalog vorkommenden primären Immundefekte ergänzt. Als Grundlage wurde dafür die Human Phenotype Ontology (HPO) gewählt.

Methoden: Die Listen mit standardisierten Vokabeln zur Beschreibung der Phänotypen sind auf Basis verschiedener Datenbanken erstellt worden. 38 Erkrankungen haben genaue Beschreibungen auf Basis des HPO-ORDO ontological module (HOOM) erhalten, die Daten sind mittels SPARQL abgefragt worden und in Form von Excel Dokumenten gesammelt worden. Insgesamt 34 Erkrankungen haben ihre Beschreibung durch die Verwendung von OMIM (Online Mendelian Inheritance in Man) erhalten. Hier sind die Daten direkt über HPO

abgerufen wurden und wiederum in Form von Excel Dokumenten gesammelt worden. Für drei Erkrankungen sind in diesen Datenbanken keine phänotypischen Informationen verfügbar gewesen, weswegen die Listen auf Basis von verfügbaren Publikationen erstellt worden sind.

Ergebnisse und Conclusio: Insgesamt 75 Tabellen mit standardisiertem Vokabular für die einzelnen Erkrankungen des Kataloges der ESID sind in den Katalog integriert worden und anschließend auf der Website des ESID Register veröffentlicht worden. Im Weiteren kann angedacht werden die Verwendung dieses standardisierten Vokabulars im Register auszuweiten und diese bei Eingabe neuer Patientinnen und Patienten wie auch beim jährlichen follow-up zu verwenden, was eine longitudinale Beobachtung der Patientinnen und Patienten ermöglichen würde. Zusätzlich könnte durch die Verwendung die Verarbeitung der Daten durch KI-gestützte Systeme erfolgen.

Abstract

Background: Rare diseases such as inborn errors of immunity (IEI) may be diagnosed by characteristic clinical and laboratory features, and/or, ideally, genetically confirmed. Because not all patients with IEI have a known monogenic cause of their disease, and to ascertain correct entry into an international patient registry, the European Society for Immunodeficiencies (ESID) published expert-generated and peer-reviewed clinical diagnosis criteria. However, the current version of ESID diagnosis criteria is not using a standardized vocabulary, which would be crucial not only for making the diagnosis but also for the comparability of patient records in registries, for a transferrable phenotypic description of presentations with novel variants, as well as for filtering in bioinformatic steps of modern diagnostic processes such as next-generation sequencing. Therefore, the ESID diagnostic criteria were critically reviewed and revised, and, in the course thereof, a standardized vocabulary in the form of the human phenotype ontology (HPO) was integrated into the diagnostic criteria.

Methods: Lists with standardized vocabulary for each of the 75 entities in the ESID diagnosis criteria catalogue were created. For this purpose, different databases were used. Thirty-eight entities were annotated with HPO terms using the HPO-ORDO ontological module (HOOM). The sought data was retrieved using SPARQL and then transferred into Excel sheets. Thirty-four entities altogether were annotated based on data coming from OMIM (Online Mendelian Inheritance in Man). The data was directly retrieved from the HPO webpage and then again transferred into Excel sheets. In the case of three entities, there was no phenotypic information available neither in HOOM nor in OMIM. Therefore the diseases were annotated based on available publications.

Results & Conclusion: Altogether, 75 lists with HPO terms were created, one for each entity of the ESID diagnosis criteria, which were then integrated into the criteria. The updated version of the ESID diagnosis criteria with attached HPO terms can be found on the ESID registry website. In the future, it can be envisioned that the selection of appropriate HPO terms for each patient entered into the ESID registry as well as in the course of the annual follow-up becomes obligatory, which would allow longitudinal monitoring of symptoms, lab values, and the disease

course. Furthermore enables the use of this standardized vocabulary processing of the data using computer-based algorithms.

1 Introduction

1.1 *Inborn errors of immunity (IEI)*

Inborn errors of immunity are a diverse group of disorders defined by different defects in innate and/or adaptive immune system (1). X-linked agammaglobulinemia was the first IEI described in 1952 (2), since then much more IEIs were discovered due to improved methods of detection and advanced laboratory methodology leading to now known 430 monogenic IEIs and further polygenic disorders (3,4).

IEI are classified according to the principal immunological mechanisms that are disrupted, as well as their dominant clinical features. The most common type of an IEI is an antibody deficiency making up for about half of all these disorders. Combined B- and T-cell defects, phagocyte defects, and other syndromes each account for between 10% and 20% of the total. The rest – diseases of immune dysregulation, disorders of innate immunity, autoinflammatory disorders, and complement deficiencies – is relatively rare, each accounting for less than 1% of the total (5).

IEI are presenting themselves with various signs and symptoms of infections. The infections are mostly caused by common pathogens but are of unusual severity, frequency, and duration; often, the infections are refractory to therapy (5). Severe IEI can also be characterised by infections with low-grade or opportunistic organisms (6). Other complications of IEI are autoimmune diseases like inflammatory arthropathies, inflammatory bowel diseases, or vasculitides and malignancies, which are occurring with higher frequency in patients with IEI (7,8). Because of this variety in pathogenesis as well as symptoms of IEI different classifications and diagnostic criteria for these disorders have emerged.

1.1.1 **IUIS classification for Human Inborn Errors of Immunity**

The IUIS classification for Human Inborn Errors of Immunity was curated and maintained by the Inborn Errors of Immunity Committee of the IUIS to ensure a vetted and up-to-date list of these immunological disorders. The first list was published in 1973 (9), since then, the list was revised every two years, leading to the current 2019 update (3). The 2019 update reports the key clinical and laboratory features of 430 IEI, adding further 64 gene defects in comparison to the 2017 update

(10), most of them identified using next-generation sequencing. The IUIS classification consists of 10 tables, each group sharing a given pathogenesis:

- Combined immunodeficiencies
- Combined immunodeficiencies with syndromic features
- Predominantly antibody deficiencies
- Diseases of immune dysregulation
- Congenital defects of phagocytes
- Defects in intrinsic and innate immunity
- Autoinflammatory diseases
- Complement deficiencies
- Bone marrow failure
- Phenocopies of inborn errors of immunity

1.1.2 IUIS Phenotypical Classification for Human Inborn Errors of Immunity

Since 2013 the IEI Committee of the IUIS publishes a phenotypic classification of IEI, which accompanies the IUIS genotypic classification and in parallel, consists of 10 tables. This phenotypical classification aims to help a clinician diagnose patients with IEI presenting a typical phenotype. In the 2019 IUIS Phenotypical Classification all disorders mentioned in the 2019 update of the IUIS IEI classification were included and to each of the ten groups a phenotypic driven algorithm was assigned (3,11,12).

I. Immunodeficiencies affecting cellular and humoral immunity.					
(a) Severe combined immunodeficiencies SCID, defined by CD3 T cell lymphopenia*.					
CD19 NL : SCID T- B+			CD19 ↓ : SCID T-B-		
SCID T-B+NK-		SCID T-B+NK+		SCID T-B-NK-	SCID T-B-NK+
XL, CD 132 def γc deficiency IL2RG	IL7Rα . IL7R	Coronin-1A def* . CORO1A	ADA def . ADA	Microcephaly ?	
	No γ/δ T cells: CD3δ* . CD3D CD3ε* . CD3E CD3ζ** . CD3Z	Detectable	Chondrosternal dysplasia, deafness, may have pulmonary alveolar proteinosis, cognitive defects	Yes	No
AR, CD 132+ JAK-3 def JAK3	NI γ/δ T cells : CD45* PTPRC	Winged helix def* . FOXN1.	Reticular dysgenesis. AK2	Radiation sensitivity - With facial dysmorphism: DNA ligase IV def . LIG4	Increased risk of graft rejection, possibly due to activated NK cells
	LAT def* . LAT. Typical SCID or CID with adenopathy, splenomegaly, autoimmunity. High Ig.	Severe infections; abnormal thymic epithelium; congenital alopecia, nail dystrophy, neural tube defect. Ig: decreased .Tc: Very low.	Activated Rac2 defect* . RAC2, AD GOF	- Without facial dysmorphism: DNA PKcs def* PRKDC	RAG 1/2 def (RAG1/ RAG2)
			Recurrent bacterial and viral infections, lymphoproliferation; neutropenia	- Without facial dysmorphism: DNA PKcs def* PRKDC	DCLRE1C def DCLRE1C (ARTEMIS). + Radiation sensitivity
				Variable Ig levels	

Figure 1: Immunodeficiencies affecting cellular and humoral immunity. (a) Severe combined immunodeficiencies defined by T cell lymphopenia, taken from Bousfiha et al. 2020 (12)

I. Immunodeficiencies affecting cellular and humoral immunity						
b- Combined Immunodeficiencies Generally Less Profound than Severe Combined Immunodeficiency						
Low CD4: MHCII Expression ?	Low CD8	Low Bc:	Ig : often NL	Ig Low	Normal Ig but Poor Specific Antibody response	
Absent	Present	Omenn sd (hypomorphic mutations). Erythroderma, Alopecia, Adp, HSM, Eo ↑, IgE ↑	CD3γ def*. CD3β TCR low. Autoimmunity	DOCK2 def. DOCK2. Early invasive herpes viral, bacterial infections, NI NK number, but defective function. Poor interferon responses. IgG NL or low; poor antibody responses.	MALT1 def*. MALT1. Bacterial, fungal and viral infections. Impaired Tc proliferation.	
MHC-II def RFXANK, CITA, RFX5, RFXAP	LCK def. LCK. AR, immune dysregulation, auto-immunity. Low Treg, restricted T cell repertoire, poor TCR signaling. ↑ IgE.	DOCK8 def. DOCK8. Severe Eczema. Cutaneous viral and staphylococcal infections; severe atopy; cancer, diabetes. High IgE, Low IgM, eosinophilia. ↓ NK with poor function. ↑ Bc, ↓ memory Bc. Poor peripheral Bc tolerance. ↑ exhausted CD8+ TEM cells	RHOH def*. RHOH. HPV infection, lung granulomas, molluscum contagiosum, lymphoma. Low naive T cells, restricted repertoire, poor proliferation to CD3.	CARD11 deficiency (LOF). CARD11. Pneumocystis jirovecii pneumonia, bacterial & viral infections. Ig: Absent/low. Tc: NL number, poor proliferation.	RelB def*. RELB. Recurrent infections Tc: poor diversity, ↓ proliferation to mitogens; no response to Ag; Bc: marked increase	
AR, Failure to thrive, respiratory and gastrointestinal infections, liver/biliary tract disease	Polymerase δ def*. AR. POLD1 or POLD2. Recurrent respiratory tract infections, skin infections, warts and molluscum, short stature, intellectual disability. Low Bc, Low Ig.	STK4 def. STK4. Intermittent neutropenia, bacterial, viral (HPV, EBV, molluscum), candidal infections, lymphoproliferation, autoimmune cytopenias, lymphoma, congenital heart disease. ↓ : CD4 Tc, naive Tc, ↑ TEM and TEMRA cells, poor proliferation. ↓ : memory Bc, IgM & Ab responses. ↑ IgE, IgA, IgE	TCRA def*. TRAC. Recurrent viral, bacterial, fungal infections; diarrhea; immune dysregulation and autoimmunity. Absent TCRα except for a minor CD3-dim TCRαβ population; poor proliferation.	ICOS def. ICOS. Recurrent infections, autoimmunity, gastroenteritis, granulomas.		
CD8 def*. CD8A	AD : UNC119 def UNC119	IL21 def. IL21. Severe early onset colitis. Tc: NL / low function. Hypogammaglobulinemia, poor specific antibody responses; ↑ IgE	QK40 def*. QK40. Kaposi's sarcoma, impaired immunity to HHV8. Low memory Bc. Tc: low Ag specific memory CD4+	TFRC deficiency* TFRC. Recurrent infections. Neutropenia, thrombocytopenia. Bc: NI number, low memory Bc. Tc: NI number, poor proliferation.		
NI MHC -I on lymphocytes. ZAP-70 def. ZAP70. May have immune dysregulation, autoimmunity. NI Ig. CD4: Low function		NIK def*. MAP3K14. Bacterial, viral and Cryptosporidium infections. ↓ : NK, Ig levels & switched memory Bc. Tc: Ag poor proliferation	FCHO1 def*. FCHO1. Lymphoproliferation, failure to thrive. Tc: Low. Bc & Ig : NI increased activation-induced T-cell death, defective clathrin-mediated endocytosis	CD40 ligand def. (CD154). XL, CD40LG. or CD40 def. AR, CD40. Opportunistic infections, biliary tract and liver disease, Cryptosporidium. Neutropenia, HIGM: IgM normal or high, other Ig isotypes low. Bc: sIgM+, IgD+ cells present, absent sIgG, IgA+ and IgE+ cells. Tc: NL to low.		
Absent MHC -I on lymphocytes. MHC-I def. TAP2, TAP1 or TAPBP : Vasculitis, pyoderma gangrenosum. NI Ig. B2M* : Sinopulmonary infections, cutaneous granulomas. NI Ig. Hypoprotidemia. Absent β2m associated proteins MHC-I, CD1a, CD1b, CD1c.		Moessin def*. MSN. XL. Recurrent infections with bacteria, varicella; neutropenia. ↓ Ig over time. Tc: defective migration, proliferation.	RelA haploinsufficiency*. RELA, AD. Chronic mucocutaneous ulceration. Impaired NF-κB activation; reduced production of inflammatory cytokines	IL21R def*. IL21R. Recurrent infections; Pneumocystis, Cryptosporidium, liver disease. Tc: low cytokine production; poor antigen proliferation. Decreased memory and switched B cells. Poor specific antibody responses; increased IgE		
C-REL def*. REL. Recurrent infections with bacteria, mycobacteria, salmonella and opportunistic organisms. Defective innate immunity. Low Ig. Tc: decreased memory CD4, poor proliferation.			ITK deficiency. ITK. EBV associated Bc lymphoproliferation, lymphoma, immune dysregulation. NI or low Ig. Progressive CD4 T cell lymphopenia; reduced T cell activation			
ICOSL def*. ICOSL. Recurrent respiratory tract viral infections. hypogammaglobulinemia, and Low Tc, slowly progressive neutropenia						
IKAROS def*. (CD154). AD DN, IKZF1. Opportunistic infections, including P. jirovecii, bacterial, viral and other fungal infections. Increased risk to T-ALL. Agammaglobulinemia, high recent thymic emigrant/naive/Th0 cells; low-absent memory T cells						

Figure 2: Immunodeficiencies affecting cellular and humoral immunity. (B) Combined immunodeficiencies, taken from Bousfiha et al. 2020 (12)

IIa. CID with associated or syndromic features			
Congenital thrombocytopenia	DNA Repair Defects other than those listed in Table1: Karyotype	Immuno- osseous dysplasias	Thymic Defects with Additional Congenital Anomalies
<p>XI: Wiskott Aldrich Sd or XI thrombocytopenia WAS (LOF). Recurrent bacterial and viral infections; bloody diarrhea; eczema; lymphoma; autoimmune disease; IgA nephropathy; vasculitis. Small platelets; Decreased IgM. Low antibody to polysaccharides; often increased IgA and IgE. NI Bc. Tc: Progressive decrease in numbers; Low Tc responses to anti-CD3.</p> <p>Patients with XI-thrombocytopenia have later onset of complications and more favourable life expectancy but eventually develop similar complications as observed in WAS</p> <p>AR: WIP deficiency*, WIPF1, WAS protein absent, +/- small platelets; increased IgE. Bc: NI to low. Tc: Reduced; defective lymphocyte responses to anti-CD3.</p> <p>AR: Defective Arp2/3-mediated filament branching, ARPC2B. Recurrent invasive infections, colitis, vasculitis. Mild thrombocytopenia, normal sized platelets; autoantibodies (ANA, ANCA); eosinophilia. High IgA and IgE.</p>		<p>Cartilage Hair Hypoplasia RMRP. Short-limbed dwarfism with metaphyseal dysostosis, sparse hair, bone marrow failure; autoimmunity; susceptibility to lymphoma and other cancers; impaired spermatogenesis; neuronal dysplasia of the intestine. Ig: NI or ↓. Tc: Varies from ↓↓ (SCID) to NI; impaired lymphocyte proliferation.</p>	<p>AD, Hypoparathyroidism, conotruncal cardiac malformation, velocardial insufficiency, facial dysmorphism, intellectual disability. Ig: Normal or decreased. Tc: ↓ or NI. May have low TRECs at NBS.</p> <p>DiGeorge/velocardiofacial Sd, Chr22q13.2 deletion Sd, 22q11.2DS.</p> <p>TBX1 deficiency, 78X1</p>
<p>Ataxia telangiectasia. ATM: Ataxia; telangiectasia; pulmonary infections; lymphoreticular and other malignancies; increased α-fetoprotein; increased radiosensitivity, chromosomal instability and translocations. Often decreased IgA, IgE and IgG subclasses; increased IgM; antibodies variably decreased. Tc: Progressive decrease, abnormal prolifer to Mitogens.</p>		<p>Schimke Sd SMARCAL1 Short stature, spondyloepiphyseal dysplasia, IUGR; nephropathy; bacterial, viral, fungal infections; may present as SCID; bone marrow failure. Tc: ↓</p>	<p>Chromosome 10p13-p14 deletion Syndrome, 10p13-p14DS. AD. Hypoparathyroidism; renal disease; deafness; growth retardation; facial dysmorphism; cardiac defects may be present</p>
<p>Nijmegen breakage Sd, NBS1. Microcephaly; bird-like face; lymphomas; solid tumors; increased radiosensitivity; chromosomal instability. Often decreased IgA, IgE and IgG subclasses; increased IgM; antibodies variably decreased. Bc: Variably reduced. Tc: progressive decrease.</p>		<p>MOPD1 Deficiency, RNU4ATAC. Recurrent bacterial infections, lymphadenopathy, Spondyloepiphyseal dysplasia, IUGR, retinal dystrophy, facial dysmorphism; +/- microcephaly. short stature. Ig: ↓, specific antibodies variably decreased</p>	<p>AD, CHARGE Sd, CHD7, SEMA3E. Coloboma, heart anomaly, choanal atresia, intellectual disability, genital and ear anomalies; CNS malformation; some are SCID-like and have low TRECs. Ig: Normal or decreased. Tc: Decreased or normal, response to PHA may be decreased</p>
<p>Bloom sd, BLM. Short stature; bird like face; sun-sensitive erythema; marrow failure; leukemia; lymphoma; chromosomal instability. Low Ig.</p>		<p>Immunoskeletal dysplasia with neurodevelopmental abnormalities, EXTL3. Short stature; cervical spinal stenosis, neurodevelopmental impairment. Eosinophilia; Ig: variably ↓. Tc: ↓</p>	<p>Jacobson Sd, 11q23del. Recurrent respiratory infections; multiple warts; facial dysmorphism, growth retardation. Lymphopenia, Low NK, Bc and switched memory Bc. Hypogammaglobulinemia.</p>
<p>PMS2 def, PMS2. Café-au-lait spots; lymphoma, colorectal carcinoma, brain tumors. HIGM and abnormal antibody responses. Reduced Bc, switched and non-switched.</p>		<p>MYSM1 def* MYSM1, AR Short stature, congenital bone marrow failure, myelodysplasia. Skeletal anomalies; cataracts; developmental delay. Affects granulocytes. Bc: immature. Tc: lymphopenia, reduced naive Tc. Hypogammaglobulinemia</p>	<p>FOXN1 haploinsufficiency, FOXN1, AD Recurrent, viral and bacterial respiratory tract infections; skin involvement (eczema, dermatitis), nail dystrophy. T cell lymphopenia may normalize by adulthood.</p>
<p>Immunodeficiency with centromeric instability and facial anomalies: ICF1. DNMT3B; ICF2.ZBTB24; ICF3.CDCA7; ICF4.JELLS. Facial dysmorphism; macroglossia; bacterial/opportunistic infections; malabsorption; malignancies. Cytopenias; multiradial configurations of chromosomes 1,9,16; no DNA breaks. Ig: Hypogammaglobulinemia; Tc and Bc: decreased or NI.</p>			
<p>MCMA4 def, MCMA4. Viral infections:EBV,HSV,VZV. short stature. Bc lymphoma; Adrenal failure; NKc low number and function.</p>			
<p>RNF168 def* (RIDDOLE sd), RNF168. Short stature; mild defect of motor control to ataxia; normal intelligence to learning difficulties; mild facial dysmorphism to microcephaly; increased radiosensitivity. Low IgG or IgA.</p>			
<p>POLE1 (Polymerase ε subunit 1) deficiency (FILS syndrome), POLE1. Recurrent respiratory infections; meningitis; facial dysmorphism, livido, short stature. Low IgM, lack of antibody to PPS. Low memory Bc. Decreased Tc proliferation.</p>			
<p>POLE2 (Polymerase ε subunit 2) deficiency**, POLE2. Recurrent infection, disseminated BCG infections, autoimmunity (type 1 diabetes, hypothyroidism), facial dysmorphism; Low Ig; Very low Bc. Lymphopenia, lack of TRECS, absent proliferation of antigens.</p>			
<p>NSMCE3 deficiency*, NSMCE3. Severe lung disease (possibly viral); thymic hypoplasia, Chromosomal breakage; radiation sensitivity. Ig: Decreased Ab responses to PPS, normal IgG, IgA, normal to elevated IgM. Tc: Low, poor responses to mitogens and antigens.</p>			
<p>Ligase I deficiency*, LIG1 Recurrent bacterial and viral infections; growth retardation; sun sensitivity; lymphoma; radiation sensitivity. Macrocytic red blood cells. Hypogammaglobulinemia. Reduced Ab response. Lymphopenia, increased γδTc, decreased mitogen response.</p>			
<p>GINS1 def*, GINS1. IUGR. Neutropenia, NK cells very low. Tc and Bc: low or normal. High IgA, Low IgG and IgM.</p>			
<p>BMF52 (Hebo def), ERCC62L, AR. Facial dysmorphism; microcephaly, learning difficulties. Bone marrow failure.</p>			

Figure 3: CID with associated or syndromic features, taken from Bousfiha et al. 2020 (12)

IIb. CID with associated or syndromic features			
Hyper-IgE syndromes (HIES)	Defects of Vitamin B12 and Folate Metabolism:	Anhidrotic Ectodermodyplasia with ID	Others
<p>AD-HIES (Job sd), STAT3, AD LOF. Distinctive facial features (broad nasal bridge); bacterial infections (boils and pulmonary abscesses, pneumatoceles) due to <i>S. aureus</i>, <i>Aspergillus</i>, <i>Pneumocystis jirovecii</i>; eczema; mucocutaneous candidiasis; hyperextensible joints, osteoporosis and bone fractures, scoliosis, retention of primary teeth; aneuresym formation. IgE ↑↑; specific antibody production ↓. Bc: Normal; reduced switched and non-switched memory Bc; BAFF expression ↑. Tc: NI overall; Th-17 & T-follicular helper cells ↓</p>	<p>Megaloblastic anemia, Ig: decreased.</p> <p>Transcobalamin 2 deficiency, TCN2. pancytopenia, if untreated for prolonged periods results in intellectual disability.</p> <p>Deficiency causing hereditary folate malabsorption, SLC46A1. failure to thrive, if untreated for prolonged periods results in intellectual disability</p> <p>Methylene-tetrahydrofolate dehydrogenase 1 deficiency, MTHFD1. Recurrent bacterial infection, <i>Pneumocystis jirovecii</i>, failure to thrive, neutropenia; seizures, intellectual disability; folate-responsive ↓ Bc, ↓ antibody responses to conjugated polysaccharide antigens.</p>	<p>Anhidrotic ectodermof dysplasia, various infections (bacteria, mycobacteria, viruses and fungi), colitis, variable defects of skin, hair and teeth.</p> <p>NEMO deficiency, IKKγ (NEMO), XI, monocyte dysfunction. Ig decreased, some with elevated IgA, IgM, poor specific antibody responses, absent antibody to polysaccharide antigens. Bc: NI. Low memory and isotype switched Bc. Tc: NI/ decreased, TCR activation impaired.</p> <p>EDA-ID due to IRA4 GOF mutation, IRA4 (IRBA) AD Tc and monocyte dysfunction Decreased IgG and IgA, elevated IgM, poor specific antibody responses, absent antibody to polysaccharide antigens. Normal Bc numbers, impaired BCR activation, low memory and isotype switched Bc. Normal total Tc, TCR activation impaired.</p> <p>EDA-ID due to IRK3 GOF mutation* IRK3, AD. Low Tc. Bc: NI number, poor function. Low Ig.</p>	<p>Purine nucleoside phosphorylase deficiency, PNP. Autoimmune haemolytic anemia, neurological impairment. Hypouricemia. Ig: NI/low. Bc: NI. Tc: Progressive decrease</p> <p>Calcium Channel Defects. Autoimmunity, EDA, non-progressive myopathy. Ig and Bc: NI. Tc: Normal, defective TCR mediated activation. ORAI1 deficiency*, ORAI1, STIM1 deficiency*, STIM1</p> <p>ID with multiple intestinal atresias, TTC7A. Bacterial (sepsis), fungal, viral infections, multiple intestinal atresias, often with intrauterine polyhydramnios and early demise, some with SCID phenotype. Markedly decreased IgG, IgM, IgA, Bc: NI/low. Tc: Variable/absent, low TRECS (may present with SOD at birth)</p> <p>Hepatic veno-occlusive disease with immunodeficiency (VOD), SP110. Hepatic veno-occlusive disease, <i>Pneumocystis jirovecii</i> pneumonia, CMV, candida, thrombocytopenia, hepatosplenomegaly, cerebrospinal leukodystrophy. Decreased IgG, IgA, IgM, absent germinal centers and tissue plasma cells. Decreased memory Bc, Decreased memory Tc.</p> <p>STAT5b deficiency, STAT5B, AR. Growth-hormone insensitive dwarfism, dysmorphic features, eczema, lymphocytic interstitial pneumonitis, autoimmunity, Hypogammaglobulinemia, High IgE. AD DN: Growth failure and eczema only. High IgE.</p> <p>BCL11B deficiency, BCL11B, AD. Congenital abnormalities: neonatal teeth, dysmorphic facies; absent corpus callosum; neurocognitive deficits. Tc: Low, poor proliferation.</p> <p>Hennekam lymphangiectasia-lymphedema syndrome*, CCR6, FAT4. Lymphangiectasia and lymphedema with facial abnormalities and other dysmorphic features. Ig: decreased. Bc and Tc: Variable.</p>
<p>ZNF341 deficiency, ZNF341, AR. Phenocopy of AD-HIES: Mild facial dysmorphism, early onset eczema, MCC, bacterial skin infections, abscesses, recurrent bacterial respiratory infections (<i>S. aureus</i>), lung abscesses and pneumatoceles, hyperextensible joints, bone fractures and retention of primary teeth</p>			
<p>Camel Netherton Sd, SPINK5; Congenital ichthyosis, bamboo hair, atopic diathesis; ↑ bacterial infections, failure to thrive. ↑ IgE and IgA; Other Ig: variably decreased. Bc: Switched and non-switched Bc are ↓.</p>			
<p>PGM3 deficiency, PGM3. Severe atopy; autoimmunity; skeletal anomalies: short stature, brachydactyly, dysmorphic facial features. Recurrent pneumonia, recurrent skin abscesses, bacterial and viral infections; cognitive impairment; delayed CNS myelination in some. Ig: NI or elevated. Elevated IgE; eosinophilia. Reduced B and memory Bc. CD8 and CD4 Tc may be ↓.</p>			
<p>CID with early-onset asthma, eczema and food allergies, autoimmunity ID with atopic dermatitis (CADINS)*, CARD11, AD LOF. Variable atopy, cutaneous viral infections, recurrent respiratory infections, lymphoma. Eosinophilia, ↓ Tc proliferation. NI to low Bc.</p>			
<p>ERBIN deficiency**, ERBB2IP. Recurrent respiratory infections, susceptibility to <i>S. aureus</i>, eczema, hyperextensible joints, scoliosis, arterial dilatation in some. Moderately increased IgE; increased Treg.</p>			
<p>IL6R deficiency*, IL6R. Recurrent pyogenic infections, cold abscesses, high circulating IL-6 levels.</p>			
<p>IL6ST deficiency*, IL6ST. Bacterial infections, boils, eczema, pulmonary abscesses, pneumatoceles, bone fractures, scoliosis, retention of primary teeth, craniosynostosis. ↓ B-cell memory.</p>			
<p>Loes-Dietz syndrome, TGFBR1, TGFBR2. Recurrent respiratory infections, eczema, food allergies, hyperextensible joints, scoliosis, retention of primary teeth; aortic aneurisms.</p>			
	<p>Bacterial infections, autoinflammation, amylopectinosis. Bc: M; decreased memory Bc.</p> <p>HOLL1 deficiency, HOLL1. Poor Ab responses to polysaccharides. HOP deficiency*, HNF31. Lymphangiectasia. Ig: decreased.</p>		
	<p>Vici syndrome, ENOS. Agnesis of the corpus callosum, cataracts, cardiomyopathy, skin hypopigmentation, intellectual disability, microcephaly, CMC. Ig: Decreased IgG; Bc: Defective. Profound depletion of CD4+ cells.</p>		
	<p>Kabuki Sd, KMT2D (MLL2); AD, KDM6A; XL. Typical facial abnormalities, cleft or high arched palate, skeletal abnormalities, short stature, intellectual disability, congenital heart defects, recurrent infections (otitis media, pneumonia) in 50% of patients. Autoimmunity may be present. Low IgA and occasionally low IgG.</p>		
	<p>Wiedemann-Steiner Sd, KMT2A (MLL); AD Respiratory infections; short stature; hyperkeratosis; hairy elbows; developmental delay, intellectual disability. Hypogammaglobulinemia, decreased memory Bc.</p>		
	<p>Immunodeficiency, developmental delay and hypohomocysteinemia, INDDHIM*, Activating de-novo mutations in NFZL2, AD. Recurrent respiratory and skin infection, growth retardation, developmental delay, white matter cerebral lesions, decreased level of homocysteine; increased expression of stress response genes. Hypogammaglobulinemia. Bc: Decreased switched-memory Bc.</p>		
	<p>Ticho-Hepato-Enteric syndrome, TTC73; SKIVX2*. Respiratory infections, IUGR, woolly hair, early onset intractable diarrhea, liver cirrhosis, platelet abnormalities. Impaired IFNγ production, Hypogammaglobulinemia, low antibody responses. Bc: Variably low switched-memory Bc.</p>		

Figure 4: CID with associated or syndromic features, taken from Bousfiha et al. 2020 (12)

III. Predominantly Antibody deficiencies. a: Hypogammaglobulinemia	
IgG, IgA and/or IgM ↓↓	
Exclude second causes: drugs [Hx], myeloma [bone marrow], lymphoma. Ig loss (not hypo-IgM) in urine, gastro-intestinal or skin. → B Lymphocyte (CD19+) enumeration (CMF)	
Bc absent	Bc >1 %
<p>Severe bacterial infection. All Ig isotypes decreased.</p> <p>X-Linked Agammaglobulinemia. BTK. Some patients have detectable Ig. ProBc: NI</p> <p>AR :</p> <p>μ heavy chain Def.IGHM</p> <p>Igα def. CD79A, Igβ def. CD79B</p> <p>BLNK def. BLNK, A5 def. IGLL1, ProBc: NI</p> <p>E47 transcription factor def. TCF3</p> <p>Severe, failure to thrive.</p> <p>p85 def. PIK3R1. Cytopenia. ProBc: ↓</p> <p>p110s def. PIK3CD. Autoimmune complications.</p> <p>ZFP7 def. SLC39A7. Early onset infections, blistering dermatosis, thrombocytopenia</p> <p>AD</p> <p>E47 transcription factor def. TCF3.</p> <p>Hoffman syndrome. TOP2B. Facial dysmorphism, limb anomalies</p>	<p style="text-align: center;">Commun Variable Immunodeficiency Phenotype</p> <p>CVID with no gene defect specified. Clinical phenotypes vary: most have recurrent infections, some have polyclonal lymphoproliferation, autoimmune cytopenias and/or granulomatous disease</p> <p>Activated p110s syndrome (APDS) AD. Severe bacterial infections. Lymphadenopathy, lymphoproliferation, lymphoma. Reduced memory Bc and increased transitional Bc. PIK3CD GOF. EBV± CMV viremia, autoimmunity. PIK3RI. Developmental delay.</p> <p>PTEN Deficiency (LOF)*. PTEN. AD. Lymphoproliferation, Autoimmunity. Developmental delay.</p> <p>ARHGEF1 deficiency**. ARHGEF. Recurrent infections, bronchiectasis.</p> <p>SH3KBP1 deficiency** SH3KBP1 (CIN85). XL. Severe bacterial infections.</p> <p>SEC61A1 deficiency*. SEC61A1. AD, Severe recurrent respiratory tract infections</p> <p>RAC2 deficiency**. RAC2, AR. Recurrent sinopulmonary infections, poststreptococcal glomerulonephritis; urticaria. Some have selective IgA def.</p>
<p>CD20 deficiency**. CD20. Recurrent infections. Low IgG, NI or elevated IgM and IgA.</p> <p>TAC1 deficiency. TNFRSF13B (TAC1). AD or AR. Variable clinical expression and penetrance for monoallelic variants.</p> <p>BAFF receptor deficiency*. TNFRSF13C (BAFF-R). Variable clinical expression. Low IgG and IgM.</p> <p>TWEAK deficiency**. TWEAK (TNFSF12). AD. Pneumonia, bacterial infections, warts, thrombocytopenia. Neutropenia. Low IgM and A, lack of anti-pneumococcal antibody.</p> <p>IRF2BP2 deficiency**. IRF2BP2. Recurrent infections, possible autoimmunity and inflammatory disease. Hypogammaglobulinemia, absent IgA.</p>	<p>CD19 deficiency*. CD19. Recurrent infections, may have glomerulonephritis.</p> <p>CD81 deficiency*. CD81. Recurrent infections, may have glomerulonephritis. Phenocopy of CD19 deficiency.</p> <p>CD21 deficiency*. CD21. Recurrent infections. Low IgG, impaired anti-pneumococcal response.</p> <p>TRNT1 deficiency. TRNT1. Congenital sideroblastic anemia, deafness, developmental delay. B cell deficiency and hypogammagl.</p> <p>NFKB1 deficiency. NFKB1. AD. Recurrent sinopulmonary infections, COPD, EBV proliferation, autoimmune cytopenias, alopecia and autoimmune thyroiditis. Ig NI or ↓, Bc ↓ or NI, ↓ memory Bc.</p> <p>NFKB2 deficiency. NFKB2. AD. Recurrent sinopulmonary infections, alopecia and endorinopathies (ie, central adrenal insufficiency). Low Bc.</p> <p>IKAROS haploinsufficiency. IKZF1. AD. Recurrent sinopulmonary infections; increased risk of ALL, autoimmunity. Decreased pro-Bc, low or normal Bc reducing levels with age.</p> <p>ATP6AP1 deficiency. ATP6AP1. XL. Hepatopathy, leukopenia, low copper. Variable Ig findings.</p> <p>Mannosyl-oligosaccharide glucosidase deficiency (MOGS)*. MOGS (GCS1). Low bacterial and viral infections in comparison to the level of hypogammaglobulinemia, severe neurologic disease, also known as congenital disorder of glycosylation type IIb (CDG-IIb).</p>

Figure 5: Predominantly antibody deficiencies. (a) Hypogammaglobulinemias, taken from Bousfiha et al. 2020 (12)

III. Predominantly Antibody deficiencies.		
b: Other Antibody deficiencies		
<p style="text-align: center;">Severe Reduction in Serum IgG and IgA with Normal or elevated IgM and Normal Numbers of Bc : Hyper IgM Syndromes</p>	<p style="text-align: center;">Isotype, Light Chain, or Functional Deficiencies with Generally NI Numbers of Bc</p>	<p style="text-align: center;">High Bc numbers due to constitutive NF-κB activation</p>
<p>AID deficiency.</p> <p>AICDA. AR or AD.</p> <p>Bacterial infections, enlarged lymph nodes and germinal centers. NI memory Bc, but lacking somatic hypermutation in AR form.</p>	<p>Selective IgA deficiency. Unknown.</p> <p>May be asymptomatic. Bacterial infections, autoimmunity mildly increased. Very low to absent IgA with other isotypes normal, normal subclasses and specific antibodies.</p>	<p>CARD11 GOF.</p> <p>CARD11. AD. BENTA syndrome</p>
<p>UNG deficiency. UNG.</p> <p>Enlarged lymph nodes and germinal centers.</p>	<p>Transient hypogammaglobulinemia of infancy. Unknown.</p> <p>Usually not associated with significant infections, normal ability to produce antibodies to vaccine antigens. IgG and IgA decreased.</p>	<p>Splenomegaly,</p> <p>lymphadenopathy,</p> <p>poor vaccine responses.</p>
<p>INO80 def*. INO80.</p> <p>Severe bacterial infections.</p>	<p>IgG subclass deficiency with IgA deficiency. Unknown.</p> <p>Recurrent bacterial infections. May be asymptomatic. Reduced IgA with decrease in one or more IgG subclass.</p>	
<p>MSH6*. MSH6.</p> <p>Family or personal history of cancer. Variable IgG, defects, increased IgM in some, NI Bc, low switched memory Bc.</p>	<p>Isolated IgG subclass deficiency. Unknown.</p> <p>Usually asymptomatic, a minority may have poor antibody response to specific antigens and recurrent viral/bacterial infections. Reduction in one or more IgG subclass.</p>	
	<p>Specific antibody deficiency with normal Ig levels and normal B cells. Unknown.</p> <p>Reduced ability to produce antibodies to specific antigens. Ig: NI.</p>	
	<p>Ig heavy chain mutations and deletions. Mutation or chromosomal deletion at 14q32.</p> <p>May be asymptomatic. One or more IgG and/or IgA subclasses as well as IgE may be absent.</p>	
	<p>Kappa chain deficiency*. IGKC.</p> <p>Asymptomatic. All immunoglobulins have lambda light chain.</p>	
	<p>Selective IgM deficiency. Unknown. Pneumococcal / bacterial infections. Absent serum IgM.</p>	

Figure 6: Predominantly antibody deficiencies. (b) Other antibody deficiencies, taken from Bousfiha et al. 2020 (12)

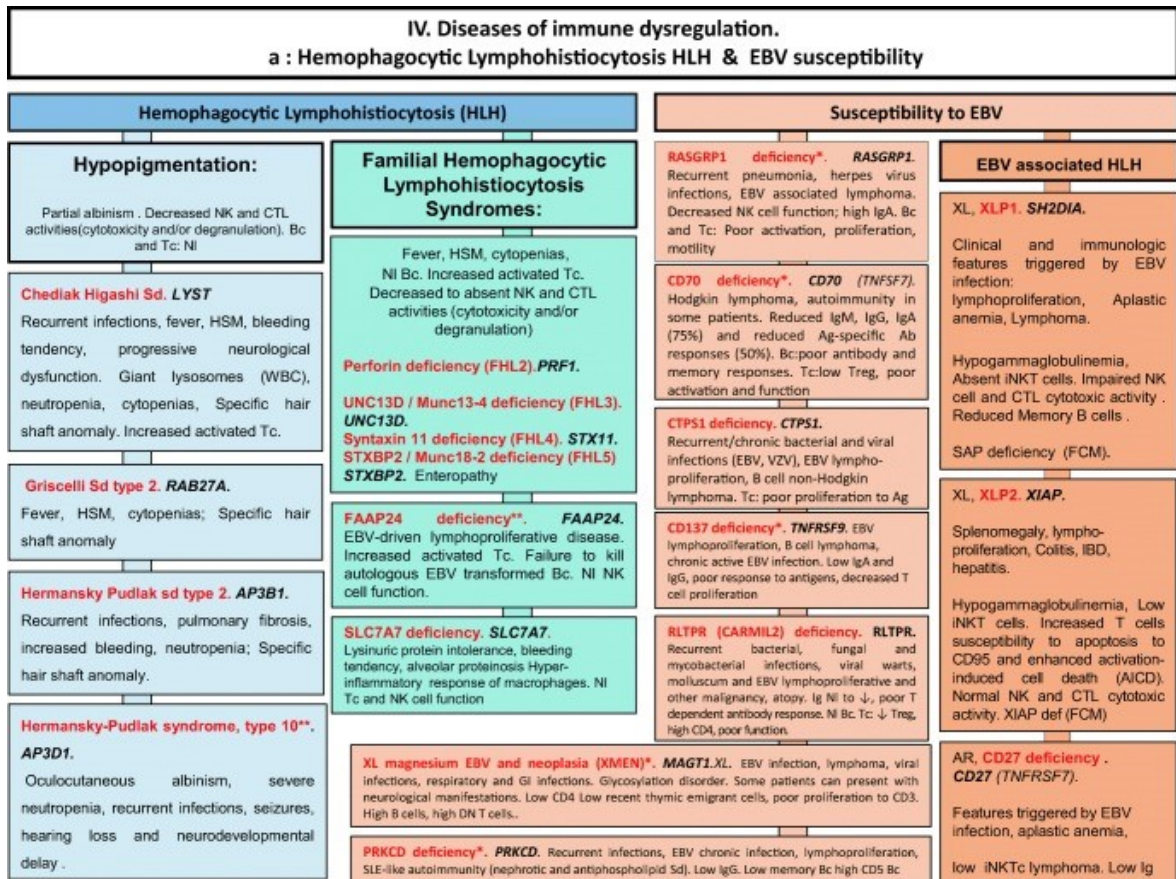


Figure 7: Diseases of immune dysregulation. (a) Hemophagocytic lymphohistiocytosis, taken from Bousfiha et al. 2020 (12)

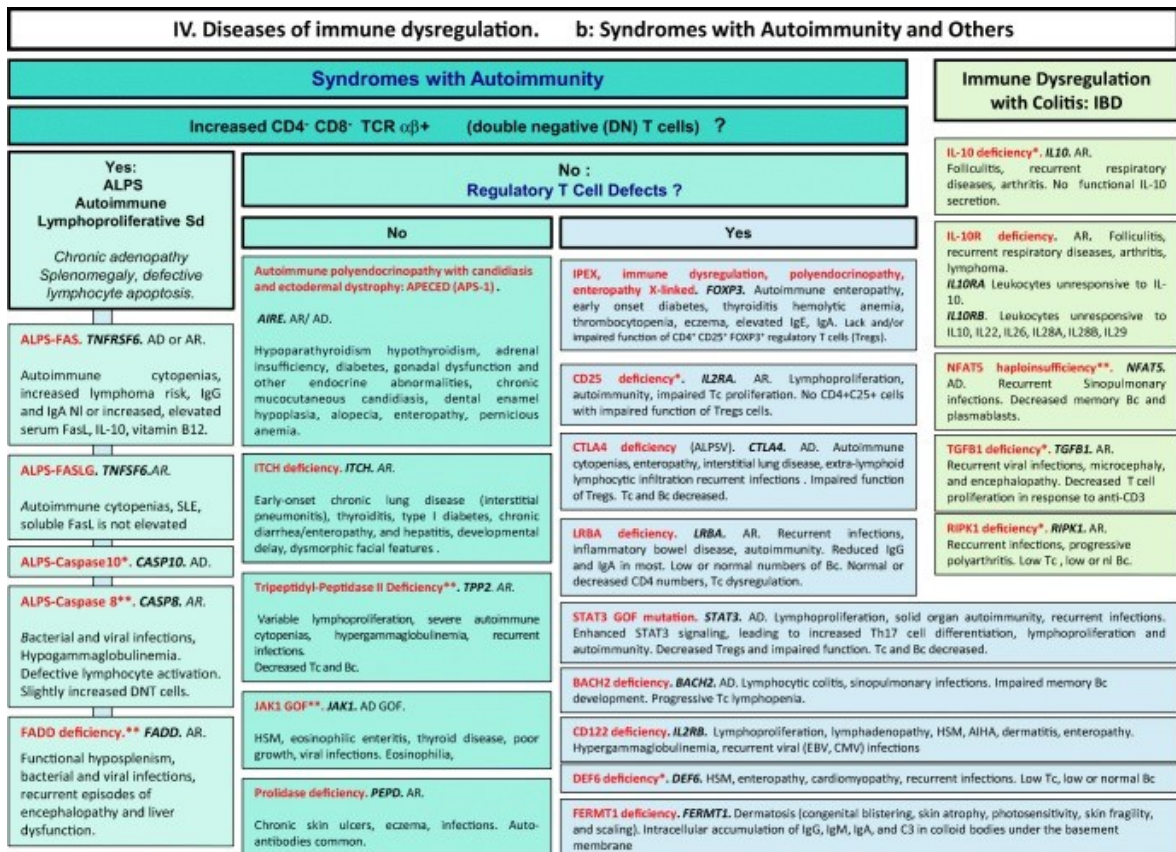


Figure 8: Diseases of immune dysregulation. (b) Other diseases of immune dysregulation, taken from Bousfiha et al. 2020 (12)

V. Congenital defects of phagocyte number, function, or both. a : Neutropenia (without anti-PMN)	
Syndrome associated	No syndrome associated
Shwachman-Diamond Syndrome. DNAJC21. AR. EFL1*. AR. Pancytopenia, exocrine pancreatic insufficiency. SBD5. AR. +chondrodysplasia SRP54 deficiency*. SRP54. AD. Neutropenia and exocrine pancreatic insufficiency .	Elastase deficiency. (SCN1). ELANE. AD. Susceptibility to MDS/leukemia. Severe congenital neutropenia or cyclic neutropenia (perform CBC twice weekly/ 4 weeks).
G6PC3 deficiency (SCN4). G6PC3. AR. Structural heart defects, urogenital abnormalities, inner ear deafness, and venous angiectasias of trunks and limbs. Affected functions: Myeloid differentiation, chemotaxis, O ₂ ⁻ production.	HAX1 deficiency (Kostmann Disease) (SCN3). HAX1. AR. Cognitive and neurological defects in patients with defects in both HAX1 isoforms, susceptibility to MDS/leukemia
Glycogen storage disease type 1b. G6PT1. AR. Fasting hypoglycemia, lactic acidosis, hyperlipidemia, hepatomegaly.	GFI 1 deficiency (SCN2)**. GFI1. AD. B/T lymphopenia
Cohen syndrome. COH1. AR. Dysmorphism, mental retardation, obesity, deafness.	X-linked neutropenia/ myelodysplasia WAS GOF. WAS. XL GOF. Myeloid maturation arrest, monocytopenia, variable lymphoid anomalies .
3-Methylglutaconic aciduria. CLPB. AR. Neurocognitive developmental aberrations, microcephaly, hypoglycemia, hypotonia, ataxia, seizures, cataracts, IUGR.	G-CSF receptor deficiency*. CSF3R. AR. Stress granulopoiesis disturbed
Barth Syndrome (3-Methylglutaconic aciduria type II). TAZ. XL. Cardiomyopathy, myopathy, growth retardation.	Neutropenia with combined immune deficiency *. MKL1. AR. Mild thrombocytopenia. Lymphopenia.
Clericuzio syndrome (Poikiloderma with neutropenia). C16ORF57 (USB1). AR. Retinopathy, developmental delay, facial dysmorphism, poikiloderma.	
VPS45 deficiency (SCN5). VPS45. AR. Extramedullary hematopoiesis, bone marrow fibrosis, nephromegaly.	
JAGN1 deficiency. JAGN1. AR. Osteopenia. Myeloid maturation arrest.	
WDR1 deficiency. WDR1. AR. Poor wound healing, severe stomatitis, neutrophil nuclei herniate. Mild neutropenia.	
SMARCD2 deficiency*. SMARCD2. AR. Developmental aberrations, bones defect, myelodysplasia	
Specific granule deficiency*. CEBPE. AR. Neutrophils with bilobed nuclei. Chronic neutropenia.	
HYOU1 deficiency**. HYOU1. AR. Hypoglycemia, inflammatory complications.	
P14/LAMTOR2 deficiency**. LAMTOR2. AR. Partial albinism, growth failure. Hypogammaglobulinemia, reduced CD8 cytotoxicity.	

V. Congenital defects of phagocyte. b : Functional defects			
Syndrome associated		No Syndrome associated: DHR assay (or NBT test) ?	
		Normal	Abnormal
Cystic fibrosis. CFTR. AR. Pancreatic insufficiency, Respiratory infections, elevated sweat chloride	Leukocyte adhesion deficiency <i>Skin infections evolve to large ulcers. Leukocytosis with neutrophilia (WBC > 25000)</i>	GATA2 def. GATA2, AD. Susceptibility to Mycobacteria, Papilloma Viruses, Histoplasmosis, Lymphedema. Alveolar proteinosis, myelodysplasia/ AML/ CMML . Multi lineage cytopenias. Low NK.	CGD: Early onset of severe and recurrent infections affecting mainly lungs, lymph nodes, skin, and eventually inner structures (liver, spleen, bones, brain, and +++ hepatic abscess). Autoinflammatory phenotype, IBD Granulomata obstructing respiratory, urinary or gastrointestinal tracts. Inflammatory bowel disease (Crohn's like disease) and perianal disease : up to 30 % Pathogens : typically catalase negative bacteria (<i>S. aureus</i> and gram-negative bacilli, <i>Aspergillus</i> , <i>Candida</i>); other: <i>Burkholderia cepacia</i> , <i>Chromobacterium violaceum</i> , <i>Nocardia</i> , and invasive <i>Serratia marcescens</i> . In developing countries, BCG : adverse effects in up to 20 % . Microscopic granulomas. XL CGD: CYBB (gp91 ^{phox}) NCF1 (p47 ^{phox}) , AR CYBA (p22 ^{phox}) , AR NCF4 (p40 ^{phox}) , AR NCF2 (p67 ^{phox}) , AR CYBC1** , AR
Papillon-Lefèvre . CTSC. Periodontitis, palmoplantar hyperkeratosis in some patients	LAD I . ITGB2 Delayed cord separation with omphalitis+++ , no pus formation, lack of inflammation is observed in infection area. Periodontitis leads to early loss of teeth. Severity of the disease correlates with the degree of deficiency in CD18 (FCM). (WBC 20,000–150,000 with 60–85 % neutrophils)	Pulmonary alveolar proteinosis. CSF2RA, AR. CSF2RB*, XL. Affected cells: Alveolar macrophages. Affected fonction: GM-CSF signaling	Rac 2 def** . RAC2. Poor wound healing. LAD phenotype (leukocytosis).
Localized juvenile periodontitis . FPR1. Periodontitis only	LAD II (Congenital disorder of glycosylation, type IIc) SLC35C1 Recurrent infections. Mild LAD type 1 features with hh-blood group, growth retardation, developmental delay , facial dysmorphism (depressed nasal bridge).		G6PD def Class I. G6PD. Infections.
β-Actin . ACTB Mental retardation, short stature	LAD III FERMT3 Severe bacterial infections and severe bleeding disorder. Platelet aggregation assay.		

Figure 9: Congenital defects of phagocyte number, function, or both, taken from Bousfiha et al. 2020 (12)

VI. Defects in Intrinsic and Innate immunity. a : Bacterial and Parasitic Infections :					
Predisposition to Invasive Bacterial infections (pyogens): <i>meningitis, sepsis, arthritis, osteomyelitis and abscesses, often in the absence of fever.</i>		Predisposition to Parasitic and Fungal infections		Others	
Predominant pathogens (<i>S. pneumoniae</i> , <i>S. aureus</i> and <i>Pseudomonas aeruginosa</i>). Non-invasive bacterial infections (skin infections and upper respiratory tract infections). Improve with age. Routine Usual screening tests are normal. Specific screening tests (lack of proinflammatory cytokine production and CD62L shedding) : available only in specialized clinical immunology laboratories. IRAK4 def. IRAK4, AR MyD88 def. MYD88, AR.		Mucocutaneous Candidiasis (CMC) Chronic Mucocutaneous Candidiasis without ectodermal dysplasia STAT1 GOF. STAT1, AD various fungal, bacterial and viral (HSV) infections, autoimmunity (thyroiditis, diabetes, cytopenias), enteropathy IL-17F deficiency*. IL17F, AD. Folliculitis. IL-17RA deficiency. IL17RA, AR Folliculitis. Susceptibility to <i>S. aureus</i> (skin infections) and chronic bacterial infections. IL-17RC deficiency. IL17RC, AR. ACT1 deficiency*. ACT1, AR. Blepharitis, folliculitis and macroglossia.		CARD9 def. CARD9, AR. Predisposition to INVASIVE Fungal Diseases. Invasive candidiasis infection, deep dermatophytoses, other invasive fungal infections. Trypanosomiasis APOLI, AD Trypanosomiasis.	Osteopetrosis. TNFRSF11A, PLEKHM1 AR. TCIRG1, AR. + hypocalcemia CLCN7, OSTM1, AR. + hypocalcemia, neurologic features SNX10, AR. + visual impairment TNFSF11, AR. + severe growth retardation Hydradenitis suppurativa. PSENE1, AD. MCSTN, AD. + acne PSEN, AD. + hyperpigmentation Acute liver failure due to NBAS def. NBAS, AR. Fever induces liver failure Acute necrotizing encephalopathy. RANBP2, AD. Fever induces acute encephalopathy IRF4 haploinsufficiency*. IRF4, AD. Whipple's disease
IRAK-1 def**. IRAK1, XL. X-linked MECP2 deficiency-related syndrome due to a large <i>de novo</i> Xq28 chromosomal deletion encompassing both <i>MECP2</i> and <i>IRAK1</i>					
TIRAP def**. TIRAP, AR. Staphylococcal disease during childhood.					
Isolated congenital asplenia. Bacteremia (encapsulated bacteria). No spleen. RPSA, AD HMOX*, AR. Hemolysis, nephritis, inflammation					
VI. Defects in Intrinsic and Innate immunity. b : MSMD and Viral infection					
Mendelian Susceptibility to mycobacterial disease (MSMD)		Predominant susceptibility to viral infection			
Severe phenotypes.	Moderate phenotypes.	Epidermodysplasia verruciformis (HPV)	Predisposition to Severe Viral Infection	Herpes simplex Encephalitis	
Complete IFNGR1 Def and IFNGR2 Def : IFNGR1, IFNGR2. AR. Serious disseminated BCG and environmental mycobacterial infections (soft tissue, bone marrow, lungs, skin, bones and lymph nodes), <i>Salmonella</i> spp., <i>Listeria</i> <i>monocytogenes</i> and viruses	With Susceptibility to <i>Salmonella</i> IL-12 and IL-23 receptor b1 chain deficiency. IL12RB1. AR. IL-12p40 (IL-12 and IL-23) def. IL12B .AR. IL-12Rb2 deficiency**. IL12RB2. AR IL-23R deficiency**. IL23R. AR. STAT1 LOF STAT1(AD) Partial IFNγR1, IFNGR1. AR. Partial IFNγR2, IFNGR2. AR. AD IFNGR1 IFNGR1. AD. Mycobacterial osteomyelitis SPPL2a deficiency*. SPPL2A. AR. Tyk2 deficiency, TYK2. AR. Susceptibility to viruses, +/- elevated IgE. multiple cytokine signaling defect. P1104A TYK2 homozygosity MSMD or tuberculosis. Macrophage gp91 phox deficiency CYBB, XL IRF8 deficiency, IRF8 AD ISG15 Def, ISG15. AR. Brain calcification. IFN γ production defect. IRF8 deficiency, IRF8 AR Multiple other infectious agents. Myeloproliferation RORγt deficiency*. RORC AR. Susceptibility to <i>Candida</i> . IFN γ production defect, complete absence of IL-17A/F-producing Tc JAK1 (LOF)*, JAK1. AR. Susceptibility to viruses, urothelial carcinoma. ↓ IFN γ production.	HPV (group B1) infections and cancer of the skin EVER1 def. TMC6. AR. EVER2 def. TMC8. AR. CIB1 def. CIB1. AR. WHIM (Warts, Hypogammaglobulinemia, infections, myelokathexis) sd CXCR4 AD GOF. Warts (HPV) infection, neutropenia, low B cell number, hypogammaglobulinemia.	STAT1 Def (AR LOF). STAT1. (+ Mycobacteria) STAT2 deficiency*. STAT2. AR. Disseminated vaccine-strain measles IRF7 deficiency**. IRF7. AR. IRF9 deficiency*. IRF9. AR. Severe influenza disease. IFNAR1 deficiency*. IFNAR1 AR. Severe disease caused by Yellow Fever vaccine and Measles vaccine IFNAR2 deficiency**. IFNAR2 AR. Disseminated vaccine-strain measles, HHV6. No response to IFN- α . CD16 deficiency*. FCGR3A. AR. Severe herpes viral infections, particularly VZV, EBV, and HPV. MDAS deficiency (LOF)*. IFIH1. AR. Rhinovirus and other RNA viruses RNA polymerase III def*. POLR3A. POLR3C. POLR3F. AD. Severe VZV infection. IL-18BP def**. IL18BP. AR. Fulminant viral hepatitis	Dominant clinical phenotype is <i>Herpes simplex encephalitis</i> (HSE) during primary infection with herpes simplex virus type 1 (HSV1), usually between 3 months and 6 years of age. Incomplete clinical penetrance for all etiologies listed here. Routine screening tests are normal. Specific tests examining the TLR3 pathway : marked decrease in the ability of patient's fibroblasts to produce IFN- α and β in response to HSV1 infection. UNC93B1 (AR), TRAF3** (AD), TICAM1 (TRIF)* (AR,AD), TBK1* (AD), IRF3* (AD) TLR3 (AD,AR), + severe pulmonary influenza, VZV DBR1* (AR) + other viral infections of the brainstem	

Figure 10: Defects in intrinsic and innate immunity, taken from Bousfiha et al. 2020 (12)

VIIa. Auto-inflammatory disorders		
Recurrent inflammation	Systemic inflammation with urticaria rash	Others
<p>Recurrent fever</p> <p>Familial Mediterranean Fever (FMF) * MEFV. AR or AD (Usually M694del variant)</p> <p>DA: 1–4 days FA : Variable.</p> <p>Polyserositis, Abdominal pain, Arthritis, Amyloidosis. Erysipelas-like erythema. Predisposes to vasculitis and inflammatory bowel disease .</p> <p>Colchicine-responsive +++.</p>	<p>Familial Cold Autoinflammatory Syndrome (CAPS) * . NLRP3, NLRP12. AD GOF DA: 24-48H</p> <p>Non-pruritic urticaria, arthritis, chills, fever and leukocytosis after cold exposure.</p>	<p>CANDLE sd (chronic atypical neutrophilic dermatitis with lipodystrophy). PSMB8, AR and AD. Contractures, panniculitis, ICC, fevers. PSMG2, AR. Panniculitis, lipodystrophy, AIHA. <i>(Variants in PSMB4, PSMB5, PSMA3, and POMP have been proposed to cause a similar CANDLE phenotype in compound heterozygous monogenic, digenic, and AD monogenic models).</i></p>
<p>Mevalonate kinase def* (Hyper IgD sd). MVK. AR</p> <p>DA: 3–7 days FA: 1–2 monthly.</p> <p>Cervical adenopathy. Oral aphthosis. Diarrhea. Mevalonate aciduria during attacks. Leukocytosis with high IgD levels.</p>	<p>Muckle Wells syndrome (CAPS) * NLRP3. AD GOF.</p> <p>Ethnic group : North European</p> <p>Continuous fever. Often worse in the evenings. Urticaria, Deafness (SNHL), Conjunctivitis, Amyloidosis.</p>	<p>COPA defect. COPA. AD Autoimmune inflammatory arthritis and interstitial lung disease with Th17 dysregulation and autoantibody production</p>
<p>TNF receptor-associated periodic syndrome; TRAPS. TNFRSF1A. AD.</p> <p>DA: 1–4 weeks FA : Variable</p> <p>Prolonged fever. Serositis, rash, Periorbital edema and conjunctivitis.</p> <p>Amyloidosis. Joint inflammation.</p>	<p>Neonatal onset multisystem inflammatory disease (NOMID) or chronic infantile neurologic cutaneous and articular syndrome (CINCA) * . NLRP3. AD GOF.</p> <p>Neonatal onset rash, with continuous fever and inflammation. Aseptic and chronic meningitis, chronic arthropathy. Mental retardation, Sensorineural deafness. and Visual loss in some patients.</p>	<p>NLR4-MAS (macrophage activating syndrome)*. NLR4. AD GOF. Severe enterocolitis and macrophage activation syndrome (HLH). Triggered by cold exposure.</p>
	<p>A20 haploinsufficiency TNFAIP3. AD LOF. Arthralgia, mucosal ulcers, ocular inflammation.</p>	<p>NLRP1 GOF. NLRP1. AD GOF. Palmoplantar carcinoma, corneal scarring; recurrent respiratory papillomatosis. Increased IL1β.</p>
	<p>PLAID (PLCg2 associated antibody deficiency and immune dysregulation), or APLAID*. PLC2G. AD GOF.</p> <p>Cold Urticaria. Impaired humoral immunity. Hypogammaglobulinemia, autoinflammation.</p>	<p>ALPI deficiency*. ALPI. AR. TRIM22 def*. TRIM22. AR Inflammatory bowel disease.</p>
	<p>NLRP1 deficiency*. NLRP1. AR. Dyskeratosis, autoimmunity and arthritis.</p>	<p>T-cell lymphoma subcutaneous panniculitis-like (TIM3 deficiency). HAVCR2. AR. Panniculitis, HLH, polyclonal cutaneous T cell infiltrates or T-cell lymphoma</p>

VIIb. Auto-inflammatory disorders		
Sterile inflammation (skin / bone / joints)	Predominant on the skin	Type 1 Interferonopathies
<p>Predominant on the bone / joints</p> <p>Pyogenic sterile arthritis, pyoderma gangrenosum, acne (PAPA) syndrome, hyperzinemia and hypercalprotectinemia. PSTPIP1 (C2BP1). AD</p> <p>DA: 5 days FA: Fixed interval : 4-6 weeks</p> <p>Destructive arthritis, Pyoderma gangrenosum, inflammatory skin rash, Myositis. Acute-phase response during attacks</p>	<p>Blau syndrome. NOD2 (CARD15). AD. Continuous inflammation.</p> <p>Uveitis, Granulomatous synovitis, Camptodactyly, Rash, Cranial neuropathies, 30% develop Crohn colitis. Sustained modest acute-phase response.</p>	<p><i>Progressive encephalopathy, ICC, Cerebral atrophy, HSMG, leukodystrophy, Thrombocytopenia, Elevated hepatic transaminases. Chronic cerebrospinal fluid (CSF) lymphocytosis</i></p> <p>Aicardi-Goutieres Syndromes : TREX1 AR-AD (+SLE, FCL), RNASEH2A, RNASEH2B (+SP), RNASEH2C, SAMHD1 (+ FCL), ADAR1 (+BSN, SP), IFIH1 GOF AD (+SLE, SP, SMS), DNASE2</p>
<p>Chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anemia (Majeed syndrome). LPIN2. AR</p> <p>DA : Few days FA : 1-3 / month</p> <p>Chronic recurrent multifocal osteomyelitis, severe pain, tender soft tissue swelling, Transfusion-dependent anemia, cutaneous inflammatory disorders</p>	<p>CAMPS CARD14. AD. Psoriasis.</p>	<p>Spondyloenchondro-dysplasia with immune dysregulation (SPENCDI). ACPS. Short stature, SP, ICC, SLE-like auto-immunity (Sjögren's syndrome, hypothyroidism, inflammatory myositis, Raynaud's disease and vitiligo), hemolytic anemia, thrombocytopenia, skeletal dysplasia, possibly recurrent bacterial and viral infections.</p>
<p>DIRA (Deficiency of the Interleukin 1 Receptor Antagonist) IL1RN. AR Continuous inflammation. Neonatal onset of sterile multifocal osteomyelitis, periostitis and pustulosis.</p>	<p>DITRA. (Deficiency of IL-36 receptor antagonist). IL-36RN. AR .</p> <p>Life-threatening, multisystemic inflammatory disease characterized by episodic widespread, pustular psoriasis, malaise, and leukocytosis.</p>	<p>STING-associated vasculopathy, infantile-onset. TMEM173. Early-onset inflammatory disease, Skin vasculopathy, inflammatory lung disease, systemic autoinflammation and ICC, FCL.</p>
<p>Cherubism. SH3BP2. AR. Bone degeneration in jaws</p>	<p>ADAM17 deficiency*. ADAM17. AR. Early onset diarrhea and skin lesions. Severe bacteremia. Defective TNFα production.</p>	<p>ADA2 deficiency. CECR1. Polyarteritis nodosa, childhood-onset, early-onset recurrent ischemic stroke and fever, Livedo racemosa, some patients develop hypogammaglobulinemia</p>
	<p>SLC29A3 mutation. SLC29A3. AR. Hyperpigmentation hypertrichosis, histiocytosis-lymphadenopathy plus syndrome</p>	<p>XL reticulate pigmentary disorder. POLA1. Hyperpigmentation, reticulate pattern. Inflammatory lung and Gastroenteritis or colitis. Corneal scarring, characteristic facies</p>
	<p>Otulipenia/ORAS*. OTULIN. AR. Neonatal onset of recurrent fever, Arthralgia, lipodystrophy. Dermatitis, diarrhea, Neutrophilia</p>	<p>USP18 def *. USP18. TORCH like syndrome.</p>
	<p>AP153 deficiency*. AP153. AR. Pustular psoriasis</p>	<p>Pediatric systemic lupus erythematosus. DNASE1L3. Very early onset SLE, reduced complement levels, autoantibodies (dsDNA, ANCA), lupus nephritis, hypocomplementemic urticarial vasculitis syndrome.</p>
		<p>OAS1 def*. OAS1. AD GOF. Pulmonary alveolar proteinosis, skin rash.</p>

Figure 11: Autoinflammatory disorders, taken from Bousfiha et al. 2020 (12)

VIII. Complement deficiencies			
Susceptibility to infections			
High		Low	
Disseminated Neisserial infections		SLE-like syndrome. Infections with encapsulated organisms	Atypical Hemolytic Uremic Syndrome
Absent CH50 and AH50 hemolytic activity. Defective bactericidal activity.	Normal CH50. Absent AH50 hemolytic activity	Absent CH50 hemolytic activity	C3 GOF. C3. AD. Glomerulonephritis. Increased activation of complement
C5 def. C5		C1q def. C1QA, C1QB, C1QC.	Factor B GOF. CFB. AD. Increased spontaneous AH50
C6 def. C6		C1r def. C1R. Ehlers Danlos phenotype	Factor H def. CFH. AR or AD. Infections, disseminated neisserial infections, preeclampsia. Spontaneous activation of the alternative complement pathway with consumption of C3
C7 def. C7.	Properdin def.	C1s def. C1S.	Factor H-related protein deficiencies. CFHR1-5. AR or AD. Later onset, disseminated neisserial infections. Normal CH50, AH50, autoantibodies to Factor H.
+ Vasculitis	PFC. XL	Multiple autoimmune diseases; Ehlers Danlos phenotype	Factor I deficiency. AR. Infections, disseminated neisserial infections, preeclampsia. Spontaneous activation of the alternative complement pathway with consumption of C3
C8 def. C8A, C8B, C8G		C2 def. C2.	Thrombomodulin def. THBD. AD. Normal CH50, AH50
	Factor D def.	Vasculitis, Polymyositis, atherosclerosis	Membrane Cofactor Protein deficiency. CD46. AD. Glomerulonephritis. Infections, preeclampsia. Inhibitor of complement alternate pathway, decreased C3b binding
C9 def. C9.	CFD. AR.	Complete C4 def. C4A+C4B. AR.	Membrane Attack Complex Inhibitor deficiency. CD59. AR. Hemolytic anemia. Polyneuropathy.
Mild susceptibility.		Partial deficiency is common (either C4A or C4B) and appears to have a modest effect on host defense	CD55 deficiency (CHAPLE disease). CD55. AR. Protein losing enteropathy, thrombosis
			Periodontal Ehlers Danlos. C1R, C1S. AD GOF. Hyperpigmentation skin fragility. Normal CH50.
			C1inhibitor. SERPING1. AD. Hereditary angioedema. Spontaneous activation of the complement pathway with consumption of C4/C2

Figure 12: Complement deficiencies, taken from Bousfiha et al. 2020 (12)

IX. Bone marrow failure			
Fanconi anemia CNS, skeletal, skin, cardiac, GI, urogenital anomalies. Increased chromosomal breakage, pancytopenia.	Dyskeratosis congenita (DKC) Myelodysplasia, short telomeres. Exclude other causes: Fanconi anemia, Blackfan-Diamond	Bone marrow failure sd (BMFS) Myelodysplasia	Others
Fanconi anemia Type A-W: AR FANCA, FANCC, BRCA2, FANCD2, FANCE, FANCF, XRCC9, FANCI, BRIP1, FANCL, FANCM, PALB2, RAD51C, SLX4, ERCC4, RAD51, BRCA1, UBE2T, XRCC2, MAD2L2, RFWD3, XL FANCB	Dyskeratosis congenita : IUGR, microcephaly, pulmonary and hepatic fibrosis, nail dystrophy, sparse scalp hair and eyelashes; reticulate skin pigmentation; palmar hyperkeratosis; premalignant oral leukoplakia; pancytopenia; +/- recurrent infections. DKC1: XL, Bc and Tc: Progressive decrease. NOLA2 (NHP2), NOLA3 (NOP10): AR, Tc: Decreased. RTEL1 : AD, Tc: Decreased. TERC, TINF2, ACD : AD, Tc: variable. TERT, TPP1: AD/AR, Tc: variable. DCLRE1B/ SNM1/APOLLO, WRAP53*, DCAB1: AR, Tc: variable. Hoyeraal-Hreidarsson Syndrome (HHS) Severe phenotype with developmental delay and cerebellar hypoplasia. AR, RTEL1, PARN, ACD	SRP72- deficiency**. SRP72, AD Bone marrow failure and congenital nerve deafness	MIRAGE sd ,AD. SAMD9 (GOF) : IUGR with gonadal abnormalities, adrenal failure, MDS with chromosome 7 aberrations, predisposition to infections, enteropathy, absent spleen
		BMFS5* TP53, AD Erythroid hypoplasia, B-cell deficiency	Ataxia pancytopenia sd. AD. SAMD9L. (GOF) : Cytopenia, predisposition to MDS with chromosome 7 aberrations and progressive cerebellar dysfunction
			COATS plus Sd: Intracranial calcification, abnormal telomeres, IUGR, gastrointestinal hemorrhage due to vascular ectasia, hypocellular bone marrow. pancytopenia STN1: premature aging, CTC1 : sparse graying hair, dystrophic nails, osteopenia, retinal telangiectasia,

Figure 13: Bone marrow failure disorder, taken from Bousfiha et al. 2020 (12)

X. Phenocopies of PID	
Associated with Somatic Mutations	Associated with Auto-Antibodies
<p><i>Splenomegaly, lymphadenopathy, autoimmune cytopenias. Defective lymphocyte apoptosis.</i></p> <p>ALPS-SFAS (somatic mutations in <i>TNFRSF6</i>)/ <i>ALPS-FAS</i> (ALPS type Im)</p> <p>RALD. RAS-associated autoimmune leukoproliferative disease. (ALPS Like); <i>N-RAS GOF, K-RAS GOF</i> Sporadic; granulocytosis, monocytosis/ALPS-like</p>	<p>Chronic mucocutaneous candidiasis (isolated or with APECED syndrome) AutoAb to IL-17 and/or IL-22. Endocrinopathy, chronic mucocutaneous candidiasis /CMC. Germline mutation in <i>AIRE</i></p> <p>Adult-onset immunodeficiency with susceptibility to mycobacteria. Auto-Ab to IFNg. Mycobacterial, fungal, salmonella, VZV infections /MSMD or CID.</p>
<p>Cryopyrinopathy, (Muckle-Wells /CINCA/NOMID-like syndrome). <i>NLRP3</i>. Urticaria-like rash, arthropathy, neurological symptoms</p>	<p>Recurrent skin infection. AutoAb to IL-6. Staphylococcal infections / <i>STAT3</i> deficiency</p>
<p>Hypereosinophilic syndrome due to somatic mutations in <i>STAT5b</i>. <i>STAT5b</i>. GOF. Atopic dermatitis, urticarial rash, diarrhea. Eosinophilia.</p>	<p>Pulmonary alveolar proteinosis . AutoAb to GM-CSF. Pulmonary alveolar proteinosis, cryptococcal meningitis, disseminated nocardiosis/<i>CSF2RA</i> deficiency</p>
	<p>Acquired angiooedema . AutoAb to C1 inhibitor. Angioedema /C1 inhibitor deficiency</p>
	<p>Atypical Hemolytic Uremic Syndrome . AutoAb to Factor H. Spontaneous activation of the alternative complement pathway</p>
	<p>Thymoma with hypogammaglobulinemia (Good syndrome). AutoAb to various cytokines. Invasive bacterial, viral or opportunistic infections, autoimmunity, PRCA, lichen planus, cytopenia, colitis, chronic diarrhea. No B cells.</p>

Figure 14: Phenocopies of IEI, taken from Bousfiha et al. 2020 (12)

1.1.3 ESID Working Definitions for the Clinical Diagnosis of Inborn Errors of Immunity

The ESID Working Definitions for the Clinical Diagnosis of Inborn Errors of Immunity were created in 2014 to help diagnose and classify patients with an IEI who are lacking a definitive genetic diagnosis when entering them into the ESID registry for IEI. The ESID registry was founded in 2004 as a central IEI patient registry with the aim to provide reliable and consistent data for clinical trials and other research. In 2014 the registry was restructured to enhance data quality and in the course of this restructuring, a verification step applying the ESID Working Definitions for the Clinical Diagnosis of Inborn Errors of Immunity to the entered diagnosis was implemented (13).

As with 14.10.2019, the ESID registry contains 29642 patients in total of which 23245 have a diagnosis either verified by applying the ESID Working Definitions for the Clinical Diagnosis of Inborn Errors of Immunity or genetic testing (14). As part of the entering process, a diagnosis verification step is mandatory since 2014 to enhance the database's data quality. This verification can either be done by entering

a definitive genetic diagnosis or using the ESID Working Definitions for the Clinical Diagnosis of Inborn Errors of Immunity (13).

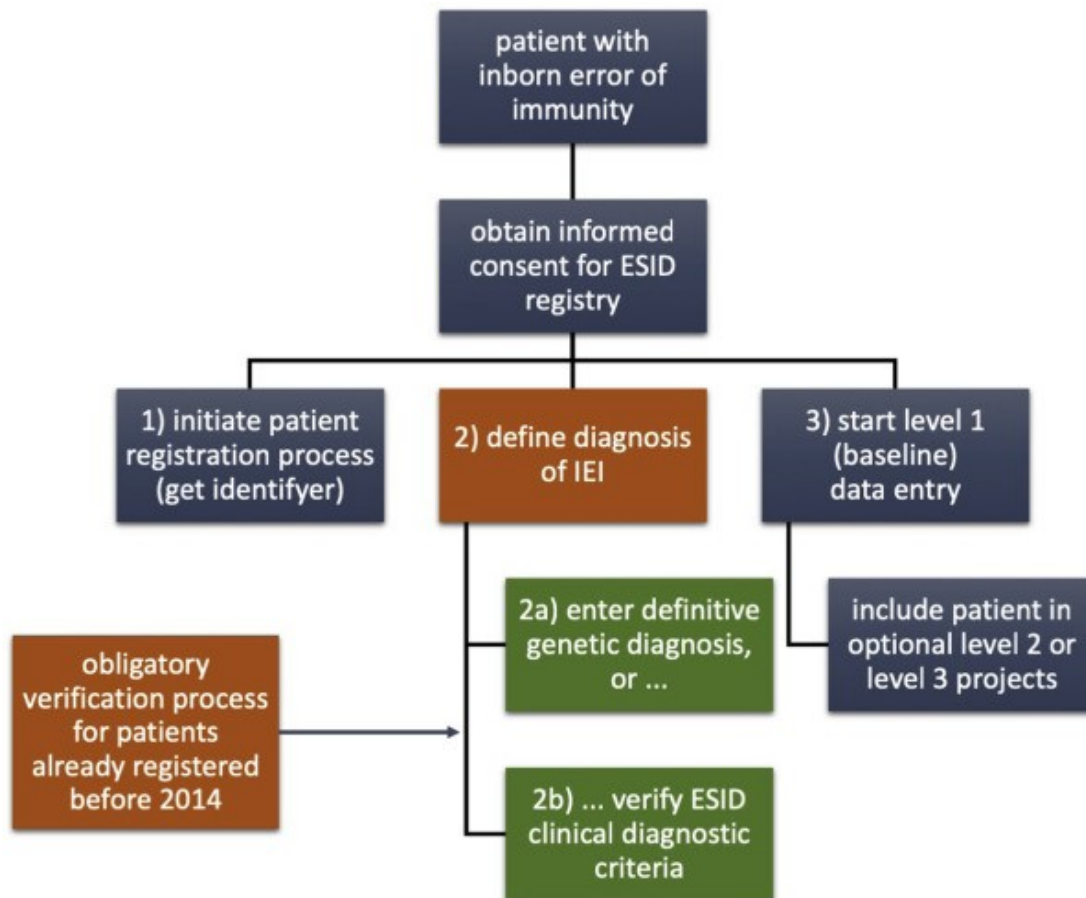


Figure 15: Patient entry process, taken from Seidel et al. 2019 (13)

The ESID Working Definitions for the Clinical Diagnosis of Inborn Errors of Immunity are consisting of 92 entities. To verify a diagnosis using the Working Definitions, different mandatory and optional features have to be fulfilled, these features can either be clinical features or laboratory values. In the present catalogue of diagnostic criteria fitting OMIM and ORPHAnet codes were added to the particular entities.

Disease	Contributors	Clinical criteria for a probable diagnosis (=clinical diagnosis)
CVID	Vojtech Thon, Natalia Martinez, Maria Kanariou, Klaus Warnatz, Isabella Quinti, Helen Chapel	<p>At least one of the following:</p> <ul style="list-style-type: none"> • increased susceptibility to infection • autoimmune manifestations • granulomatous disease • unexplained polyclonal lymphoproliferation • affected family member with antibody deficiency <p>AND marked decrease of IgG and marked decrease of IgA with or without low IgM levels (measured at least twice; <2SD of the normal levels for their age)</p> <p>AND at least one of the following:</p> <ul style="list-style-type: none"> • poor antibody response to vaccines (and/or absent isohemagglutinins); ie, absence of protective levels despite vaccination where defined • low switched memory B cells (<70% of age-related normal value) <p>AND secondary causes of hypogammaglobulinemia have been excluded (eg, infection, protein loss, medication, malignancy)</p> <p>AND diagnosis is established after the fourth year of life (but symptoms may be present before)</p> <p>AND no evidence of profound T-cell deficiency, defined as 2 of the following (y = years of life):</p> <ul style="list-style-type: none"> • CD4 numbers/microliter: 2-6 y < 300, 6-12 y < 250, >12 y < 200 • % naive of CD4: 2-6 y < 25%, 6-16 y < 20%, >16 y < 10% • T-cell proliferation absent

Figure 16: Clinical criteria for the diagnosis verification of CVID, taken from Seidel et al. 2019 (13)

1.2 HPO

The HPO was introduced in 2008 to provide a standardized vocabulary for the description of phenotypes of diseases. An ontology is a data model that represents concepts, attributes, and relationships in the form of a directed acyclic graph (DAG) (15). Graphs are formed by vertices (or nodes) and by edges (or arcs), connecting pairs of vertices. In the case of a directed graph, each edge has an orientation, leading from one vertex to another vertex. If a sequence of edges has the property that the ending vertex of each edge in the sequence is the same as the starting vertex of the next edge, it is called a path. If the starting vertex of the first edge is the same as the ending vertex of the last edge, the path forms a cycle; if there are no such cycles, the directed graph is defined as acyclic (16). Moreover, the DAG in the HPO is topological ordered, which means that for every edge, the start vertex of the edge occurs earlier in the sequence than the ending vertex.

The Human Phenotype Ontology was created with the aim of providing an exact vocabulary for all phenotypic abnormalities that can be commonly found in human monogenic diseases (15). As the basis of this ontology, the Online Mendelian

Inheritance in Man (OMIM) database (17) was chosen, in which most of the humans' Mendelian syndromes have been described and clinical descriptions are available. However, efforts in using the data contained in OMIM for computational analysis have been impeded by the lack of standardized vocabulary. For instance, the descriptions "generalized amyotrophy," "generalized muscle atrophy," "muscular atrophy, generalized," and "muscle atrophy, generalized" are used to describe different diseases in OMIM and might not be easily recognized as synonyms with a purely computational approach (15).

For the construction of the Human Phenotype Ontology, the "omim.txt" file was downloaded from the OMIM database (17) containing all data available in OMIM. Subsequently, Java programs and Perl scripts were used to parse this file and extract descriptions of each disease. For every description that occurred more than once in the omim.txt file, a term in the HPO was created. One of the main difficulties in this process using computational analysis was the lack of a standardized vocabulary in OMIM and consequently the appearance of synonyms which are difficult to recognize by computational means. (15) Therefore, each term was manually maintained using domain knowledge in human genetics in order to merge synonyms into a single, unique HPO term. (15)

Each term in the HPO describes a phenotypical abnormality. The terms are related to their parent terms by a "is a" relationship, it is possible that a term can have more than one parent term, which different aspects of phenotypic abnormalities to be explored. (15)

Since its establishment in 2008, the HPO has continually grown, today the HPO covers a standardized vocabulary of phenotypic abnormalities for over 7000 diseases and is used by thousands of researchers and clinicians, as well as electronic health record systems. Because of its detailed descriptions of clinical abnormalities and the computable disease definitions, the HPO is the de facto standard for deep phenotyping concerning rare diseases. (18)

1.2.1 HOOM

HOOM (HPO-ORDO Ontological Module) is a module that allows the annotation between a clinical entity (ORDO) and phenotypic abnormalities (HPO) according to a frequency. The HPO-ORDO phenotype-disease annotations are provided in a series of triples following the OBAN model in which associations, frequency and

provenance are modelled. (19) OBAN stands for Open Biomedical Associations. It is an ontology model used to describe associations between biomedical entities in triple format (RDF). OBAN represents these associations by coupling a subject and object (e.g. disease and associated phenotype) via a construction of the class OBAN:association. This association is supported by an evidence of class OBAN:provenance where a record for that association is described. (20)

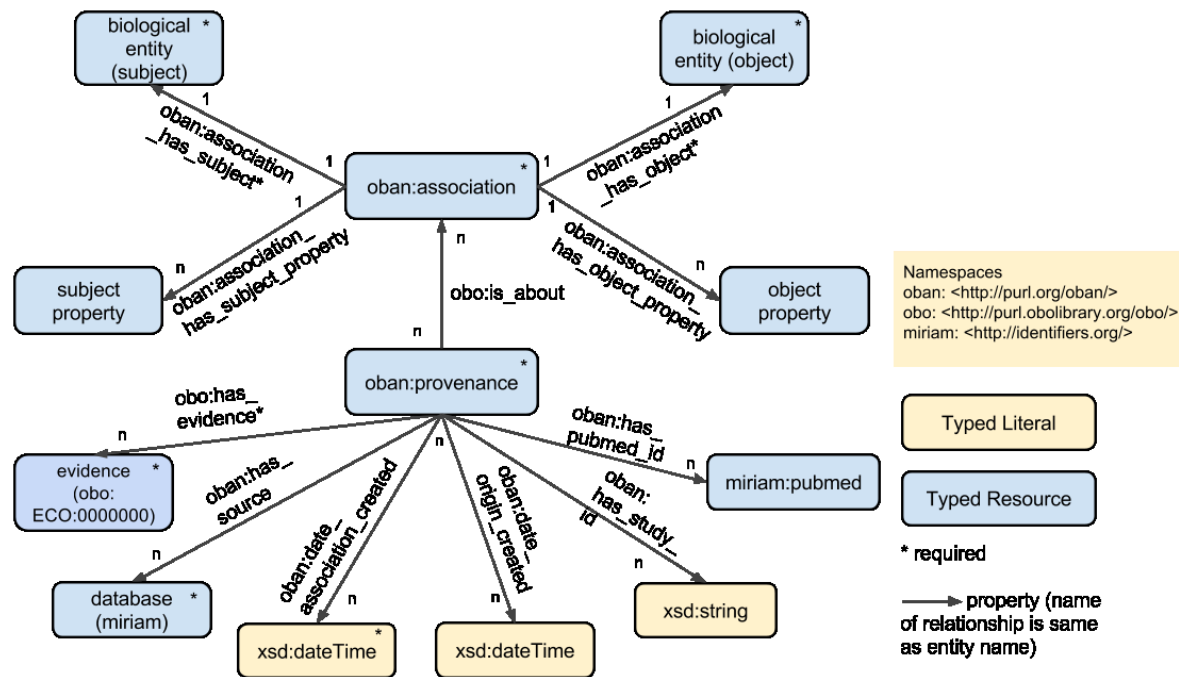


Figure 17: OBAN model, taken from Sarntivijai et al. 2016 (20)

HOOM only uses the classes “Association”, “Provenance” and “Evidence” from the OBAN model. The “biological entity (subject)” class is replaced with an “Orpha_Num” class, which provides the ORPHA number for the disease concerned. The “biological entity (object)” class is accordingly replaced with a “HPO_id” class representing the unique identifier in the HPO.

For the HOOM, two additional classes have been created: “FrequencyAssociation” and “DiagnosticCriteria”. The class “DiagnosticCriteria” has three subclasses: “criterion_DC”, “exclusion_DC” and “pathognomonic_DC”. The subclass “criterion_DC” represents the phenotypic abnormalities that are consensually used to make a clinical diagnosis. “exclusion_DC” are the phenotypic abnormalities that are absent and that make it possible to exclude the diagnosis. The subclass “pathognomonic_DC” gives phenotypic abnormalities that definitely and undoubtedly establish a diagnosis. The class “FrequencyAssociation” has five subclasses each representing a different range of probability that a phenotypic

abnormality is present in a specific disease: “obligated” (100%), “veryFrequent” (80 to 99%), “frequent” (30 to 79%), “occasional” (5 to 29%) and “veryRare” (1 to 4%).
(19)

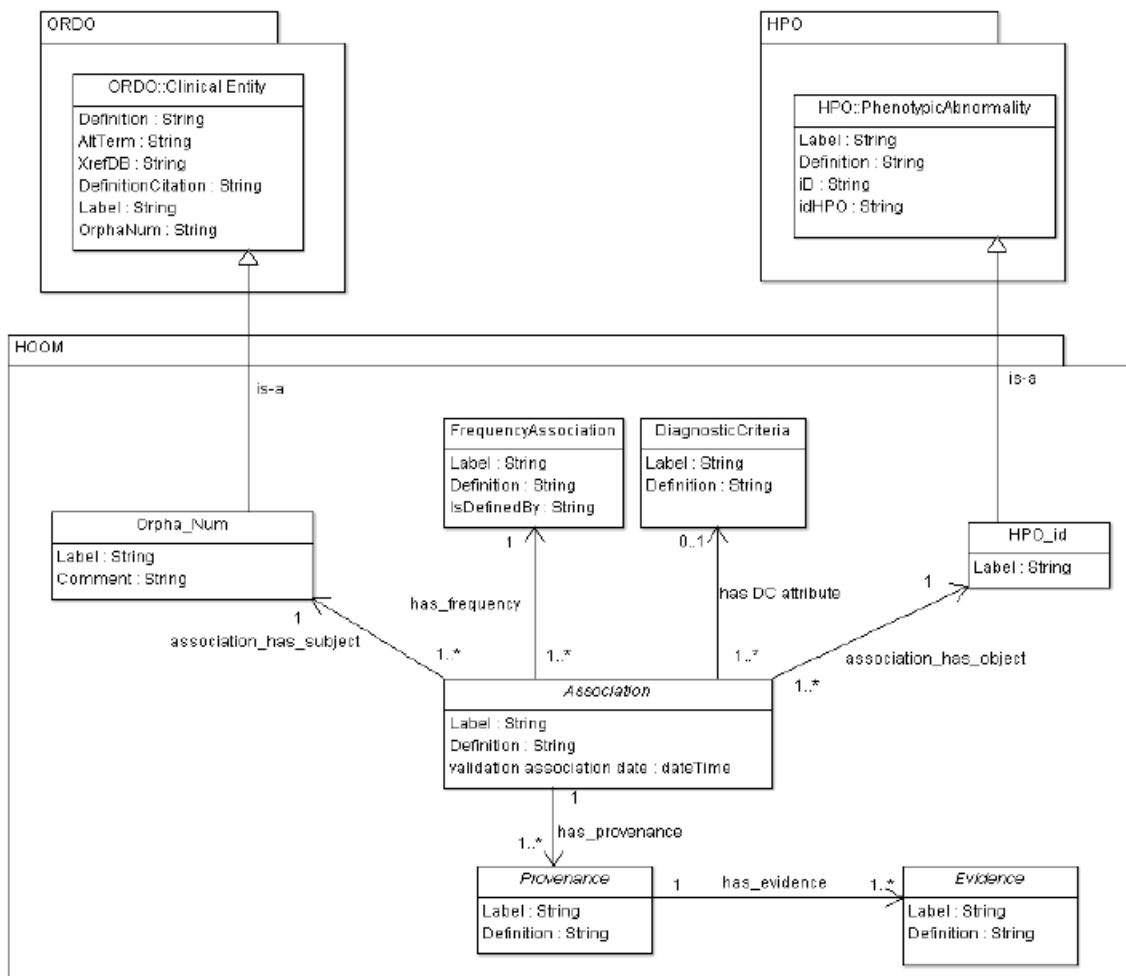


Figure 18: The HOOM model, taken from “What is HOOM (The ORDO-HPO Ontological Module)? “ 2019 (19)

Each “association” in the HOOM is connected to an “Orpha_Num” with a predicate called “association_has_subject”. The predicate “association_has_object” links the “association” to a “HPO_id”. The frequency is linked by the predicate “has_frequency”. These three properties are required to create an “association” in the HOOM. (19)

In addition, an “association” can be linked to a “DiagnosticCriteria” using the predicate “has_DC_attribute” and to a “Provenance” using the predicate “has_provenance”. (19)

2 Hypothesis and Aims of the thesis

Rare diseases such as inborn errors of immunity (IEI) may be diagnosed by characteristic clinical and laboratory features, and/or, ideally, genetically confirmed. Because not all patients with IEI have a known monogenic cause of their disease, and to ascertain correct entry into an international patient registry, the European Society for Immunodeficiencies (ESID) published expert-generated and peer-reviewed clinical diagnosis criteria. However, the current version of ESID diagnosis criteria is not using a standardized vocabulary, which would be crucial not only for making the diagnosis but also for the comparability of patient records in registries, for a transferrable phenotypic description of presentations with novel variants, as well as for filtering in bioinformatic steps of modern diagnostic processes such as next generation sequencing.

2.1 Hypothesis:

Symptoms, laboratory features, and disease-associated anatomical and functional phenotypes are often ill-defined in medical reports, clinical records, and even medical scientific literature. Descriptions of varying specificity and quality, mixing lay terms with professional jargon, might be sufficient for the exchange of information between physicians or patients and physicians. However, not only the management of patients with rare and undiagnosed diseases, but also clinical, translational, and biomedical research rely on a highly specific, ideally, standardized terminology of phenotypes and symptoms.

All this is also applicable to the field of IEI where a non-standardised, inconsistent colloquial medical language is currently used to define the specific diseases. Hence, the hypothesis of this thesis is, that the integration of a standardized terminology, namely the Human Phenotype Ontology, into the ESID diagnostic criteria will help to minimize misconceptions on the basis of semantic ambiguity and when entered into patient registries will allow an easier comparability between patient data as well as the usage of computer-based analytic tools.

2.2 Aims of the thesis:

The aim of the thesis is, to critically review and revise the ESID diagnostic criteria, and, in the course thereof, to integrate a standardized vocabulary in form of the human phenotype ontology (HPO) into the ESID Working Definitions for the Clinical Diagnosis of Inborn Errors of Immunity.

3 Methods

3.1 Data Sources

One of the primary sources of suitable HPO terms for the 75 individual diseases of the ESID Working Definitions for the Clinical Diagnosis of Inborn Errors of Immunity was the HOOM. (19) The data of this module was retrieved from Orphadata (21); the version used was 1.3 (9. December 2019). Altogether 38 entities of the ESID Working Definitions for the Clinical Diagnosis of Inborn Errors of Immunity got their suitable HPO terms using the HOOM. (19)

The second primary source of HPO terms, namely of 34 entities, was OMIM (17). Suitable terms were retrieved using the HPO web page. For the remaining three entities (Ivemark syndrome, Atypical SCID and selective IgM deficiency), suitable HPO terms were assigned manually based on publications concerning these three diseases.

3.2 Generation of HPO-term lists

3.2.1 HOOM

As the data from Orphadata (21) was based on a RDF (Resource Description Framework) syntax, SPARQL was used to retrieve the sought information from the data. SPARQL is a recursive acronym for SPARQL Protocol and RDF query language and is used to retrieve and modify data in RDF format. (22) To query the data the Virtuoso SPARQL Query Editor, which is part of OpenLink Virtuoso was used. OpenLink Virtuoso is a database engine that combines different functionalities in a single system. (23)

This query was used to retrieve, based on the number used in ORDO for the specific disease, the disease name and its associated HPO IDs with related frequencies as well as the sources and the dates of the created associations:

```
select DISTINCT ?association ?Property ?value ?date ?label ?comment
where {
    ?association owl:equivalentClass ?collection .
    ?collection owl:intersectionOf ?list .
    ?list rdf:rest*/rdf:first ?item .
    ?item owl:someValuesFrom <http://www.orpha.net/ORDO/Orphanet_2331>
```

```

OPTIONAL{
  ?association owl:equivalentClass ?node .
  ?node owl:intersectionOf ?list .
  ?list rdf:rest*/rdf:first ?item2 .
  ?item2 owl:onProperty ?Property.
OPTIONAL {
  ?item2 owl:someValuesFrom ?value .
  OPTIONAL {?value rdfs:comment ?label} .
  OPTIONAL {?value rdfs:label ?comment}
}
OPTIONAL {?item2 owl:hasValue ?date .}
}
ORDER BY ?association

```

After running the query, the found HPO IDs were conveyed into an Excel sheet sorted by their frequency and names and short descriptions of the phenotypic abnormalities were added to each found HPO ID similar to the way HPO terms can be found on the HPO web page.

3.2.2 OMIM

The HPO term lists of 34 entities of the ESID Working Definitions for the Clinical Diagnosis of Inborn Errors of Immunity are based on data from OMIM. (17)As the HPO database was initially based on data from OMIM, suitable HPO terms were retrieved directly from the HPO web page. The individual entities were requested from the HPO database with the help of the fitting Phenotype MIM numbers. The output of the queries was manually transferred into an Excel sheet and as no frequency information is available in the data from OMIM, the terms were sorted alphabetically. Same as the lists created using HOOM, names and short descriptions of the phenotypic abnormalities were added to each found HPO ID.

3.2.3 Entities missing in HOOM and OMIM

For three entities (Ivemark syndrome, Atypical SCID and selective IgM deficiency), there was no data available either in the HOOM or OMIM. To generate HPO term lists for these three entities, publications concerning these diseases were searched

in PubMed. For Ivemark syndrome, three different publications (24–26) were adduced to create lists of HPO terms. For Atypical SCID (27) respectively selective IgM deficiency (28) one publication was adduced. These publications were then manually searched for phenotypic abnormalities, which are appearing in the individual diseases. Next appropriate HPO IDs were retrieved for these phenotypic abnormalities using the HPO web page. These HPO IDs were then transferred into an Excel sheet where names and short descriptions of the phenotypic abnormalities were added.

4 Results

After creating lists of HPO terms for each of the 75 entities of the ESID Working Definitions for the Clinical Diagnosis of Inborn Errors of Immunity, they were converted into word files and integrated into the main document of the ESID Working Definitions for the Clinical Diagnosis of Inborn Errors of Immunity. The lists can be reached in the main document using hyperlinks, which can be found at every individual entity. Hereafter can be found the HPO term lists created sorted by alphabetical order.

4.1 Acquired angioedema

4.1.1.1 Very frequent

Term Identifier	Term Name	Definition
HP:0002027	Abdominal pain	An unpleasant sensation characterized by physical discomfort (such as pricking, throbbing, or aching) and perceived to originate in the abdomen.
HP:0100665	Angioedema	Rapid swelling (edema) of the dermis, subcutaneous tissue, mucosa and submucosal tissues of the skin of the face, normally around the mouth, and the mucosa of the mouth and/or throat, as well as the tongue during a period of minutes to several hours. The swelling can also occur elsewhere, typically in the hands. Angioedema is similar to urticaria, but the swelling is subcutaneous rather than on the epidermis.
HP:0000969	Edema	An abnormal accumulation of fluid beneath the skin, or in one or more cavities of the body.

4.1.1.2 Occasional

Term Identifier	Term Name	Definition
HP:0001541	Ascites	Accumulation of fluid in the peritoneal cavity.
HP:0000282	Facial edema	
HP:0005225	Intestinal edema	Accumulation of cell free, noninflammatory fluid within the wall of the intestinal tract producing uniform thickening of the mucosal folds.
HP:0005214	Intestinal obstruction	Blockage or impairment of the normal flow of the contents of the intestine towards the anal canal.
HP:0012027	Laryngeal edema	An abnormal accumulation of fluid and swelling in the tissues of the larynx.

HP:0001025	Urticaria	Raised, well-circumscribed areas of erythema and edema involving the dermis and epidermis. Urticaria is intensely pruritic, and blanches completely with pressure.
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Source: HPO-ORDO Ontological Module (21)- Validation association date: 01.06.2016 - PMID:20667117 (29), PMID:8438855 (30)

4.2 Agammaglobulinemia

4.2.1 X – linked agammaglobulinemia

4.2.1.1 Very frequent

Term Identifier	Term Name	Definition
HP:0100763	Abnormality of lymphatic system	An anomaly of the lymphatic system, a network of lymphatic vessels that carry a clear fluid called lymph unidirectionally towards either the right lymphatic duct or the thoracic duct, which in turn drain into the right and left subclavian veins respectively.
HP:0100765	Abnormality of the tonsils	An abnormality of the tonsils.
HP:0004432	Agammaglobulinemia	Absence or extremely low level of IgA, IgM, and IgG in the circulation.
HP:0002028	Chronic diarrhea	The presence of chronic diarrhea, which is usually taken to mean diarrhea that has persisted for over 4 weeks.
HP:0000389	Chronic otitis media	Chronic otitis media refers to fluid, swelling, or infection of the middle ear that does not heal and may cause permanent damage to the ear.
HP:0000509	Conjunctivitis	Inflammation of the conjunctiva.
HP:0001508	Failure to thrive	Failure to thrive (FTT) refers to a child whose physical growth is substantially below the norm.
HP:0012378	Fatigue	A subjective feeling of tiredness characterized by a lack of energy and motivation.
HP:0001945	Fever	Elevated body temperature due to failed thermoregulation.
HP:0000162	Glossoptosis	Posterior displacement of the tongue into the pharynx, i.e., a tongue that is mislocalised posteriorly.
HP:0002721	Immunodeficiency	Failure of the immune system to protect the body adequately from infection, due to the absence or insufficiency of some component process or substance.

HP:0100838	Recurrent cutaneous abscess formation	An increased susceptibility to cutaneous abscess formation, as manifested by a medical history of recurrent cutaneous abscesses.
HP:0006532	Recurrent pneumonia	An increased susceptibility to pneumonia as manifested by a history of recurrent episodes of pneumonia.
HP:0004322	Short stature	A height below that which is expected according to age and gender norms. Although there is no universally accepted definition of short stature, many refer to "short stature" as height more than 2 standard deviations below the mean for age and gender (or below the 3rd percentile for age and gender dependent norms).
HP:0000246	Sinusitis	Inflammation of the paranasal sinuses owing to a viral, bacterial, or fungal infection, allergy, or an autoimmune reaction.
HP:0000988	Skin rash	A red eruption of the skin.
HP:0200042	Skin ulcer	A discontinuity of the skin exhibiting complete loss of the epidermis and often portions of the dermis and even subcutaneous fat.

4.2.1.2 Frequent

Term Identifier	Term Name	Definition
HP:0002088	Abnormality of lung morphology	Any structural anomaly of the lung.
HP:0001369	Arthritis	Inflammation of a joint.
HP:0100658	Cellulitis	A bacterial infection and inflammation of the skin and subcutaneous tissues.
HP:0002901	Hypocalcemia	An abnormally decreased calcium concentration in the blood.
HP:0001287	Meningitis	Inflammation of the meninges.
HP:0001875	Neutropenia	An abnormally low number of neutrophils in the peripheral blood.
HP:0000407	Sensorineural hearing impairment	A type of hearing impairment in one or both ears related to an abnormal functionality of the cochlear nerve.
HP:0100806	Sepsis	Systemic inflammatory response to infection.

4.2.1.3 Occasional

Term Identifier	Term Name	Definition
HP:0001596	Alopecia	Loss of hair from the head or body.
HP:0001903	Anemia	A reduction in erythrocytes volume or hemoglobin concentration.
HP:0002960	Autoimmunity	The occurrence of an immune reaction against the organisms own cells or tissues.
HP:0012115	Hepatitis	Inflammation of the liver.
HP:0001053	Hypopigmented skin patches	
HP:0002024	Malabsorption	Impaired ability to absorb one or more nutrients from the intestine.
HP:0002664	Neoplasm	An organ or organ-system abnormality that consists of uncontrolled autonomous cell-proliferation which can occur in any part of the body as a benign or malignant neoplasm (tumour).
HP:0002754	Osteomyelitis	Osteomyelitis is an inflammatory process accompanied by bone destruction and caused by an infecting microorganism.
HP:0001873	Thrombocytopenia	A reduction in the number of circulating thrombocytes.
HP:0001824	Weight loss	Reduction in existing body weight.

4.2.2 Autosomal agammaglobulinemia

4.2.2.1 Very frequent

Term Identifier	Term Name	Definition
HP:0004432	Agammaglobulinemia	Absence or extremely low level of IgA, IgM, and IgM in the circulation.
HP:0000389	Chronic otitis media	Chronic otitis media refers to fluid, swelling, or infection of the middle ear that does not heal and may cause permanent damage to the ear.
HP:0000509	Conjunctivitis	Inflammation of the conjunctiva.
HP:0012735	Cough	A sudden, audible expulsion of air from the lungs through a partially closed glottis, preceded by inhalation.
HP:0002014	Diarrhea	Abnormally increased frequency of loose or watery bowel movements.
HP:0012378	Fatigue	A subjective feeling of tiredness characterized by a lack of energy and motivation.
HP:0001945	Fever	Elevated body temperature due to failed thermoregulation.

HP:0002721	Immunodeficiency	Failure of the immune system to protect the body adequately from infection, due to the absence or insufficiency of some component process or substance.
HP:0002719	Recurrent infections	Increased susceptibility to infections.
HP:0002205	Recurrent respiratory infections	An increased susceptibility to respiratory infections as manifested by a history of recurrent respiratory infections.
HP:0001581	Recurrent skin infections	Infections of the skin that happen multiple times.
HP:0000246	Sinusitis	Inflammation of the paranasal sinuses owing to a viral, bacterial, or fungal infection, allergy, or an autoimmune reaction.
HP:0000988	Skin rash	A red eruption of the skin.

4.2.2.2 Frequent

Term Identifier	Term Name	Definition
HP:0001369	Arthritis	Inflammation of a joint.
HP:0001508	Failure to thrive	Failure to thrive (FTT) refers to a child whose physical growth is substantially below the norm.
HP:0002754	Osteomyelitis	Osteomyelitis is an inflammatory process accompanied by bone destruction and caused by an infecting microorganism.

4.2.2.3 Occasional

Term Identifier	Term Name	Definition
HP:0002110	Bronchiectasis	Persistent abnormal dilatation of the bronchi owing to localized and irreversible destruction and widening of the large airways.
HP:0100658	Cellulitis	A bacterial infection and inflammation of the skin and subcutaneous tissues.
HP:0001944	Dehydration	
HP:0000286	Epicanthus	A fold of skin starting above the medial aspect of the upper eyelid and arching downward to cover, pass in front of and lateral to the medial canthus.
HP:0008572	External ear malformation	A malformation of the auricle of the ear.
HP:0012115	Hepatitis	Inflammation of the liver.
HP:0000218	High palate	Height of the palate more than 2 SD above the mean (objective) or palatal height at the level of the first permanent molar more than twice the height of the teeth (subjective).

HP:0000316	Hypertelorism	Interpupillary distance more than 2 SD above the mean (alternatively, the appearance of an increased interpupillary distance or widely spaced eyes).
HP:0002024	Malabsorption	Impaired ability to absorb one or more nutrients from the intestine.
HP:0001287	Meningitis	Inflammation of the meninges.
HP:0001875	Neutropenia	An abnormally low number of neutrophils in the peripheral blood.
HP:0100806	Sepsis	Systemic inflammatory response to infection.
HP:0200043	Verrucae	Warts, benign growths on the skin or mucous membranes that cause cosmetic problems as well as pain and discomfort. Warts most often occur on the hands, feet, and genital areas.

Source: HPO-ORDO Ontological Module (21) - Validation association date: 01.06.2016

4.3 Asplenia syndrome (Ivemark syndrome)

4.3.1.1 Rare

Term Identifier	Term Name	Definition
HP:0031834	Aortopulmonary collateral arteries	Small ectopic arteries or arterial branches that connect the aorta, aortic branches and/or subclavian artery regions directly to the lung parenchyma, usually seen in conjunction with pulmonary atresia, ventricular septal defect (VSD) and/or closed ductus arteriosus.
HP:0001746	Asplenia	Absence (aplasia) of the spleen.
HP:0011565	Common atrium	Complete absence of the interatrial septum with common atrioventricular valve and two atrioventricular connections.
HP:0000023	Inguinal hernia	Protrusion of the contents of the abdominal cavity through the inguinal canal.
HP:0001696	Situs inversus totalis	A left-right reversal (or "mirror reflection") of the anatomical location of the major thoracic and abdominal organs.
HP:0001636	Tetralogy of Fallot	A congenital cardiac malformation comprising pulmonary stenosis, overriding aorta, ventricular septum defect, and right ventricular hypertrophy. The diagnosis of TOF is made if at least three of the four above mentioned features are present.
HP:0005160	Total anomalous pulmonary venous return	Total anomalous pulmonary venous return refers to a congenital malformation in which all four pulmonary veins do not connect

		normally to the left atrium, but instead drain abnormally to the right atrium.
HP:0001669	Transposition of the great arteries	A complex congenital heart defect in which the aorta arises from the morphologic right ventricle and the pulmonary artery arises from the morphologic left ventricle.

4.3.1.2 No frequency available

Term Identifier	Term Name	Definition
HP:0031565	Abdominal situs ambiguus	An abnormality in which the abdominal organs are positioned in such a way with respect to each other and the left-right axis as to be not clearly lateralised and thus have neither the usual, or normal (situs solitus), nor the mirror-imaged (situs inversus) arrangements.
HP:0002101	Abnormal lung lobation	Defects in the formation of pulmonary lobules.
HP:0001274	Agenesis of corpus callosum	Absence of the corpus callosum as a result of the failure of the corpus callosum to develop, which can be the result of a failure in any one of the multiple steps of callosal development including cellular proliferation and migration, axonal growth or glial patterning at the midline.
HP:0001631	Atrial septal defect	Atrial septal defect (ASD) is a congenital abnormality of the interatrial septum that enables blood flow between the left and right atria via the interatrial septum.
HP:0001674	Complete atrioventricular canal defect	A congenital heart defect characterized by a specific combination of heart defects with a common atrioventricular valve, primum atrial septal defect and inlet ventricular septal defect.
HP:0001748	Polysplenia	Polysplenia is a congenital disease manifested by multiple small accessory spleens.
HP:0004935	Pulmonary artery atresia	A congenital anomaly with a narrowing or complete absence of the opening between the right ventricle and the pulmonary artery.
HP:0001642	Pulmonic stenosis	A narrowing of the right ventricular outflow tract that can occur at the pulmonary valve (valvular stenosis) or just below the pulmonary valve (infundibular stenosis).
HP:0011536	Right atrial isomerism	Right atrial isomerism is characterized by bilateral triangular, morphologically right atrial, appendages, both joining the atrial

		chamber along a broad front with internal terminal crest.
HP:0001750	Single ventricle	The presence of only one working lower chamber in the heart, usually with a virtual absence of the ventricular septum and usually present in conjunction with double inlet left or right ventricle.
HP:0001629	Ventricular septal defect	A hole between the two bottom chambers (ventricles) of the heart. The defect is centered around the most superior aspect of the ventricular septum.

Source: (24), (26), (25)

4.4 Ataxia telangiectasia (ATM)

4.4.1.1 Very frequent

Term Identifier	Term Name	Definition
HP:0003220	Abnormality of chromosome stability	A type of chromosomal aberration characterised by reduced resistance of chromosomes to change or deterioration.
HP:0000496	Abnormality of eye movement	An abnormality in voluntary or involuntary eye movements or their control.
HP:0100022	Abnormality of movement	An abnormality of movement with a neurological basis characterized by changes in coordination and speed of voluntary movements.
HP:0002715	Abnormality of the immune system	An abnormality of the immune system.
HP:0010515	Aplasia/Hypoplasia of the thymus	Absence or underdevelopment of the thymus.
HP:0001251	Ataxia	Cerebellar ataxia refers to ataxia due to dysfunction of the cerebellum. This causes a variety of elementary neurological deficits including asynergy (lack of coordination between muscles, limbs and joints), dysmetria (lack of ability to judge distances that can lead to under- oder overshoot in grasping movements), and dysdiadochokinesia (inability to perform rapid movements requiring antagonizing muscle groups to be switched on and off repeatedly).
HP:0005374	Cellular immunodeficiency	An immunodeficiency characterized by defective cell-mediated immunity or humoral immunity.
HP:0004313	Decreased antibody level in blood	An abnormally decreased level of immunoglobulin in blood.

HP:0000823	Delayed puberty	Passing the age when puberty normally occurs with no physical or hormonal signs of the onset of puberty.
HP:0002910	Elevated hepatic transaminases	Elevations of the levels of SGOT and SGPT in the serum. SGOT (serum glutamic oxaloacetic transaminase) and SGPT (serum glutamic pyruvic transaminase) are transaminases primarily found in the liver and heart and are released into the bloodstream as the result of liver or heart damage. SGOT and SGPT are used clinically mainly as markers of liver damage.
HP:0001288	Gait disturbance	The term gait disturbance can refer to any disruption of the ability to walk. In general, this can refer to neurological diseases but also fractures or other sources of pain that is triggered upon walking. However, in the current context gait disturbance refers to difficulty walking on the basis of a neurological or muscular disease.
HP:0002721	Immunodeficiency	Failure of the immune system to protect the body adequately from infection, due to the absence or insufficiency of some component process or substance.
HP:0001888	Lymphopenia	A reduced number of lymphocytes in the blood.
HP:0100579	Mucosal telangiectasiae	Telangiectasia of the mucosa, the mucous membranes which are involved in absorption and secretion that line cavities that are exposed to the external environment and internal organs.
HP:0002167	Neurological speech impairment	
HP:0000639	Nystagmus	Rhythmic, involuntary oscillations of one or both eyes related to abnormality in fixation, conjugate gaze, or vestibular mechanisms.
HP:0000147	Polycystic ovaries	
HP:0002216	Premature graying of hair	Development of gray hair at a younger than normal age.
HP:0007495	Prematurely aged appearance	
HP:0002205	Recurrent respiratory infections	An increased susceptibility to respiratory infections as manifested by a history of recurrent respiratory infections.
HP:0000486	Strabismus	A misalignment of the eyes so that the visual axes deviate from bifoveal fixation. The classification of strabismus may be based on a number of features including the relative position of the eyes, whether

		the deviation is latent or manifest, intermittent or constant, concomitant or otherwise and according to the age of onset and the relevance of any associated refractive error.
HP:0100585	Telangiectasia of the skin	Presence of small, permanently dilated blood vessels near the surface of the skin, visible as small focal red lesions.
HP:0001337	Tremor	An unintentional, oscillating to-and-fro muscle movement about a joint axis.

4.4.1.2 Frequent

Term Identifier	Term Name	Definition
HP:0000819	Diabetes mellitus	A group of abnormalities characterized by hyperglycemia and glucose intolerance.
HP:0001260	Dysarthria	Dysarthric speech is a general description referring to a neurological speech disorder characterized by poor articulation. Depending on the involved neurological structures, dysarthria may be further classified as spastic, flaccid, ataxic, hyperkinetic and hypokinetic, or mixed.
HP:0005599	Hypopigmentation of hair	
HP:0002664	Neoplasm	An organ or organ-system abnormality that consists of uncontrolled autonomous cell-proliferation which can occur in any part of the body as a benign or malignant neoplasm (tumour).
HP:0001250	Seizures	Seizures are an intermittent abnormality of the central nervous system due to a sudden, excessive, disorderly discharge of cerebral neurons and characterized clinically by some combination of disturbance of sensation, loss of consciousness, impairment of psychic function, or convulsive movements. The term epilepsy is used to describe chronic, recurrent seizures.
HP:0004322	Short stature	A height below that which is expected according to age and gender norms. Although there is no universally accepted definition of short stature, many refer to "short stature" as height more than 2 standard deviations below the mean for age and gender (or below the 3rd percentile for age and gender dependent norms).
HP:0003202	Skeletal muscle atrophy	The presence of skeletal muscular atrophy (which is also known as amyotrophy).

HP:0001257	Spasticity	A motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes with increased muscle tone, exaggerated (hyperexcitable) tendon reflexes.
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4.4.1.3 Occasional

Term Identifier	Term Name	Definition
HP:0000035	Abnormality of the testis	An anomaly of the testicle (the male gonad).
HP:0008065	Aplasia/Hypoplasia of the skin	
HP:0100543	Cognitive impairment	Abnormality in the process of thought including the ability to process information.
HP:0001508	Failure to thrive	Failure to thrive (FTT) refers to a child whose physical growth is substantially below the norm.
HP:0007565	Multiple cafe-au-lait spots	The presence of six or more cafe-au-lait spots.
HP:0005978	Type II diabetes mellitus	A type of diabetes mellitus initially characterized by insulin resistance and hyperinsulinemia and subsequently by glucose intolerance and hyperglycemia.

Source: HPO-ORDO Ontological Module (21) - Validation association date: 01.06.2016

4.5 Atypical SCID

4.5.1.1 No frequency available

Term Identifier	Term Name	Definition
HP:0002014	Diarrhea	Abnormally increased frequency of loose or watery bowel movements.
HP:0000976	Eczematoid dermatitis	
HP:0001508	Failure to thrive	Failure to thrive (FTT) refers to a child whose physical growth is substantially below the norm.
HP:0002240	Hepatomegaly	Abnormally increased size of the liver.
HP:0005401	Recurrent candida infections	An increased susceptibility to candida infections, as manifested by a history of recurrent episodes of candida infections.
HP:0001744	Splenomegaly	Abnormal increased size of the spleen.

HP:0003139	Panhypogammaglobulinemia	A reduction in the circulating levels of all the major classes of immunoglobulin. is characterized by profound decreases in all classes of immunoglobulin with an absence of circulating B lymphocytes.
HP:0002090	Pneumonia	Inflammation of any part of the lung parenchyma.

Source: (27)

4.6 Autoimmune lymphoproliferative syndrome (ALPS)

4.6.1.1 Very frequent

Term Identifier	Term Name	Definition
HP:0002960	Autoimmunity	The occurrence of an immune reaction against the organism's own cells or tissues.
HP:0002730	Chronic noninfectious lymphadenopathy	A chronic form of lymphadenopathy that is not related to infection.
HP:0002716	Lymphadenopathy	Enlargement (swelling) of a lymph node.
HP:0001744	Splenomegaly	Abnormal increased size of the spleen.

4.6.1.2 Frequent

Term Identifier	Term Name	Definition
HP:0001892	Abnormal bleeding	An abnormal susceptibility to bleeding, often referred to as a bleeding diathesis. A bleeding diathesis may be related to vascular, platelet and coagulation defects.
HP:0030782	Abnormal serum interleukin level	An abnormal amount of any of the interleukins, a class of cytokines, in the circulation.
HP:0001890	Autoimmune hemolytic anemia	An autoimmune form of hemolytic anemia.
HP:0001973	Autoimmune thrombocytopenia	The presence of thrombocytopenia in combination with detection of antiplatelet antibodies.
HP:0000978	Bruising susceptibility	An ecchymosis (bruise) refers to the skin discoloration caused by the escape of blood into the tissues from ruptured blood vessels. This term refers to an abnormally increased susceptibility to

		bruising. The corresponding phenotypic abnormality is generally elicited on medical history as a report of frequent ecchymoses or bruising without adequate trauma.
HP:0002851	Elevated proportion of CD4-negative, CD8-negative, alpha-beta regulatory T cells	An abnormally increased proportion of CD4-negative, CD8-negative (double negative or DN) alpha-beta regulatory T cells (Tregs) as compared to total number of T cells.
HP:0002240	Hepatomegaly	Abnormally increased size of the liver.
HP:0001971	Hypersplenism	A malfunctioning of the spleen in which it prematurely destroys red blood cells.
HP:0005404	Increased B cell count	An abnormal increase from the normal count of B cells.
HP:0003237	Increased circulating IgG level	An abnormally increased level of immunoglobulin G in blood.
HP:0010702	Increased antibody level in blood	An increased level of gamma globulin (immunoglobulin) in the blood.
HP:0001904	Neutropenia in presence of anti-neutropil antibodies	A type of neutropenia that is observed in the presence of granulocyte-specific antibodies.

4.6.1.3 Occasional

Term Identifier	Term Name	Definition
HP:0031392	Abnormal proportion of CD4 T cells	Any abnormality in the proportion of CD4 T cells relative to the total number of T cells.
HP:0031393	Abnormal proportion of CD8 T cells	Any abnormality in the proportion of CD8 T cells relative to the total number of T cells.
HP:0040126	Abnormal vitamin B12 level	A deviation from the normal concentration of cobalamin (vitamin B12) in the blood. Vitamin B12 is one of the eight B vitamins.
HP:0003453	Antineutrophil antibody positivity	The presence of autoantibodies in the serum that react against neutrophils.
HP:0003493	Antinuclear antibody positivity	The presence of autoantibodies in the serum that react against nuclei or nuclear components.
HP:0003613	Antiphospholipid antibody positivity	The presence of circulating autoantibodies to phospholipids.
HP:0012191	B-cell lymphoma	A type of lymphoma that originates in B-cells.
HP:0030080	Burkitt lymphoma	A form of undifferentiated malignant lymphoma commonly manifested as a

		large osteolytic lesion in the jaw or as an abdominal mass.
HP:0004844	Coombs-positive hemolytic anemia	A type of hemolytic anemia in which the Coombs test is positive.
HP:0004315	Decreased circulating IgG level	An abnormally decreased level of immunoglobulin G (IgG) in blood.
HP:0002850	Decreased circulating total IgM	An abnormally decreased level of immunoglobulin M (IgM) in blood.
HP:0005407	Decreased proportion of CD4-positive T cells	A decreased proportion of circulating CD4-positive helper T cells relative to total T cell count.
HP:0001880	Eosinophilia	Increased count of eosinophils in the blood.
HP:0000099	Glomerulonephritis	Inflammation of the renal glomeruli.
HP:0012115	Hepatitis	Inflammation of the liver.
HP:0012189	Hodgkin lymphoma	A type of lymphoma characterized microscopically by multinucleated Reed-Sternberg cells.
HP:0003261	Increased circulating IgA level	An abnormally increased level of immunoglobulin A in blood.
HP:0003212	Increased circulating total IgE level	An abnormally increased overall level of immunoglobulin E in blood.
HP:0100827	Lymphocytosis	Increase in the number or proportion of lymphocytes in the blood.
HP:0001888	Lymphopenia	A reduced number of lymphocytes in the blood.
HP:0012539	Non-Hodgkin lymphoma	A type of lymphoma characterized microscopically by the absence of multinucleated Reed-Sternberg cells.
HP:0001923	Reticulocytosis	An elevation in the number of reticulocytes (immature erythrocytes) in the peripheral blood circulation.
HP:0002923	Rheumatoid factor positive	The presence in the serum of an autoantibody directed against the Fc portion of IgG.
HP:0002848	Specific anti-polysaccharide antibody deficiency	The presence of normal overall immunoglobulin levels with deficiency of specific immunoglobulins directed against bacterial polysaccharides.
HP:0012190	T-cell lymphoma	A type of lymphoma that originates in T-cells.
HP:0100646	Thyroiditis	Inflammation of the thyroid gland.
HP:0001025	Urticaria	Raised, well-circumscribed areas of erythema and edema involving the dermis and epidermis. Urticaria is intensely pruritic, and blanches completely with pressure.
HP:0002633	Vasculitis	Inflammation of blood vessel.

4.6.1.4 Rare

Term Identifier	Term Name	Definition
HP:0002725	Systemic lupus erythematosus	A chronic, relapsing, inflammatory, and often febrile multisystemic disorder of connective tissue, characterized principally by involvement of the skin, joints, kidneys, and serosal membranes.
HP:0001369	Arthritis	Inflammation of a joint.
HP:0002671	Basal cell carcinoma	The presence of a basal cell carcinoma of the skin.
HP:0031020	Bone marrow hypercellularity	A larger than normal amount or percentage of hematopoietic cells relative to marrow fat.
HP:0005528	Bone marrow hypocellularity	A reduced number of hematopoietic cells present in the bone marrow relative to marrow fat.
HP:0002583	Colitis	Colitis refers to an inflammation of the colon and is often used to describe an inflammation of the large intestine (colon, cecum and rectum). Colitides may be acute and self-limited or chronic, and broadly fit into the category of digestive diseases.
HP:0010619	Fibroadenoma of the breast	A benign biphasic tumor of the breast with epithelial and stromal components.
HP:0005263	Gastritis	The presence of inflammation of the gastric mucous membrane.
HP:0002315	Headache	Cephalgia, or pain sensed in various parts of the head, not confined to the area of distribution of any nerve.
HP:0001402	Hepatocellular carcinoma	A kind of neoplasm of the liver that originates in hepatocytes and presents macroscopically as a soft and hemorrhagic tan mass in the liver.
HP:0001789	Hydrops fetalis	The abnormal accumulation of fluid in two or more fetal compartments, including ascites, pleural effusion, pericardial effusion, and skin edema.
HP:0008069	Neoplasm of the skin	A tumor (abnormal growth of tissue) of the skin.
HP:0100648	Neoplasm of the tongue	A tumor (abnormal growth of tissue) of the tongue.
HP:0012490	Panniculitis	Inflammation of adipose tissue.
HP:0008209	Premature ovarian insufficiency	Amenorrhea due to loss of ovarian function before the age of 40. Primary ovarian insufficiency (POI) is a state of female hypergonadotropic hypogonadism. It can manifest as primary amenorrhea with onset before menarche or secondary amenorrhea.

HP:0002206	Pulmonary fibrosis	Replacement of normal lung tissues by fibroblasts and collagen.
HP:0002113	Pulmonary infiltrates	
HP:0011107	Recurrent aphthous stomatitis	Recurrent episodes of ulceration of the oral mucosa, typically presenting as painful, sharply circumscribed fibrin-covered mucosal defects with a hyperemic border.
HP:0000083	Renal insufficiency	A reduction in the level of performance of the kidneys in areas of function comprising the concentration of urine, removal of wastes, the maintenance of electrolyte balance, homeostasis of blood pressure, and calcium metabolism.
HP:0001250	Seizures	Seizures are an intermittent abnormality of the central nervous system due to a sudden, excessive, disorderly discharge of cerebral neurons and characterized clinically by some combination of disturbance of sensation, loss of consciousness, impairment of psychic function, or convulsive movements. The term epilepsy is used to describe chronic, recurrent seizures.
HP:0000854	Thyroid adenoma	The presence of a adenoma of the thyroid gland.
HP:0002890	Thyroid carcinoma	The presence of a carcinoma of the thyroid gland.
HP:0000554	Uveitis	Inflammation of one or all portions of the uveal tract.

Source: HPO-ORDO Ontological Module (21) - Validation association date: 29.04.2019 – PMID:15767081 (31); PMID:11418480 (32); PMID:9028957 (33); PMID:8929361 (34); PMID:7540117 (35); PMID:1386609 (36); PMID:4165068 (37); PMID:20301287 (38); PMID:30958694 (39)

4.7 APECED / APS1 with CMC – Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED)

4.7.1.1 Very frequent

Term Identifier	Term Name	Definition
HP:0100530	Abnormality of calcium-phosphate metabolism	
HP:0100659	Abnormality of the cerebral vasculature	
HP:0001231	Abnormality of the fingernails	An abnormality of the fingernails.

HP:0008221	Adrenal hyperplasia	Enlargement of the adrenal gland.
HP:0002960	Autoimmunity	The occurrence of an immune reaction against the organism's own cells or tissues.
HP:0002728	Chronic mucocutaneous candidiasis	Recurrent or persistent superficial Candida infections of the skin, mucous membranes, and nails.
HP:0003118	Increased circulating cortisol level	Overproduction of the hormone of cortisol by the adrenal cortex, resulting in a characteristic combination of clinical symptoms termed Cushing syndrome, with truncal obesity, a round, full face, striae atrophicae and acne, muscle weakness, and other features.
HP:0004319	Decreased circulating aldosterone level	Abnormally reduced levels of aldosterone.
HP:0000829	Hypoparathyroidism	A condition caused by a deficiency of parathyroid hormone characterized by hypocalcemia and hyperphosphatemia.
HP:0007759	Opacification of the corneal stroma	Reduced transparency of the stroma of cornea.
HP:0000613	Photophobia	Excessive sensitivity to light with the sensation of discomfort or pain in the eyes due to exposure to bright light.
HP:0008207	Primary adrenal insufficiency	Insufficient production of steroid hormones (primarily cortisol) by the adrenal glands as a result of a primary defect in the glands themselves.
HP:0000505	Visual impairment	Visual impairment (or vision impairment) is vision loss (of a person) to such a degree as to qualify as an additional support need through a significant limitation of visual capability resulting from either disease, trauma, or congenital or degenerative conditions that cannot be corrected by conventional means, such as refractive correction, medication, or surgery.

4.7.1.2 Frequent

Term Identifier	Term Name	Definition
HP:0000518	Cataract	A cataract is an opacity or clouding that develops in the crystalline lens of the eye or in its capsule.

4.7.1.3 Occasional

Term Identifier	Term Name	Definition
HP:0001596	Alopecia	Loss of hair from the head or body.
HP:0002514	Cerebral calcification	The presence of calcium deposition within brain structures.
HP:0001053	Hypopigmented skin patches	

Source: HPO-ORDO Ontological Module (21)- Validation association date: 01.06.2016

4.8 Barth syndrome

4.8.1.1 Very frequent

Term Identifier	Term Name	Definition
HP:0001644	Dilated cardiomyopathy	Dilated cardiomyopathy (DCM) is defined by the presence of left ventricular dilatation and left ventricular systolic dysfunction in the absence of abnormal loading conditions (hypertension, valve disease) or coronary artery disease sufficient to cause global systolic impairment. Right ventricular dilation and dysfunction may be present but are not necessary for the diagnosis.

4.8.1.2 Frequent

Term Identifier	Term Name	Definition
HP:0008322	Abnormal mitochondrial morphology	Any structural anomaly of the mitochondria.
HP:0001874	Abnormality of neutrophils	A neutrophil abnormality.
HP:0001706	Endocardial fibroelastosis	Diffuse thickening of the ventricular endocardium and by associated myocardial dysfunction

4.8.1.3 Occasional

Term Identifier	Term Name	Definition
HP:0001875	Neutropenia	An abnormally low number of neutrophils in the peripheral blood.
HP:0001992	Organic aciduria	Excretion of non-amino organic acids in urine.
HP:0001762	Talipes equinovarus	Talipes equinovarus (also called clubfoot) typically has four main components: inversion

		and adduction of the forefoot; inversion of the heel and hindfoot; equinus (limitation of extension) of the ankle and subtalar joint; and internal rotation of the leg.
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Source: HPO-ORDO Ontological Module (21) - Validation association date: 01.06.2016

4.9 Bloom syndrome

4.9.1.1 Very frequent

Term Identifier	Term Name	Definition
HP:0003220	Abnormality of chromosome stability	A type of chromosomal aberration characterised by reduced resistance of chromosomes to change or deterioration.
HP:0000366	Abnormality of the nose	An abnormality of the nose.
HP:0000951	Abnormality of the skin	An abnormality of the skin.
HP:0002750	Delayed skeletal maturation	A decreased rate of skeletal maturation. Delayed skeletal maturation can be diagnosed on the basis of an estimation of the bone age from radiographs of specific bones in the human body.
HP:0002014	Diarrhea	Abnormally increased frequency of loose or watery bowel movements.
HP:0000268	Dolichocephaly	An abnormality of skull shape characterized by a increased anterior-posterior diameter, i.e., an increased antero-posterior dimension of the skull. Cephalic index less than 76%. Alternatively, an apparently increased antero-posterior length of the head compared to width. Often due to premature closure of the sagittal suture.
HP:0010783	Erythema	Redness of the skin, caused by hyperemia of the capillaries in the lower layers of the skin.
HP:0005598	Facial telangiectasia in butterfly midface distribution	Telangiectases (small dilated blood vessels) located near the surface of the skin in a butterfly midface distribution.
HP:0001511	Intrauterine growth retardation	An abnormal restriction of fetal growth with fetal weight below the tenth percentile for gestational age.
HP:0000272	Malar flattening	Underdevelopment of the malar prominence of the jugal bone (zygomatic bone in mammals), appreciated in profile, frontal view, and/or by palpation.

HP:0000275	Narrow face	Bizygomatic (upper face) and bigonial (lower face) width are both more than 2 standard deviations below the mean (objective); or, an apparent reduction in the width of the upper and lower face (subjective).
HP:0002664	Neoplasm	An organ or organ-system abnormality that consists of uncontrolled autonomous cell-proliferation which can occur in any part of the body as a benign or malignant neoplasm (tumour).
HP:0008897	Postnatal growth retardation	Slow or limited growth after birth.
HP:0002205	Recurrent respiratory infections	An increased susceptibility to respiratory infections as manifested by a history of recurrent respiratory infections.
HP:0004322	Short stature	A height below that which is expected according to age and gender norms. Although there is no universally accepted definition of short stature, many refer to "short stature" as height more than 2 standard deviations below the mean for age and gender (or below the 3rd percentile for age and gender dependent norms).
HP:0000246	Sinusitis	Inflammation of the paranasal sinuses owing to a viral, bacterial, or fungal infection, allergy, or an autoimmune reaction.
HP:0005585	Spotty hyperpigmentation	

4.9.1.2 Frequent

Term Identifier	Term Name	Definition
HP:0000271	Abnormality of the face	An abnormality of the face.
HP:0010669	Cheekbone underdevelopment	Underdevelopment of the zygomatic bone [UBERON_0001683]. That is, a reduction in size of the zygomatic bone, including the zygomatic process of the temporal bone of the skull, which forms part of the zygomatic arch.
HP:0000992	Cutaneous photosensitivity	An increased sensitivity of the skin to light. Photosensitivity may result in a rash upon exposure to the sun (which is known as photodermatitis). Photosensitivity can be diagnosed by phototests in which light is shone on small areas of skin.

HP:0001620	High pitched voice	An abnormal increase in the pitch (frequency) of the voice.
HP:0003196	Short nose	Distance from nasion to subnasale more than two standard deviations below the mean, or alternatively, an apparently decreased length from the nasal root to the nasal tip.
HP:0100585	Telangiectasia of the skin	Presence of small, permanently dilated blood vessels near the surface of the skin, visible as small focal red lesions.

4.9.1.3 Occasional

Term Identifier	Term Name	Definition
HP:0002488	Acute leukemia	A clonal (malignant) hematopoietic disorder with an acute onset, affecting the bone marrow and the peripheral blood. The malignant cells show minimal differentiation and are called blasts, either myeloid blasts (myeloblasts) or lymphoid blasts (lymphoblasts).
HP:0000027	Azoospermia	Absence of any measurable level of sperm in his semen.
HP:0004313	Decreased antibody level in blood	An abnormally decreased level of immunoglobulin in blood.
HP:0000868	Decreased fertility in females	
HP:0006101	Finger syndactyly	Webbing or fusion of the fingers, involving soft parts only or including bone structure. Bony fusions are referred to as "bony" Syndactyly if the fusion occurs in a radio-ulnar axis. Fusions of bones of the fingers in a proximo-distal axis are referred to as "Symphalangism".
HP:0001161	Hand polydactyly	A kind of polydactyly characterized by the presence of a supernumerary finger or fingers.
HP:0000975	Hyperhidrosis	Abnormal excessive perspiration (sweating) despite the lack of appropriate stimuli like hot and humid weather.
HP:0001053	Hypopigmented skin patches	
HP:0008064	Ichthyosis	An abnormality of the skin characterized the presence of excessive amounts of dry surface scales on the skin resulting from an abnormality of keratinization.

HP:0002720	Decreased circulating IgA level	Decreased levels of immunoglobulin A (IgA).
HP:0004315	Decreased circulating IgG level	An abnormally decreased level of immunoglobulin G (IgG) in blood.
HP:0002850	Decreased circulating total IgM	An abnormally decreased level of immunoglobulin M (IgM) in blood.
HP:0001256	Intellectual disability, mild	Mild intellectual disability is defined as an intelligence quotient (IQ) in the range of 50-69.
HP:0002665	Lymphoma	A cancer originating in lymphocytes and presenting as a solid tumor of lymphoid cells.
HP:0000252	Microcephaly	Occipito-frontal (head) circumference (OFC) less than -3 standard deviations compared to appropriate, age matched, normal standards (Ross JJ, Frias JL 1977, PMID:9683597). Alternatively, decreased size of the cranium.
HP:0007378	Neoplasm of the gastrointestinal tract	A tumor (abnormal growth of tissue) of the gastrointestinal tract.
HP:0000411	Protruding ear	Angle formed by the plane of the ear and the mastoid bone greater than the 97th centile for age (objective); or, outer edge of the helix more than 2 cm from the mastoid at the point of maximum distance (objective).
HP:0009804	Reduced number of teeth	The presence of a reduced number of teeth as in Hypodontia or as in Anodontia.
HP:0000960	Sacral dimple	A subtype of skin dimples presenting as an indentation in the skin of the intergluteal cleft
HP:0002860	Squamous cell carcinoma	The presence of squamous cell carcinoma of the skin.

Source: HPO-ORDO Ontological Module (21) - Validation association date: 01.06.2016

4.10 Cartilage hair hypoplasia

4.10.1.1 Very frequent

Term Identifier	Term Name	Definition
HP:0011849	Abnormal bone ossification	Any anomaly in the formation of bone or of a bony substance, or the conversion of fibrous tissue or of cartilage into bone or a bony substance.
HP:0000940	Abnormal diaphysis morphology	An abnormality of the structure or form of the diaphysis, i.e., of the main or mid-section (shaft) of a long bone.

HP:0003312	Abnormal form of the vertebral bodies	Abnormal morphology of vertebral body.
HP:0100569	Abnormal vertebral ossification	An abnormality of the formation and mineralization of one or more vertebrae.
HP:0005930	Abnormality of epiphysis morphology	An anomaly of epiphysis, which is the expanded articular end of a long bone that develops from a secondary ossification center, and which during the period of growth is either entirely cartilaginous or is separated from the shaft by a cartilaginous disk.
HP:0007703	Abnormality of retinal pigmentation	
HP:0001671	Abnormality of the cardiac septa	An anomaly of the intra-atrial or intraventricular septum.
HP:0009832	Abnormality of the distal phalanx of finger	Any anomaly of distal phalanx of finger.
HP:0000944	Abnormality of the metaphysis	An abnormality of one or more metaphysis, i.e., of the somewhat wider portion of a long bone that is adjacent to the epiphyseal growth plate and grows during childhood.
HP:0001732	Abnormality of the pancreas	An abnormality of the pancreas.
HP:0004625	Biconvex vertebral bodies	Presence of abnormal convexity of the upper and lower end plates of the vertebrae, i.e., an exaggerated bulging out of the upper and lower vertebral end plates.
HP:0000592	Blue sclerae	An abnormal bluish coloration of the sclera.
HP:0006487	Bowing of the long bones	A bending or abnormal curvature of a long bone.
HP:0001638	Cardiomyopathy	A myocardial disorder in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease, hypertension, valvular disease and congenital heart disease sufficient to cause the observed myocardial abnormality.
HP:0000444	Convex nasal ridge	Nasal ridge curving anteriorly to an imaginary line that connects the nasal root and tip. The nose appears often also prominent, and the columella low.
HP:0005019	Diaphyseal thickening	
HP:0008873	Disproportionate short-limb short stature	A type of disproportionate short stature characterized by a short limbs but an average-sized trunk.
HP:0002353	EEG abnormality	Abnormality observed by electroencephalogram (EEG), which is used

		to record of the brain's spontaneous electrical activity from multiple electrodes placed on the scalp.
HP:0001508	Failure to thrive	Failure to thrive (FTT) refers to a child whose physical growth is substantially below the norm.
HP:0008499	High-grade hypermetropia	A severe form of hypermetropia with over +5.00 diopters.
HP:0003307	Hyperlordosis	Abnormally increased curvature (anterior concavity) of the lumbar or cervical spine.
HP:0002901	Hypocalcemia	An abnormally decreased calcium concentration in the blood.
HP:0100729	Large face	
HP:0001377	Limited elbow extension	Limited ability to straighten the arm at the elbow joint.
HP:0003027	Mesomelia	Shortening of the middle parts of the limbs (forearm and lower leg) in relation to the upper and terminal segments.
HP:0005871	Metaphyseal chondrodysplasia	An abnormality of skeletal development characterized by a disturbance of the metaphysis and its histological structure with relatively normal epiphyses and vertebrae.
HP:0100255	Metaphyseal dysplasia	The presence of dysplastic regions in metaphyseal regions.
HP:0002983	Micromelia	The presence of abnormally small extremities.
HP:0001252	Muscular hypotonia	Muscular hypotonia is an abnormally low muscle tone (the amount of tension or resistance to movement in a muscle), often involving reduced muscle strength. Hypotonia is characterized by a diminished resistance to passive stretching.
HP:0001875	Neutropenia	An abnormally low number of neutrophils in the peripheral blood.
HP:0002093	Respiratory insufficiency	
HP:0008905	Rhizomelia	Disproportionate shortening of the proximal segment of limbs (i.e. the femur and humerus).
HP:0002650	Scoliosis	The presence of an abnormal lateral curvature of the spine.
HP:0000470	Short neck	Diminished length of the neck.
HP:0004279	Short palm	Short palm.
HP:0002652	Skeletal dysplasia	A general term describing features characterized by abnormal development of bones and connective tissues.
HP:0000535	Sparse eyebrow	Decreased density/number and/or decreased diameter of eyebrow hairs.

HP:0008070	Sparse hair	Reduced density of hairs.
HP:0010301	Spinal dysraphism	A heterogeneous group of congenital spinal anomalies that result from defective closure of the neural tube early in fetal life.
HP:0000486	Strabismus	A misalignment of the eyes so that the visual axes deviate from bifoveal fixation. The classification of strabismus may be based on a number of features including the relative position of the eyes, whether the deviation is latent or manifest, intermittent or constant, concomitant or otherwise and according to the age of onset and the relevance of any associated refractive error.
HP:0002982	Tibial bowing	A bending or abnormal curvature of the tibia.
HP:0002777	Tracheal stenosis	
HP:0000505	Visual impairment	Visual impairment (or vision impairment) is vision loss (of a person) to such a degree as to qualify as an additional support need through a significant limitation of visual capability resulting from either disease, trauma, or congenital or degenerative conditions that cannot be corrected by conventional means, such as refractive correction, medication, or surgery.

4.10.1.2 Frequent

Term Identifier	Term Name	Definition
HP:0003272	Abnormality of the hip bone	An abnormality of the hip bone.
HP:0000174	Abnormality of the palate	Any abnormality of the palate, i.e., of roof of the mouth.
HP:0005280	Depressed nasal bridge	Posterior positioning of the nasal root in relation to the overall facial profile for age.
HP:0006589	Flaring of lower rib cage	
HP:0000212	Gingival overgrowth	Hyperplasia of the gingiva (that is, a thickening of the soft tissue overlying the alveolar ridge. The degree of thickening ranges from involvement of the interdental papillae alone to gingival overgrowth covering the entire tooth crown.
HP:0000368	Low-set, posteriorly rotated ears	Ears that are low-set (HP:0000369) and posteriorly rotated (HP:0000358).

HP:0002024	Malabsorption	Impaired ability to absorb one or more nutrients from the intestine.
HP:0008155	Mucopolysacchariduria	Excessive amounts of mucopolysaccharide in the urine.
HP:0000545	Myopia	An abnormality of refraction characterized by the ability to see objects nearby clearly, while objects in the distance appear blurry.
HP:0000774	Narrow chest	Reduced width of the chest from side to side, associated with a reduced distance from the sternal notch to the tip of the shoulder.
HP:0011220	Prominent forehead	Forward prominence of the entire forehead, due to protrusion of the frontal bone.
HP:0001315	Reduced tendon reflexes	Diminution of tendon reflexes, which is an invariable sign of peripheral nerve disease.

4.10.1.3 Occasional

Term Identifier	Term Name	Definition
HP:0003220	Abnormality of chromosome stability	A type of chromosomal aberration characterised by reduced resistance of chromosomes to change or deterioration.
HP:0002644	Abnormality of pelvic girdle bone morphology	An abnormality of the bony pelvic girdle, which is a ring of bones connecting the vertebral column to the femurs.
HP:0000772	Abnormality of the ribs	An anomaly of the rib.
HP:0005616	Accelerated skeletal maturation	An abnormally increased rate of skeletal maturation. Accelerated skeletal maturation can be diagnosed on the basis of an estimation of the bone age from radiographs of specific bones in the human body.
HP:0002251	Aganglionic megacolon	An abnormality resulting from a lack of intestinal ganglion cells (i.e., an aganglionic section of bowel) that results in bowel obstruction with enlargement of the colon.
HP:0001903	Anemia	A reduction in erythrocytes volume or hemoglobin concentration.
HP:0000463	Anteverted nares	Anteriorly-facing nostrils viewed with the head in the Frankfurt horizontal and the eyes of the observer level with the eyes of the subject. This gives the

		appearance of an upturned nose (upturned nasal tip).
HP:0008056	Aplasia/Hypoplasia affecting the eye	
HP:0010318	Aplasia/Hypoplasia of the abdominal wall musculature	Absence or underdevelopment of the abdominal musculature.
HP:0000248	Brachycephaly	An abnormality of skull shape characterized by a decreased anterior-posterior diameter. That is, a cephalic index greater than 81%. Alternatively, an apparently shortened anteroposterior dimension (length) of the head compared to width.
HP:0100543	Cognitive impairment	Abnormality in the process of thought including the ability to process information.
HP:0004313	Decreased antibody level in blood	An abnormally decreased level of immunoglobulin in blood.
HP:0002750	Delayed skeletal maturation	A decreased rate of skeletal maturation. Delayed skeletal maturation can be diagnosed on the basis of an estimation of the bone age from radiographs of specific bones in the human body.
HP:0000457	Depressed nasal ridge	Lack of prominence of the nose resulting from a posteriorly-placed nasal ridge.
HP:0000286	Epicanthus	A fold of skin starting above the medial aspect of the upper eyelid and arching downward to cover, pass in front of and lateral to the medial canthus.
HP:0012722	Heart block	Impaired conduction of cardiac impulse occurring anywhere along the conduction pathway.
HP:0002240	Hepatomegaly	Abnormally increased size of the liver.
HP:0005692	Joint hyperflexibility	Increased mobility and flexibility in the joint due to the tension in tissues such as ligaments and muscles.
HP:0000400	Macrotia	Median longitudinal ear length greater than two standard deviations above the mean and median ear width greater than two standard deviations above the mean (objective); or, apparent increase in length and width of the pinna (subjective).
HP:0000768	Pectus carinatum	A deformity of the chest caused by overgrowth of the ribs and characterized by protrusion of the sternum.
HP:0000960	Sacral dimple	A subtype of skin dimples presenting as an indentation in the skin of the intergluteal cleft.

HP:0010306	Short thorax	Reduced inferior to superior extent of the thorax.
HP:0200055	Small hand	Disproportionately small hand.
HP:0000431	Wide nasal bridge	Increased breadth of the nasal bridge (and with it, the nasal root).

Source: HPO-ORDO Ontological Module (21) - Validation association date: 01.06.2016

4.11 CD8 deficiency

4.11.1.1 No frequency available

Term Identifier	Term Name	Definition
HP:0000007	Autosomal recessive inheritance	A mode of inheritance that is observed for traits related to a gene encoded on one of the autosomes (i.e., the human chromosomes 1-22) in which a trait manifests in individuals with two pathogenic alleles, either homozygotes (two copies of the same mutant allele) or compound heterozygotes (whereby each copy of a gene has a distinct mutant allele).
HP:0002205	Recurrent respiratory infections	An increased susceptibility to respiratory infections as manifested by a history of recurrent respiratory infections.
HP:0002110	Bronchiectasis	Persistent abnormal dilatation of the bronchi owing to localized and irreversible destruction and widening of the large airways.
HP:0002718	Recurrent bacterial infections	Increased susceptibility to bacterial infections, as manifested by recurrent episodes of bacterial infection.
HP:0004429	Recurrent viral infections	Increased susceptibility to viral infections, as manifested by recurrent episodes of viral infection.
HP:0005422	Absence of CD8-positive T cells	Lack of detectible CD8-positive T cells

Source: OMIM Clinical synopsis - #608957; Creation date: 30.09.2004, Cassandra L. Kniffin

4.12 Chronic mucocutaneous candidiasis (CMC)

4.12.1.1 Very frequent

Term Identifier	Term Name	Definition
HP:0008388	Abnormal toenail morphology	An anomaly of the toenail.
HP:0001231	Abnormality of the fingernails	An abnormality of the fingernails.

HP:0002715	Abnormality of the immune system	An abnormality of the immune system.
HP:0000159	Abnormal lip morphology	An abnormality of the lip.
HP:0000153	Abnormality of the mouth	An abnormality of the mouth.
HP:0001597	Abnormality of the nail	Abnormality of the nail.
HP:0000951	Abnormality of the skin	An abnormality of the skin.
HP:0001821	Broad nail	Increased width of nail.
HP:0100825	Cheilitis	Inflammation of the lip.
HP:0010783	Erythema	Redness of the skin, caused by hyperemia of the capillaries in the lower layers of the skin.
HP:0000962	Hyperkeratosis	Hyperkeratosis is thickening of the outer layer of the skin, the stratum corneum, which is composed of large, polyhedral, plate-like envelopes filled with keratin which are the dead cells that have migrated up from the stratum granulosum.
HP:0002719	Recurrent infections	Increased susceptibility to infections.
HP:0000988	Skin rash	A red eruption of the skin.
HP:0200042	Skin ulcer	A discontinuity of the skin exhibiting complete loss of the epidermis and often portions of the dermis and even subcutaneous fat.

4.12.1.2 Frequent

Term Identifier	Term Name	Definition
HP:0000142	Abnormal vagina morphology	Any structural abnormality of the vagina.
HP:0030016	Dyspareunia	Recurrent or persistent genital pain associated with sexual intercourse.
HP:0200034	Papule	A circumscribed, solid elevation of skin with no visible fluid, varying in size from a pinhead to less than 10mm in diameter at the widest point.

4.12.1.3 Occasional

Term Identifier	Term Name	Definition
HP:0000682	Abnormality of dental enamel	An abnormality of the dental enamel.

HP:0004370	Abnormality of temperature regulation	An abnormality of temperature homeostasis.
HP:0004306	Abnormal endocardium morphology	An abnormality of the endocardium.
HP:0000478	Abnormality of the eye	Any abnormality of the eye, including location, spacing, and intraocular abnormalities.
HP:0000504	Abnormality of vision	<i>Abnormality of eyesight (visual perception).</i>
HP:0012735	Cough	A sudden, audible expulsion of air from the lungs through a partially closed glottis, preceded by inhalation.
HP:0008872	Feeding difficulties in infancy	Impaired feeding performance of an infant as manifested by difficulties such as weak and ineffective sucking, brief bursts of sucking, and falling asleep during sucking. There may be difficulties with chewing or maintaining attention.
HP:0000790	Hematuria	The presence of blood in the urine. Hematuria may be gross hematuria (visible to the naked eye) or microscopic hematuria (detected by dipstick or microscopic examination of the urine).
HP:0002105	Hemoptysis	Coughing up (expectoration) of blood or blood-streaked sputum from the larynx, trachea, bronchi, or lungs.
HP:0012115	Hepatitis	Inflammation of the liver.
HP:0000103	Polyuria	An increased rate of urine production.
HP:0000989	Pruritus	Pruritus is an itch or a sensation that makes a person want to scratch. This term refers to an abnormally increased disposition to experience pruritus.
HP:0002205	Recurrent respiratory infections	An increased susceptibility to respiratory infections as manifested by a history of recurrent respiratory infections.
HP:0000010	Recurrent urinary tract infections	Repeated infections of the urinary tract.
HP:0001250	Seizures	Seizures are an intermittent abnormality of the central nervous system due to a sudden, excessive, disorderly discharge of cerebral neurons and characterized clinically by some combination of disturbance of sensation, loss of consciousness, impairment of psychic function, or convulsive movements. The term epilepsy is used to describe chronic, recurrent seizures.

Source: HPO-ORDO Ontological Module (21) - Validation association date: 01.06.2016

4.13 Complement component 1q deficiency (C1q deficiency)

4.13.1.1 No frequency available

Term Identifier	Term Name	Definition
HP:0000007	Autosomal recessive inheritance	A mode of inheritance that is observed for traits related to a gene encoded on one of the autosomes (i.e., the human chromosomes 1-22) in which a trait manifests in individuals with two pathogenic alleles, either homozygotes (two copies of the same mutant allele) or compound heterozygotes (whereby each copy of a gene has a distinct mutant allele).
HP:0000793	Membranoproliferative glomerulonephritis	A type of glomerulonephritis characterized by diffuse mesangial cell proliferation and the thickening of capillary walls due to subendothelial extension of the mesangium. The term membranoproliferative glomerulonephritis is often employed to denote a general pattern of glomerular injury seen in a variety of disease processes that share a common pathogenetic mechanism, rather than to describe a single disease entity
HP:0002725	Systemic lupus erythematosus	A chronic, relapsing, inflammatory, and often febrile multisystemic disorder of connective tissue, characterized principally by involvement of the skin, joints, kidneys, and serosal membranes.
HP:0002960	Autoimmunity	The occurrence of an immune reaction against the organism's own cells or tissues.
HP:0005356	Decreased serum complement factor I	A reduced level of the complement component Factor I in circulation.
HP:0002719	Recurrent infections	Increased susceptibility to infections.

Source: OMIM Clinical synopsis - #613652; Creation date: 05.03.2012, Joanna S. Amberger

4.14 Complement component 1r deficiency (C1r deficiency)

4.14.1.1 No frequency available

Term Identifier	Term Name	Definition
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HP:0004431	Complement deficiency	An immunodeficiency defined by the absent or suboptimal functioning of one of the complement system proteins.
HP:0002960	Autoimmunity	The occurrence of an immune reaction against the organism's own cells or tissues.
HP:0007417	Discoid lupus rash	Cutaneous lesion that develops as a dry, scaly, red patch that evolves to an indurated and hyperpigmented plaque with adherent scale. Scarring may result in central white patches (loss of pigmentation) and skin atrophy.
HP:0000123	Nephritis	The presence of inflammation affecting the kidney.
HP:0002837	Recurrent bronchitis	An increased susceptibility to bronchitis as manifested by a history of recurrent bronchitis.
HP:0001369	Arthritis	Inflammation of a joint.
HP:0002829	Arthralgia	Joint pain.
HP:0002719	Recurrent infections	Increased susceptibility to infections.
HP:0000007	Autosomal recessive inheritance	A mode of inheritance that is observed for traits related to a gene encoded on one of the autosomes (i.e., the human chromosomes 1-22) in which a trait manifests in individuals with two pathogenic alleles, either homozygotes (two copies of the same mutant allele) or compound heterozygotes (whereby each copy of a gene has a distinct mutant allele).

Source: OMIM Clinical synopsis - %216950

4.15 Complement component 1s deficiency (C1s deficiency)

4.15.1.1 No frequency available

Term Identifier	Term Name	Definition
HP:0012115	Hepatitis	Inflammation of the liver.
HP:0002725	Systemic lupus erythematosus	A chronic, relapsing, inflammatory, and often febrile multisystemic disorder of connective tissue, characterized principally by involvement of the skin, joints, kidneys, and serosal membranes.
HP:0005339	Abnormality of complement system	An abnormality of the complement system.
HP:0000872	Hashimoto thyroiditis	A chronic, autoimmune type of thyroiditis associated with hypothyroidism.
HP:0002719	Recurrent infections	Increased susceptibility to infections.

Source: OMIM - #613783; Creation date: 01.03.2011, Carol A.Bocchini

4.16 Complement component 2 deficiency

4.16.1.1 No frequency available

Term Identifier	Term Name	Definition
HP:0000979	Purpura	Purpura (from Latin: purpura, meaning "purple") is the appearance of red or purple discolorations on the skin that do not blanch on applying pressure. They are caused by bleeding underneath the skin. This term refers to an abnormally increased susceptibility to developing purpura. Purpura are larger than petechiae.
HP:0002725	Systemic lupus erythematosus	A chronic, relapsing, inflammatory, and often febrile multisystemic disorder of connective tissue, characterized principally by involvement of the skin, joints, kidneys, and serosal membranes.
HP:0007417	Discoid lupus rash	Cutaneous lesion that develops as a dry, scaly, red patch that evolves to an indurated and hyperpigmented plaque with adherent scale. Scarring may result in central white patches (loss of pigmentation) and skin atrophy.
HP:0005339	Abnormality of complement system	An abnormality of the complement system.
HP:0000007	Autosomal recessive inheritance	A mode of inheritance that is observed for traits related to a gene encoded on one of the autosomes (i.e., the human chromosomes 1-22) in which a trait manifests in individuals with two pathogenic alleles, either homozygotes (two copies of the same mutant allele) or compound heterozygotes (whereby each copy of a gene has a distinct mutant allele).
HP:0002960	Autoimmunity	The occurrence of an immune reaction against the organism's own cells or tissues.

Source: OMIM - #217000; Creation date: 15.06.1995, John F. Jackson

4.17 Complement component 3 deficiency (C3)

4.17.1.1 No frequency available

Term Identifier	Term Name	Definition
HP:0000100	Nephrotic syndrome	Nephrotic syndrome is a collection of findings resulting from glomerular dysfunction with an increase in

		glomerular capillary wall permeability associated with pronounced proteinuria. Nephrotic syndrome refers to the constellation of clinical findings that result from severe renal loss of protein, with Proteinuria and hypoalbuminemia, edema, and hyperlipidemia.
HP:0000083	Renal insufficiency	A reduction in the level of performance of the kidneys in areas of function comprising the concentration of urine, removal of wastes, the maintenance of electrolyte balance, homeostasis of blood pressure, and calcium metabolism.
HP:0000793	Membranoproliferative glomerulonephritis	A type of glomerulonephritis characterized by diffuse mesangial cell proliferation and the thickening of capillary walls due to subendothelial extension of the mesangium. The term membranoproliferative glomerulonephritis is often employed to denote a general pattern of glomerular injury seen in a variety of disease processes that share a common pathogenetic mechanism, rather than to describe a single disease entity.
HP:0005421	Decreased serum complement C3	A reduced level of the complement component C3 in circulation.
HP:0002725	Systemic lupus erythematosus	A chronic, relapsing, inflammatory, and often febrile multisystemic disorder of connective tissue, characterized principally by involvement of the skin, joints, kidneys, and serosal membranes.
HP:0002718	Recurrent bacterial infections	Increased susceptibility to bacterial infections, as manifested by recurrent episodes of bacterial infection.
HP:0005430	Reccurent Neisserial infections	Recurrent infections by bacteria of the genus Neisseria, including N. meningitidis (one of the most common causes of bacterial meningitis).

Source: OMIM Clinical synopsis- #613779; Creation date: 15.06.1995, John F. Jackson; revised: 20.04.2011, Cassandra L. Kniffin

4.18 Complement component 4 deficiency (C4a, C4b)

4.18.1.1 No frequency available

Term Identifier	Term Name	Definition
HP:0000979	Purpura	Purpura (from Latin: purpura, meaning "purple") is the appearance of red or purple discolorations on the skin that do not blanch on applying pressure. They are caused by bleeding underneath the skin. This term refers to an abnormally increased susceptibility to developing purpura. Purpura are larger than petechiae.
HP:0002633	Vasculitis	Inflammation of blood vessel.
HP:0004431	Complement deficiency	An immunodeficiency defined by the absent or suboptimal functioning of one of the complement system proteins.
HP:0002725	Systemic lupus erythematosus	A chronic, relapsing, inflammatory, and often febrile multisystemic disorder of connective tissue, characterized principally by involvement of the skin, joints, kidneys, and serosal membranes.
HP:0000099	Glomerulonephritis	Inflammation of the renal glomeruli.
HP:0000992	Cutaneous photosensitivity	An increased sensitivity of the skin to light. Photosensitivity may result in a rash upon exposure to the sun (which is known as photodermatitis). Photosensitivity can be diagnosed by phototests in which light is shone on small areas of skin.
HP:0005430	Recurrent Neisserial infections	Recurrent infections by bacteria of the genus Neisseria, including N. meningitidis (one of the most common causes of bacterial meningitis).
HP:0045043	Decreased serum complement C4a	A reduced level of the complement component C4a in circulation.
HP:0045044	Decreased serum complement C4b	A reduced level of the complement component C4b in circulation.
HP:0200120	Chronic active hepatitis	Chronic hepatitis associated with recurrent clinical exacerbations, extrahepatic manifestations, and progression to cirrhosis.
HP:0001287	Meningitis	Inflammation of the meninges.

Source: OMIM Clinical synopsis- #614380; Creation date: 15.06.1995, John F. Jackson; reviewed: 15.05.2000, Ada Hamosh
 OMIM # 614379; Creation date: 06.12.2011, Matthew B. Gross; updated: 29.03.2012, Cassandra L. Kniffin

4.19 Complement component 5 deficiency

4.19.1.1 No frequency available

Term Identifier	Term Name	Definition
HP:0002719	Recurrent infections	Increased susceptibility to infections.
HP:0007569	Generalized seborrheic dermatitis	Seborrheic dermatitis that is not localized to any one particular region.
HP:0004431	Complement deficiency	An immunodeficiency defined by the absent or suboptimal functioning of one of the complement system proteins.
HP:0000007	Autosomal recessive inheritance	A mode of inheritance that is observed for traits related to a gene encoded on one of the autosomes (i.e., the human chromosomes 1-22) in which a trait manifests in individuals with two pathogenic alleles, either homozygotes (two copies of the same mutant allele) or compound heterozygotes (whereby each copy of a gene has a distinct mutant allele).
HP:0002041	Intractable diarrhea	
HP:0006946	Recurrent meningitis	An increased susceptibility to meningitis as manifested by a medical history of recurrent episodes of meningitis.

Source: OMIM #609536; Creation date: 17.08.2005, Victor A. McKusick; updated: 23.03.2011, Paul J. Converse

4.20 Complement component 6 deficiency

4.20.1.1 No frequency available

Term Identifier	Term Name	Definition
HP:0004431	Complement deficiency	An immunodeficiency defined by the absent or suboptimal functioning of one of the complement system proteins.
HP:0005381	Recurrent meningococcal disease	Recurrent infections by <i>Neisseria meningitidis</i> (one of the most common causes of bacterial meningitis), which is also known as meningococcus.
HP:0000007	Autosomal recessive inheritance	A mode of inheritance that is observed for traits related to a gene encoded on one of the autosomes (i.e., the human chromosomes 1-22) in which a trait manifests in individuals with two pathogenic alleles, either homozygotes (two copies of the same mutant allele) or compound heterozygotes (whereby

		each copy of a gene has a distinct mutant allele).
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Source: OMIM #612446; Creation date: 01.12.2008, Matthew B. Gross; updated: 23.03.2011, Paul J. Converse

4.21 Complement component 7 deficiency

4.21.1.1 No frequency available

Term Identifier	Term Name	Definition
HP:0004431	Complement deficiency	An immunodeficiency defined by the absent or suboptimal functioning of one of the complement system proteins.
HP:0005381	Recurrent meningococcal disease	Recurrent infections by <i>Neisseria meningitidis</i> (one of the most common causes of bacterial meningitis), which is also known as meningococcus.
HP:0000007	Autosomal recessive inheritance	A mode of inheritance that is observed for traits related to a gene encoded on one of the autosomes (i.e., the human chromosomes 1-22) in which a trait manifests in individuals with two pathogenic alleles, either homozygotes (two copies of the same mutant allele) or compound heterozygotes (whereby each copy of a gene has a distinct mutant allele).

Source: OMIM #610102; Creation date: 10.05.2006, Victor A. McKusick; updated: 23.03.2011, Paul J. Converse

4.22 Complement component 8 deficiency (C8A, C8B, C8G)

4.22.1.1 No frequency available

Term Identifier	Term Name	Definition
HP:0000007	Autosomal recessive inheritance	A mode of inheritance that is observed for traits related to a gene encoded on one of the autosomes (i.e., the human chromosomes 1-22) in which a trait manifests in individuals with two pathogenic alleles, either homozygotes (two copies of the same mutant allele) or compound heterozygotes (whereby each copy of a gene has a distinct mutant allele).
HP:0001287	Meningitis	Inflammation of the meninges.
HP:0004434	C8 deficiency	A reduced level of the complement component C8 in circulation.

HP:0002725	Systemic lupus erythematosus	A chronic, relapsing, inflammatory, and often febrile multisystemic disorder of connective tissue, characterized principally by involvement of the skin, joints, kidneys, and serosal membranes.
HP:0005430	Recurrent Neisserial infections	Recurrent infections by bacteria of the genus <i>Neisseria</i> , including <i>N. meningitidis</i> (one of the most common causes of bacterial meningitis).

Source: OMIM Clinical synopsis #613790 – Creation date: 15.06.1995, John F. Jackson

OMIM Clinical synopsis #613789 – Creation date: 05.03.2012, Joanna S. Amberger

4.23 Complement component 9 deficiency

4.23.1.1 No frequency available

Term Identifier	Term Name	Definition
HP:0012308	Decreased serum complement C9	A reduced level of the complement component C9 in circulation.
HP:0005430	Recurrent Neisserial infections	Recurrent infections by bacteria of the genus <i>Neisseria</i> , including <i>N. meningitidis</i> (one of the most common causes of bacterial meningitis).

Source: OMIM #613825 – Creation date: 23.03.2011, Matthew B. Gross

4.24 CSR defects and HIGM syndrome

4.24.1.1 No frequency available

Term Identifier	Term Name	Definition
HP:0000007	Autosomal recessive inheritance	A mode of inheritance that is observed for traits related to a gene encoded on one of the autosomes (i.e., the human chromosomes 1-22) in which a trait manifests in individuals with two pathogenic alleles, either homozygotes (two copies of the same mutant allele) or compound heterozygotes (whereby each copy of a gene has a distinct mutant allele).
HP:0200117	Recurrent upper and lower respiratory tract infections	Increased susceptibility to upper and lower respiratory tract infections, as manifested by recurrent episodes of upper and lower respiratory tract infections.

HP:0000031	Epididymitis	The presence of inflammation of the epididymis.
HP:0002716	Lymphadenopathy	Enlargment (swelling) of a lymph node.
HP:0003496	Increased circulating IgM level	An abnormally increased level of immunoglobulin M in blood.
HP:0002720	Decreased circulating IgA level	Decreased levels of immunoglobulin A (IgA).
HP:0004315	Decreased circulating IgG level	An abnormally decreased level of immunoglobulin G (IgG) in blood.
HP:0002959	Impaired Ig class switch recombination	An impairment of the class-switch recombination process that normally leads B lymphocytes to produce IgG, IgA, or IgE.
HP:0002718	Recurrent bacterial infections	Increased susceptibility to bacterial infections, as manifested by recurrent episodes of bacterial infection.
HP:0002721	Immunodeficiency	Failure of the immune system to protect the body adequately from infection, due to the absence or insufficiency of some component process or substance.
HP:0002110	Bronchiectasis	Persistent abnormal dilatation of the bronchi owing to localized and irreversible destruction and widening of the large airways.
HP:0004798	Recurrent infection of the gastrointestinal tract	Recurrent infection of the gastrointestinal tract.
HP:0002754	Osteomyelitis	Osteomyelitis is an inflammatory process accompanied by bone destruction and caused by an infecting microorganism.
HP:0001890	Autoimmune hemolytic anemia	An autoimmune form of hemolytic anemia.
HP:0001973	Autoimmune thrombocytopenia	The presence of thrombocytopenia in combination with detection of antiplatelet antibodies.
HP:0002849	Absence of lymph node germinal center	Absence of germinal centers in lymph nodes. Germinal centers are the parts of lymph nodes in which B lymphocytes proliferate, differentiate, mutate through somatic hypermutation and class switch during antibody responses.
HP:0002863	Myelodysplasia	Clonal hematopoietic stem cell disorders characterized by dysplasia (ineffective production) in one or more hematopoietic cell lineages, leading to anemia and cytopenia.

Source: OMIM Clinical synopsis #608106 – Creation date: 08.10.2004, Kelly A. Przylepa;
OMIM Clinical synopsis #608184 – Creation date: 20.01.2004, Kelly A. Przylepa;

4.25 Chédiak Higashi syndrome (CHS)

4.25.1.1 Very frequent

Term Identifier	Term Name	Definition
HP:0001881	Abnormal leukocyte morphology	An abnormality of leukocytes.
HP:0012145	Abnormality of multiple cell lineages in the bone marrow	
HP:0000504	Abnormality of vision	Abnormality of eyesight (visual perception).
HP:0001903	Anemia	A reduction in erythrocytes volume or hemoglobin concentration.
HP:0001284	Areflexia	Absence of neurologic reflexes such as the knee-jerk reaction.
HP:0000978	Bruising susceptibility	An ecchymosis (bruise) refers to the skin discoloration caused by the escape of blood into the tissues from ruptured blood vessels. This term refers to an abnormally increased susceptibility to bruising. The corresponding phenotypic abnormality is generally elicited on medical history as a report of frequent ecchymoses or bruising without adequate trauma.
HP:0001945	Fever	Elevated body temperature due to failed thermoregulation.
HP:0007513	Generalized hypopigmentation	
HP:0011358	Generalized hypopigmentation of hair	Reduced pigmentation of hair diffusely.
HP:0000225	Gingival bleeding	Hemorrhage affecting the gingiva.
HP:0001263	Global developmental delay	A delay in the achievement of motor or mental milestones in the domains of development of a child, including motor skills, speech and language, cognitive skills, and social and emotional skills. This term should only be used to describe children younger than five years of age.
HP:0002240	Hepatomegaly	Abnormally increased size of the liver.
HP:0002721	Immunodeficiency	Failure of the immune system to protect the body adequately from infection, due to the absence or insufficiency of some component process or substance.

HP:0007730	Iris hypopigmentation	An abnormal reduction in the amount of pigmentation of the iris.
HP:0002716	Lymphadenopathy	Enlargment (swelling) of a lymph node.
HP:0001875	Neutropenia	An abnormally low number of neutrophils in the peripheral blood.
HP:0003401	Paresthesia	Abnormal sensations such as tingling, pricking, or numbness of the skin with no apparent physical cause.
HP:0000704	Periodontitis	Inflammation of the periodontium.
HP:0009830	Peripheral neuropathy	Peripheral neuropathy is a general term for any disorder of the peripheral nervous system. The main clinical features used to classify peripheral neuropathy are distribution, type (mainly demyelinating versus mainly axonal), duration, and course.
HP:0100838	Recurrent cutaneous abscess formation	An increased susceptibility to cutaneous abscess formation, as manifested by a medical history of recurrent cutaneous abscesses.
HP:0002205	Recurrent respiratory infections	An increased susceptibility to respiratory infections as manifested by a history of recurrent respiratory infections.
HP:0200042	Skin ulcer	A discontinuity of the skin exhibiting complete loss of the epidermis and often portions of the dermis and even subcutaneous fat.
HP:0001744	Splenomegaly	Abnormal increased size of the spleen.
HP:0011364	White hair	Hypopigmented hair that appears white.
HP:0001873	Thrombocytopenia	A reduction in the number of circulating thrombocytes.

4.25.1.2 Frequent

Term Identifier	Term Name	Definition
HP:0000646	Amblyopia	Reduced visual acuity that is uncorrectable by lenses in the absence of detectable anatomic defects in the eye or visual pathways.
HP:0000969	Edema	An abnormal accumulation of fluid beneath the skin, or in one or more cavities of the body.
HP:0000421	Epistaxis	Epistaxis, or nosebleed, refers to a hemorrhage localized in the nose.
HP:0002665	Lymphoma	A cancer originating in lymphocytes and presenting as a solid tumor of lymphoid cells.
HP:0000639	Nystagmus	Rhythmic, involuntary oscillations of one or both eyes related to abnormality in fixation, conjugate gaze, or vestibular mechanisms.

HP:0000613	Photophobia	Excessive sensitivity to light with the sensation of discomfort or pain in the eyes due to exposure to bright light.
HP:0001250	Seizures	Seizures are an intermittent abnormality of the central nervous system due to a sudden, excessive, disorderly discharge of cerebral neurons and characterized clinically by some combination of disturbance of sensation, loss of consciousness, impairment of psychic function, or convulsive movements. The term epilepsy is used to describe chronic, recurrent seizures.
HP:0001337	Tremor	An unintentional, oscillating to-and-fro muscle movement about a joint axis.

4.25.1.3 Occasional

Term Identifier	Term Name	Definition
HP:0002071	Abnormality of extrapyramidal motor function	A neurological condition related to lesions of the basal ganglia leading to typical abnormalities including akinesia (inability to initiate changes in activity and perform volitional movements rapidly and easily), muscular rigidity (continuous contraction of muscles with constant resistance to passive movement), chorea (widespread arrhythmic movements of a forcible, rapid, jerky, and restless nature), athetosis (inability to sustain the muscles of the fingers, toes, or other group of muscles in a fixed position), and akathisia (inability to remain motionless).
HP:0100022	Abnormality of movement	An abnormality of movement with a neurological basis characterized by changes in coordination and speed of voluntary movements.
HP:0001251	Ataxia	Cerebellar ataxia refers to ataxia due to dysfunction of the cerebellum. This causes a variety of elementary neurological deficits including asynergy (lack of coordination between muscles, limbs and joints), dysmetria (lack of ability to judge distances that can lead to under- or overshoot in grasping movements), and dysdiadochokinesia (inability to perform rapid movements requiring antagonizing muscle groups to be switched on and off repeatedly).
HP:0001631	Atrial septal defect	Atrial septal defect (ASD) is a congenital abnormality of the interatrial septum that

		enables blood flow between the left and right atria via the interatrial septum.
HP:0002067	Bradykinesia	Bradykinesia literally means slow movement, and is used clinically to denote a slowness in the execution of movement (in contrast to hypokinesia, which is used to refer to slowness in the initiation of movement).
HP:0001272	Cerebellar atrophy	Atrophy (wasting) of the cerebellum.
HP:0002376	Developmental regression	Loss of developmental skills, as manifested by loss of developmental milestones.
HP:0002239	Gastrointestinal hemorrhage	Hemorrhage affecting the gastrointestinal tract.
HP:0007440	Generalized hyperpigmentation	
HP:0000995	Melanocytic nevus	A oval and round, colored (usually medium-to dark brown, reddish brown, or flesh colored) lesion. Typically, a melanocytic nevus is less than 6 mm in diameter, but may be much smaller or larger.
HP:0002063	Rigidity	Continuous involuntary sustained muscle contraction. When an affected muscle is passively stretched, the degree of resistance remains constant regardless of the rate at which the muscle is stretched. This feature helps to distinguish rigidity from muscle spasticity.

Source: HPO-ORDO Ontological Module (21) - Validation association date: 01.06.2016

4.26 Chronic granulomatous disease (CGD)

4.26.1.1 Very frequent

Term Identifier	Term Name	Definition
HP:0001874	Abnormality of neutrophils	A neutrophil abnormality.
HP:0006510	Chronic obstructive pulmonary disease	An anomaly that is characterized progressive airflow obstruction that is only partly reversible, inflammation in the airways, and systemic effects or comorbidities.
HP:0000992	Cutaneous photosensitivity	An increased sensitivity of the skin to light. Photosensitivity may result in a rash upon exposure to the sun (which is known as photodermatitis). Photosensitivity can be diagnosed by

		phototests in which light is shone on small areas of skin.
HP:0001945	Fever	Elevated body temperature due to failed thermoregulation.
HP:0002240	Hepatomegaly	Abnormally increased size of the liver.
HP:0001034	Hypermelanotic macule	A hyperpigmented circumscribed area of change in normal skin color without elevation or depression of any size.
HP:0012733	Macule	A flat, distinct, discolored area of skin less than 1 cm wide that does not involve any change in the thickness or texture of the skin.
HP:0002024	Malabsorption	Impaired ability to absorb one or more nutrients from the intestine.
HP:0100721	Mediastinal lymphadenopathy	Swelling of lymph nodes within the mediastinum, the central compartment of the thoracic cavities that contains the heart and the great vessels, the esophagus, and trachea and other structures including lymph nodes.
HP:0000388	Otitis media	Inflammation or infection of the middle ear.
HP:0002021	Pyloric stenosis	An abnormal narrowing of the pylorus.
HP:0002205	Recurrent respiratory infections	An increased susceptibility to respiratory infections as manifested by a history of recurrent respiratory infections.
HP:0000246	Sinusitis	Inflammation of the paranasal sinuses owing to a viral, bacterial, or fungal infection, allergy, or an autoimmune reaction.
HP:0002575	Tracheoesophageal fistula	An abnormal connection (fistula) between the esophagus and the trachea.

4.26.1.2 Occasional

Term Identifier	Term Name	Definition
HP:0000964	Eczema	Eczema is a form of dermatitis. The term eczema is broadly applied to a range of persistent skin conditions and can be related to a number of underlying conditions. Manifestations of eczema can include dryness and recurring skin rashes with redness, skin edema, itching and dryness, crusting, flaking, blistering, cracking, oozing, or bleeding.
HP:0000230	Gingivitis	Inflammation of the gingiva.
HP:0100533	Inflammatory abnormality of the eye	Inflammation of the eye, parts of the eye or the periorbital region.

HP:0100523	Liver abscess	The presence of an abscess of the liver.
HP:0001287	Meningitis	Inflammation of the meninges.
HP:0100806	Sepsis	Systemic inflammatory response to infection.
HP:0200042	Skin ulcer	A discontinuity of the skin exhibiting complete loss of the epidermis and often portions of the dermis and even subcutaneous fat.
HP:0001744	Splenomegaly	Abnormal increased size of the spleen.

Source: HPO-ORDO Ontological Module (21) - Validation association date: 01.06.2016

4.27 Clericuzio-type poikiloderma with neutropenia syndrome

4.27.1.1 Occasional

Term Identifier	Term Name	Definition
HP:0000316	Hypertelorism	Interpupillary distance more than 2 SD above the mean (alternatively, the appearance of an increased interpupillary distance or widely spaced eyes).
HP:0000272	Malar flattening	Underdevelopment of the malar prominence of the jugal bone (zygomatic bone in mammals), appreciated in profile, frontal view, and/or by palpation.

4.27.1.2 Rare

Term Identifier	Term Name	Definition
HP:0003236	Elevated serum creatine kinase	An elevation of the level of the enzyme creatine kinase (also known as creatine phosphokinase, CPK; EC 2.7.3.2) in the blood. CPK levels can be elevated in a number of clinical disorders such as myocardial infarction, rhabdomyolysis, and muscular dystrophy.
HP:0025435	Increased lactate dehydrogenase activity	An elevated activity of the enzyme lactate dehydrogenase in serum.
HP:0011800	Midface retrusion	Posterior positions and/or vertical shortening of the infraorbital and perialar regions, or increased concavity of the face and/or reduced nasolabial angle.
HP:0001875	Neutropenia	An abnormally low number of neutrophils in the peripheral blood.
HP:0007556	Plantar hyperkeratosis	Hyperkeratosis affecting the sole of the foot.
HP:0001029	Poikiloderma	Poikiloderma refers to a patch of skin with (1) reticulated hypopigmentation and

		hyperpigmentation, (2) wrinkling secondary to epidermal atrophy, and (3) telangiectasias.
HP:0000403	Recurrent otitis media	Increased susceptibility to otitis media, as manifested by recurrent episodes of otitis media.
HP:0006532	Recurrent pneumonia	An increased susceptibility to pneumonia as manifested by a history of recurrent episodes of pneumonia.
HP:0011108	Recurrent sinusitis	A recurrent form of sinusitis.
HP:0004322	Short stature	A height below that which is expected according to age and gender norms. Although there is no universally accepted definition of short stature, many refer to "short stature" as height more than 2 standard deviations below the mean for age and gender (or below the 3rd percentile for age and gender dependent norms).
HP:0001744	Splenomegaly	Abnormal increased size of the spleen.

4.27.1.3 No frequency available

Term Identifier	Term Name	Definition
HP:0000007	Autosomal recessive inheritance	A mode of inheritance that is observed for traits related to a gene encoded on one of the autosomes (i.e., the human chromosomes 1-22) in which a trait manifests in individuals with two pathogenic alleles, either homozygotes (two copies of the same mutant allele) or compound heterozygotes (whereby each copy of a gene has a distinct mutant allele).
HP:0000498	Blepharitis	Inflammation of the eyelids.
HP:0000509	Conjunctivitis	Inflammation of the conjunctiva.

Source: National Center for Advancing Translational Sciences – GARD (last updated 01.08.2019);
OMIM Clinical synopsis #604173 – Creation date: 02.11.2011, Marla J.F. O’Neill

4.28 COHEN syndrome

4.28.1.1 Very frequent

Term Identifier	Term Name	Definition
HP:0000164	Abnormality of the dentition	Any abnormality of the teeth.
HP:0000499	Abnormal eyelash morphology	An abnormality of the eyelashes.

HP:0000492	Abnormal eyelid morphology	An abnormality of the eyelids.
HP:0010295	Aplasia/Hypoplasia of the tongue	Absence or underdevelopment of the tongue.
HP:0001166	Arachnodactyly	Abnormally long and slender fingers ("spider fingers").
HP:0010669	Hypoplasia of the zygomatic bone	Underdevelopment of the zygomatic bone [UBERON_0001683]. That is, a reduction in size of the zygomatic bone, including the zygomatic process of the temporal bone of the skull, which forms part of the zygomatic arch.
HP:0001135	Chorioretinal dystrophy	
HP:0000494	Downslanted palpebral fissures	The palpebral fissure inclination is more than two standard deviations below the mean.
HP:0000212	Gingival overgrowth	Hyperplasia of the gingiva (that is, a thickening of the soft tissue overlying the alveolar ridge. The degree of thickening ranges from involvement of the interdental papillae alone to gingival overgrowth covering the entire tooth crown.
HP:0001263	Global developmental delay	A delay in the achievement of motor or mental milestones in the domains of development of a child, including motor skills, speech and language, cognitive skills, and social and emotional skills. This term should only be used to describe children younger than five years of age.
HP:0002705	High, narrow palate	The presence of a high and narrow palate.
HP:0000327	Hypoplasia of the maxilla	Abnormally small dimension of the Maxilla. Usually creating a malocclusion or malalignment between the upper and lower teeth or resulting in a deficient amount of projection of the base of the nose and lower midface region.
HP:0001249	Intellectual disability	Subnormal intellectual functioning which originates during the developmental period. Intellectual disability, previously referred to as mental retardation, has been defined as an IQ score below 70.
HP:0000527	Long eyelashes	Mid upper eyelash length >10 mm or increased length of the eyelashes (subjective).
HP:0000294	Low anterior hairline	Distance between the hairline (trichion) and the glabella (the most prominent point on the frontal bone above the root of the nose), in the midline, more than two SD below the mean. Alternatively, an

		apparently decreased distance between the hairline and the glabella.
HP:0000252	Microcephaly	Head circumference below 2 standard deviations below the mean for age and gender.
HP:0000347	Micrognathia	Developmental hypoplasia of the mandible.
HP:0001252	Muscular hypotonia	Muscular hypotonia is an abnormally low muscle tone (the amount of tension or resistance to movement in a muscle), often involving reduced muscle strength. Hypotonia is characterized by a diminished resistance to passive stretching.
HP:0000545	Myopia	An abnormality of refraction characterized by the ability to see objects nearby clearly, while objects in the distance appear blurry.
HP:0002167	Neurological speech impairment	
HP:0001875	Neutropenia	An abnormally low number of neutrophils in the peripheral blood.
HP:0000194	Open mouth	A facial appearance characterized by a permanently or nearly permanently opened mouth.
HP:0000426	Prominent nasal bridge	Anterior positioning of the nasal root in comparison to the usual positioning for age.
HP:0009804	Reduced number of teeth	The presence of a reduced number of teeth as in Hypodontia or as in Anodontia.
HP:0001852	Sandal gap	A widely spaced gap between the first toe (the great toe) and the second toe.
HP:0000322	Short philtrum	Distance between nasal base and midline upper lip vermilion border more than 2 SD below the mean. Alternatively, an apparently decreased distance between nasal base and midline upper lip vermilion border.
HP:0011308	Slender toe	Toes that are disproportionately narrow (reduced girth) for the hand/foot size or build of the individual.
HP:0001182	Tapered finger	The gradual reduction in girth of the finger from proximal to distal.
HP:0000574	Thick eyebrow	Increased density/number and/or increased diameter of eyebrow hairs.

4.28.1.2 Frequent

Term Identifier	Term Name	Definition
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HP:0001000	Abnormality of skin pigmentation	An abnormality of the pigmentation of the skin.
HP:0200046	Cat cry	The presence of a characteristic high-pitched cry that sounds similar to the meowing of a kitten.
HP:0004209	Clinodactyly of the 5th finger	Clinodactyly refers to a bending or curvature of the fifth finger in the radial direction (i.e., towards the 4th finger).
HP:0002967	Cubitus valgus	Abnormal positioning in which the elbows are turned out.
HP:0001558	Decreased fetal movement	An abnormal reduction in quantity or strength of fetal movements.
HP:0000823	Delayed puberty	Passing the age when puberty normally occurs with no physical or hormonal signs of the onset of puberty.
HP:0001531	Failure to thrive in infancy	
HP:0008872	Feeding difficulties in infancy	Impaired feeding performance of an infant as manifested by difficulties such as weak and ineffective sucking, brief bursts of sucking, and falling asleep during sucking. There may be difficulties with chewing or maintaining attention.
HP:0006101	Finger syndactyly	Webbing or fusion of the fingers, involving soft parts only or including bone structure. Bony fusions are referred to as "bony" Syndactyly if the fusion occurs in a radio-ulnar axis. Fusions of bones of the fingers in a proximo-distal axis are referred to as "Symphalangism".
HP:0002857	Genu valgum	The legs angle inward, such that the knees are close together and the ankles far apart.
HP:0001511	Intrauterine growth retardation	An abnormal restriction of fetal growth with fetal weight below the tenth percentile for gestational age.
HP:0005692	Joint hyperflexibility	Increased mobility and flexibility in the joint due to the tension in tissues such as ligaments and muscles.
HP:0001572	Macrodonia	Increased size of the teeth, which can be defined as a mesiodistal tooth diameter (width) more than 2 SD above mean for age. Alternatively, an apparently increased maximum width of the tooth.
HP:0004283	Narrow palm	For children from birth to 4 years of age, the palm width is more than 2 SD below the mean; for children from 4 to 16 years of age the palm width is below the 5th centile; or, the width of the palm appears disproportionately narrow for its length.
HP:0001513	Obesity	Accumulation of substantial excess body fat.

HP:0004322	Short stature	A height below that which is expected according to age and gender norms. Although there is no universally accepted definition of short stature, many refer to "short stature" as height more than 2 standard deviations below the mean for age and gender (or below the 3rd percentile for age and gender dependent norms).
HP:0100874	Thick hair	Increased density of hairs, i.e., and elevated number of hairs per unit area.
HP:0001612	Weak cry	

4.28.1.3 Occasional

Term Identifier	Term Name	Definition
HP:0007703	Abnormality of retinal pigmentation	
HP:0003272	Abnormality of the hip bone	An abnormality of the hip bone.
HP:0009906	Aplasia/Hypoplasia of the earlobes	Absence or underdevelopment of the ear lobes.
HP:0000028	Cryptorchidism	Testis in inguinal canal. That is, absence of one or both testes from the scrotum owing to failure of the testis or testes to descend through the inguinal canal to the testis.
HP:0000612	Iris coloboma	A coloboma of the iris.
HP:0002808	Kyphosis	Exaggerated anterior convexity of the thoracic vertebral column.
HP:0000568	Microphthalmia	A developmental anomaly characterized by abnormal smallness of one or both eyes.
HP:0001634	Mitral valve prolapse	One or both of the leaflets (cusps) of the mitral valve bulges back into the left atrium upon contraction of the left ventricle.
HP:0000639	Nystagmus	Rhythmic, involuntary oscillations of one or both eyes related to abnormality in fixation, conjugate gaze, or vestibular mechanisms.
HP:0000648	Optic atrophy	Atrophy of the optic nerve. Optic atrophy results from the death of the retinal ganglion cell axons that comprise the optic nerve and manifesting as a pale optic nerve on funduscopy.
HP:0000767	Pectus excavatum	A defect of the chest wall characterized by a depression of the sternum, giving the chest ("pectus") a caved-in ("excavatum") appearance.

HP:0000384	Preauricular skin tag	A rudimentary tag of skin often containing ear tissue including a core of cartilage and located just anterior to the auricle (outer part of the ear).
HP:0002650	Scoliosis	The presence of an abnormal lateral curvature of the spine.
HP:0001250	Seizures	Seizures are an intermittent abnormality of the central nervous system due to a sudden, excessive, disorderly discharge of cerebral neurons and characterized clinically by some combination of disturbance of sensation, loss of consciousness, impairment of psychic function, or convulsive movements. The term epilepsy is used to describe chronic, recurrent seizures.
HP:0000407	Sensorineural hearing impairment	A type of hearing impairment in one or both ears related to an abnormal functionality of the cochlear nerve.
HP:0000486	Strabismus	A misalignment of the eyes so that the visual axes deviate from bifoveal fixation. The classification of strabismus may be based on a number of features including the relative position of the eyes, whether the deviation is latent or manifest, intermittent or constant, concomitant or otherwise and according to the age of onset and the relevance of any associated refractive error.
HP:0001629	Ventricular septal defect	A hole between the two bottom chambers (ventricles) of the heart. The defect is centered around the most superior aspect of the ventricular septum.

Source: HPO-ORDO Ontological Module (21) - Validation association date: 01.06.2016

4.29 Common variable immunodeficiency disorders (CVID)

4.29.1.1 Very frequent

Term Identifier	Term Name	Definition
HP:0001973	Autoimmune thrombocytopenia	The presence of thrombocytopenia in combination with detection of antiplatelet antibodies.
HP:0000248	Brachycephaly	An abnormality of skull shape characterized by a decreased anterior-posterior diameter. That is, a cephalic index greater than 81%. Alternatively, an apparently shortened anteroposterior dimension (length) of the head compared to width.

HP:0000389	Chronic otitis media	Chronic otitis media refers to fluid, swelling, or infection of the middle ear that does not heal and may cause permanent damage to the ear.
HP:0002721	Immunodeficiency	Failure of the immune system to protect the body adequately from infection, due to the absence or insufficiency of some component process or substance.
HP:0001888	Lymphopenia	A reduced number of lymphocytes in the blood.
HP:0000388	Otitis media	Inflammation or infection of the middle ear.
HP:0002090	Pneumonia	Inflammation of any part of the lung parenchyma.
HP:0002205	Recurrent respiratory infections	An increased susceptibility to respiratory infections as manifested by a history of recurrent respiratory infections.
HP:0002837	Recurrent bronchitis	An increased susceptibility to bronchitis as manifested by a history of recurrent bronchitis.

4.29.1.2 Frequent

Term Identifier	Term Name	Definition
HP:0001392	Abnormality of the liver	An abnormality of the liver.
HP:0002023	Anal atresia	Congenital absence of the anus, i.e., the opening at the bottom end of the intestinal tract.
HP:0002110	Bronchiectasis	Persistent abnormal dilatation of the bronchi owing to localized and irreversible destruction and widening of the large airways.
HP:0002910	Elevated hepatic transaminase	Elevations of the levels of SGOT and SGPT in the serum. SGOT (serum glutamic oxaloacetic transaminase) and SGPT (serum glutamic pyruvic transaminase) are transaminases primarily found in the liver and heart and are released into the bloodstream as the result of liver or heart damage. SGOT and SGPT are used clinically mainly as markers of liver damage.
HP:0001878	Hemolytic anemia	A type of anemia caused by premature destruction of red blood cells (hemolysis).
HP:0002716	Lymphadenopathy	Enlargement (swelling) of a lymph node.
HP:0000979	Purpura	Purpura (from Latin: purpura, meaning "purple") is the appearance of red or purple discolorations on the skin that do not

		blanch on applying pressure. They are caused by bleeding underneath the skin. This term refers to an abnormally increased susceptibility to developing purpura. Purpura are larger than petechiae.
HP:0001744	Splenomegaly	Abnormal increased size of the spleen.

4.29.1.3 Occasional

Term Identifier	Term Name	Definition
HP:0002829	Arthralgia	Joint pain.
HP:0002097	Emphysema	
HP:0001531	Failure to thrive in infancy	
HP:0100723	Gastrointestinal stroma tumor	
HP:0002665	Lymphoma	A cancer originating in lymphocytes and presenting as a solid tumor of lymphoid cells.
HP:0006783	Posterior pharyngeal cleft	
HP:0002091	Restrictive ventilatory defect	A functional defect characterized by reduced total lung capacity (TLC) not associated with abnormalities of expiratory airflow or airway resistance. Restrictive lung disease may be caused by alterations in lung parenchyma or because of a disease of the pleura, chest wall, or neuromuscular apparatus.
HP:0002633	Vasculitis	Inflammation of blood vessel.

Source: HPO-ORDO Ontological Module (21) - Validation association date: 01.06.2016

4.30 Congenital neutropenia

4.30.1.1 Always present

Term Identifier	Term Name	Definition
HP:0001875	Neutropenia	An abnormally low number of neutrophils in the peripheral blood.

4.30.1.2 Very frequent

Term Identifier	Term Name	Definition
HP:0002718	Recurrent bacterial infections	Increased susceptibility to bacterial infections, as manifested by recurrent episodes of bacterial infection.

HP:0004429	Recurrent viral infections	Increased susceptibility to viral infections, as manifested by recurrent episodes of viral infection.
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4.30.1.3 Frequent

Term Identifier	Term Name	Definition
HP:0002027	Abdominal pain	An unpleasant sensation characterized by physical discomfort (such as pricking, throbbing, or aching) and perceived to originate in the abdomen.
HP:0002014	Diarrhea	Abnormally increased frequency of loose or watery bowel movements.
HP:0001945	Fever	Elevated body temperature due to failed thermoregulation.
HP:0000230	Gingivitis	Inflammation of the gingiva.
HP:0001888	Lymphopenia	A reduced number of lymphocytes in the blood.
HP:0012311	Monocytosis	An increased number of circulating monocytes.
HP:0000155	Oral ulcer	Erosion of the mucous membrane of the mouth with local excavation of the surface, resulting from the sloughing of inflammatory necrotic tissue.
HP:0000704	Periodontitis	Inflammation of the periodontium.
HP:0025439	Pharyngitis	Inflammation (due to infection or irritation) of the pharynx.
HP:0002090	Pneumonia	Inflammation of any part of the lung parenchyma.
HP:0011107	Recurrent aphthous stomatitis	Recurrent episodes of ulceration of the oral mucosa, typically presenting as painful, sharply circumscribed fibrin-covered mucosal defects with a hyperemic border.
HP:0410018	Recurrent ear infections	Increased susceptibility to ear infections, as manifested by recurrent episodes of ear infections.
HP:0001581	Recurrent skin infections	Infections of the skin that happen multiple times.
HP:0005425	Recurrent sinopulmonary infections	An increased susceptibility to infections involving both the paranasal sinuses and the lungs, as manifested by a history of recurrent sinopulmonary infections.
HP:0004798	Recurrent infection of the gastrointestinal tract	Recurrent infection of the gastrointestinal tract.
HP:0012384	Rhinitis	Inflammation of the nasal mucosa with nasal congestion.

4.30.1.4 Occasional

Term Identifier	Term Name	Definition
HP:0006721	Acute lymphoblastic leukemia	A form of acute leukemia characterized by excess lymphoblasts.
HP:0004808	Acute myeloid leukemia	A form of leukemia characterized by overproduction of an early myeloid cell.
HP:0003453	Antineutrophil antibody positivity	The presence of autoantibodies in the serum that react against neutrophils.
HP:0001915	Aplastic anemia	Aplastic anemia is defined as pancytopenia with a hypocellular marrow.
HP:0100658	Cellulitis	A bacterial infection and inflammation of the skin and subcutaneous tissues.
HP:0001880	Eosinophilia	Increased count of eosinophils in the blood.
HP:0001028	Hemangioma	A hemangioma is a benign tumor characterized by blood-filled spaces lined by benign endothelial cells. A hemangioma characterized by large endothelial spaces (caverns) is called a cavernous hemangioma (in contrast to a hemangioma with small endothelial spaces, which is called capillary hemangioma).
HP:0001909	Leukemia	A cancer of the blood and bone marrow characterized by an abnormal proliferation of leukocytes.
HP:0002863	Myelodysplasia	Clonal hematopoietic stem cell disorders characterized by dysplasia (ineffective production) in one or more hematopoietic cell lineages, leading to anemia and cytopenia.
HP:0000938	Osteopenia	Osteopenia is a term to define bone density that is not normal but also not as low as osteoporosis. By definition from the World Health Organization osteopenia is defined by bone densitometry as a T score -1 to -2.5.
HP:0006480	Premature loss of teeth	Premature loss of teeth not related to trauma or neglect.
HP:0025452	Pyoderma gangrenosum	A deep skin ulcer with a well defined border, which is usually violet or blue. The ulcer edge is often undermined (worn and damaged) and the surrounding skin is erythematous and indurated. The ulcer often starts as a small papule or collection of papules, which break down to form small ulcers with a so called cat's paw appearance. These coalesce and

		the central area then undergoes necrosis to form a single ulcer.
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Source: HPO-ORDO Ontological Module (21) - Validation association date: 16.04.2019 - PMID:28593997 (40), PMID:28875503 (41)

*applies only to autosomal dominant congenital neutropenia

4.31 Cyclic neutropenia

4.31.1.1 Very frequent

Term Identifier	Term Name	Definition
HP:0001903	Anemia	A reduction in erythrocytes volume or hemoglobin concentration.
HP:0012378	Fatigue	A subjective feeling of tiredness characterized by a lack of energy and motivation.
HP:0001875	Neutropenia	An abnormally low number of neutrophils in the peripheral blood.
HP:0000155	Oral ulcer	Erosion of the mucous mebrane of the mouth with local excavation of the surface, resulting from the sloughing of inflammatory necrotic tissue.
HP:0001845	Overlapping toe	Describes a foot digit resting on the dorsal surface of an adjacent digit when the foot is at rest.
HP:0001581	Recurrent skin infections	Infections of the skin that happen multiple times.
HP:0100806	Sepsis	Systemic inflammatory response to infection.

4.31.1.2 Frequent

Term Identifier	Term Name	Definition
HP:0000704	Periodontitis	Inflammation of the periodontium.

4.31.1.3 Occasional

Term Identifier	Term Name	Definition
HP:0002027	Abdominal pain	An unpleasant sensation characterized by physical discomfort (such as pricking, throbbing, or aching) and perceived to originate in the abdomen.
HP:0001879	Abnormal eosinophil morphology	An abnormal count or structure of eosinophils.
HP:0000670	Carious teeth	Caries is a multifactorial bacterial infection affecting the structure of the tooth. This term has been used to

		describe the presence of more than expected dental caries.
HP:0002716	Lymphadenopathy	Enlargement (swelling) of a lymph node.
HP:0002205	Recurrent respiratory infections	An increased susceptibility to respiratory infections as manifested by a history of recurrent respiratory infections.
HP:0011107	Recurrent aphthous stomatitis	Recurrent episodes of ulceration of the oral mucosa, typically presenting as painful, sharply circumscribed fibrin-covered mucosal defects with a hyperemic border.
HP:0001873	Thrombocytopenia	A reduction in the number of circulating thrombocytes.

Source: HPO-ORDO Ontological Module (21) - Validation association date: 01.06.2016

4.32 Defects in TLR/NFkappa-B signalling

4.32.1.1 Very frequent

Term Identifier	Term Name	Definition
HP:0002721	Immunodeficiency	Failure of the immune system to protect the body adequately from infection, due to the absence or insufficiency of some component process or substance.
HP:0001875	Neutropenia	An abnormally low number of neutrophils in the peripheral blood.
HP:0002718	Recurrent bacterial infections	Increased susceptibility to bacterial infections, as manifested by recurrent episodes of bacterial infection.
HP:0007499	Recurrent staphylococcal infections	Increased susceptibility to staphylococcal infections, as manifested by recurrent episodes of staphylococcal infections.
HP:0005366	Recurrent streptococcus pneumoniae infections	Increased susceptibility to streptococcus pneumoniae infections as manifested by a history of recurrent infections by streptococcus pneumoniae.

Source: HPO-ORDO Ontological Module (21) - Validation association date: 01.06.2016

*applies only to Immunodeficiency due to interleukin-1 receptor-associated kinase-4 deficiency

4.33 DiGeorge syndrome

4.33.1.1 Very frequent

Term Identifier	Term Name	Definition
HP:0001999	Abnormal facial shape	An abnormal morphology (form) of the face or its components.
HP:0012303	Abnormal aortic arch morphology	An anomaly of the arch of aorta.
HP:0000600	Abnormality of the pharynx	An anomaly of the pharynx, i.e., of the tubular structure extending from the base of the skull superiorly to the esophageal inlet inferiorly.
HP:0001641	Abnormal pulmonary valve morphology	Any structural abnormality of the pulmonary valve.
HP:0001631	Atrial septal defect	Atrial septal defect (ASD) is a congenital abnormality of the interatrial septum that enables blood flow between the left and right atria via the interatrial septum.
HP:0000414	Bulbous nose	Increased volume and globular shape of the anteroinferior aspect of the nose.
HP:0000175	Cleft palate	Cleft palate is a developmental defect of the palate resulting from a failure of fusion of the palatine processes and manifesting as a separation of the roof of the mouth (soft and hard palate).
HP:0000405	Conductive hearing impairment	An abnormality of vibrational conductance of sound to the inner ear leading to impairment of sensory perception of sound.
HP:0002357	Dysphasia	
HP:0000286	Epicanthus	A fold of skin starting above the medial aspect of the upper eyelid and arching downward to cover, pass in front of and lateral to the medial canthus.
HP:0000778	Hypoplasia of the thymus	Underdevelopment of the thymus.
HP:0002721	Immunodeficiency	Failure of the immune system to protect the body adequately from infection, due to the absence or insufficiency of some component process or substance.
HP:0000369	Low-set ears	Upper insertion of the ear to the scalp below an imaginary horizontal line drawn between the inner canthi of the eye and extending posteriorly to the ear.
HP:0001252	Muscular hypotonia	Muscular hypotonia is an abnormally low muscle tone (the amount of tension or resistance to movement in a muscle), often involving reduced muscle strength.

		Hypotonia is characterized by a diminished resistance to passive stretching.
HP:0001611	Nasal speech	A type of speech characterized by the presence of an abnormally increased nasal airflow during speech.
HP:0002691	Platybasia	A developmental malformation of the occipital bone and upper end of the cervical spine, in which the latter appears to have pushed the floor of the occipital bone upward such that there is an abnormal flattening of the skull base.
HP:0000426	Prominent nasal bridge	Anterior positioning of the nasal root in comparison to the usual positioning for age.
HP:0000506	Telecanthus	Distance between the inner canthi more than two standard deviations above the mean (objective); or, apparently increased distance between the inner canthi.
HP:0001636	Tetralogy of Fallot	A congenital cardiac malformation comprising pulmonary stenosis, overriding aorta, ventricular septum defect, and right ventricular hypertrophy. The diagnosis of TOF is made if at least three of the four above mentioned features are present.
HP:0001660	Truncus arteriosus	A single arterial trunk arises from the cardiac mass. The pulmonary arteries, aorta and coronary arteries arise from this single trunk with no evidence of another outflow tract.
HP:0000582	Upslanted palpebral fissure	The palpebral fissure inclination is more than two standard deviations above the mean for age (objective); or, the inclination of the palpebral fissure is greater than typical for age.
HP:0001629	Ventricular septal defect	A hole between the two bottom chambers (ventricles) of the heart. The defect is centered around the most superior aspect of the ventricular septum.
HP:0000431	Wide nasal bridge	Increased breadth of the nasal bridge (and with it, the nasal root).
HP:0030680	Abnormality of cardiovascular system morphology	Any structural anomaly of the heart and great vessels.

4.33.1.2 Frequent

Term Identifier	Term Name	Definition
HP:0000164	Abnormality of the dentition	Any abnormality of the teeth.
HP:0000492	Abnormal eyelid morphology	An abnormality of the eyelids.
HP:0000929	Abnormal skull morphology	An abnormality of the skull, the bony framework of the head which is comprised of eight cranial and fourteen facial bones.
HP:0100765	Abnormality of the tonsils	An abnormality of the tonsils.
HP:0001061	Acne	A skin condition in which there is an increase in sebum secretion by the pilosebaceous apparatus associated with open comedones (blackheads), closed comedones (whiteheads), and pustular nodules (papules, pustules, and cysts).
HP:0012732	Anorectal anomaly	An abnormality of the anus or rectum.
HP:0001166	Arachnodactyly	Abnormally long and slender fingers ("spider fingers").
HP:0007018	Attention deficit hyperactivity disorder	Attention deficit hyperactivity disorder (ADHD) manifests at age 2-3 years or by first grade at the latest. The main symptoms are distractibility, impulsivity, hyperactivity, and often trouble organizing tasks and projects, difficulty going to sleep, and social problems from being aggressive, loud, or impatient.
HP:0000670	Carious teeth	Caries is a multifactorial bacterial infection affecting the structure of the tooth. This term has been used to describe the presence of more than expected dental caries.
HP:0000389	Chronic otitis media	Chronic otitis media refers to fluid, swelling, or infection of the middle ear that does not heal and may cause permanent damage to the ear.
HP:0002019	Constipation	Infrequent or difficult evacuation of feces.
HP:0011496	Corneal neovascularization	Ingrowth of new blood vessels into the cornea.
HP:0001263	Global developmental delay	A delay in the achievement of motor or mental milestones in the domains of development of a child, including motor skills, speech and language, cognitive skills, and social and emotional skills. This term should only be used to describe children younger than five years of age.

HP:0000365	Hearing impairment	A decreased magnitude of the sensory perception of sound.
HP:0002901	Hypocalcemia	An abnormally decreased calcium concentration in the blood.
HP:0000829	Hypoparathyroidism	A condition caused by a deficiency of parathyroid hormone characterized by hypocalcemia and hyperphosphatemia.
HP:0005435	Impaired T cell function	Abnormally reduced ability of T cells to perform their functions in cell-mediated immunity.
HP:0001256	Intellectual disability, mild	Mild intellectual disability is defined as an intelligence quotient (IQ) in the range of 50-69.
HP:0000276	Long face	Facial height (length) is more than 2 standard deviations above the mean (objective); or, an apparent increase in the height (length) of the face (subjective).
HP:0000343	Long philtrum	Distance between nasal base and midline upper lip vermilion border more than 2 SD above the mean. Alternatively, an apparently increased distance between nasal base and midline upper lip vermilion border.
HP:0000272	Malar flattening	Underdevelopment of the malar prominence of the jugal bone (zygomatic bone in mammals), appreciated in profile, frontal view, and/or by palpation.
HP:0002435	Meningocele	Protrusion of the meninges through a defect of the vertebral column.
HP:0003326	Myalgia	Pain in muscle.
HP:0007271	Occipital myelomeningocele	
HP:0000396	Overfolded helix	A condition in which the helix is folded over to a greater degree than normal. That is, excessive curling of the helix edge, whereby the free edge is parallel to the plane of the ear.
HP:0000627	Posterior embryotoxon	A posterior embryotoxon is the presence of a prominent and anteriorly displaced line of Schwalbe.
HP:0000508	Ptosis	The upper eyelid margin is positioned 3 mm or more lower than usual and covers the superior portion of the iris (objective); or, the upper lid margin obscures at least part of the pupil (subjective).
HP:0000089	Renal hypoplasia	Hypoplasia of the kidney.
HP:0001051	Seborrheic dermatitis	Seborrheic dermatitis is a form of eczema which is closely related to dandruff. It causes dry or greasy peeling of the scalp,

		eyebrows, and face, and sometimes trunk.
HP:0000470	Short neck	Diminished length of the neck.
HP:0004322	Short stature	A height below that which is expected according to age and gender norms. Although there is no universally accepted definition of short stature, many refer to "short stature" as height more than 2 standard deviations below the mean for age and gender (or below the 3rd percentile for age and gender dependent norms).
HP:0000385	Small earlobe	Reduced volume of the earlobe.
HP:0001328	Specific learning disability	Impairment of certain skills such as reading or writing, coordination, self-control, or attention that interfere with the ability to learn. The impairment is not related to a global deficiency of intelligence.
HP:0001281	Tetany	A condition characterized by intermittent involuntary contraction of muscles (spasms) related to hypocalcemia or occasionally magnesium deficiency.

4.33.1.3 Occasional

Term Identifier	Term Name	Definition
HP:0000682	Abnormality of dental enamel	An abnormality of the dental enamel.
HP:0001646	Abnormal aortic valve morphology	Any abnormality of the aortic valve.
HP:0000765	Abnormality of the thorax	Any abnormality of the thorax (the region of the body formed by the sternum, the thoracic vertebrae and the ribs).
HP:0000130	Abnormality of the uterus	An abnormality of the uterus.
HP:0001872	Abnormal thrombocyte morphology	An abnormality of platelets.
HP:0002251	Aganglionic megacolon	An abnormality resulting from a lack of intestinal ganglion cells (i.e., an aganglionic section of bowel) that results in bowel obstruction with enlargement of the colon.
HP:0002023	Anal atresia	Congenital absence of the anus, i.e., the opening at the bottom end of the intestinal tract.

HP:0000739	Anxiety	Intense feelings of nervousness, tenseness, or panic, often in reaction to interpersonal stresses; worry about the negative effects of past unpleasant experiences and future negative possibilities; feeling fearful, apprehensive, or threatened by uncertainty; fears of falling apart or losing control.
HP:0002139	Arrhinencephaly	
HP:0001369	Arthritis	Inflammation of a joint.
HP:0002099	Asthma	Asthma is characterized by increased responsiveness of the tracheobronchial tree to multiple stimuli, leading to narrowing of the air passages with resultant dyspnea, cough, and wheezing.
HP:0100750	Atelectasis	Collapse of part of a lung associated with absence of inflation (air) of that part.
HP:0000717	Autism	Autism is a neurodevelopmental disorder characterized by impaired social interaction and communication, and by restricted and repetitive behavior. Autism begins in childhood. It is marked by the presence of markedly abnormal or impaired development in social interaction and communication and a markedly restricted repertoire of activity and interest. Manifestations of the disorder vary greatly depending on the developmental level and chronological age of the individual (DSM-IV).
HP:0002960	Autoimmunity	The occurrence of an immune reaction against the organism's own cells or tissues.
HP:0000708	Behavioral abnormality	An abnormality of mental functioning including various affective, behavioural, cognitive and perceptual abnormalities.
HP:0007302	Bipolar affective disorder	
HP:0002607	Bowel incontinence	Involuntary fecal soiling in adults and children who have usually already been toilet trained.
HP:0000518	Cataract	A cataract is an opacity or clouding that develops in the crystalline lens of the eye or in its capsule.
HP:0000453	Choanal atresia	Absence or abnormal closure of the choana (the posterior nasal aperture).
HP:0001081	Cholelithiasis	Hard, pebble-like deposits that form within the gallbladder.
HP:0006510	Chronic obstructive pulmonary disease	An anomaly that is characterized progressive airflow obstruction that is only

		partly reversible, inflammation in the airways, and systemic effects or comorbidities.
HP:0000028	Cryptorchidism	Testis in inguinal canal. That is, absence of one or both testes from the scrotum owing to failure of the testis or testes to descend through the inguinal canal to the testis.
HP:0000716	Depressivity	Frequent feelings of being down, miserable, and/or hopeless; difficulty recovering from such moods; pessimism about the future; pervasive shame; feeling of inferior self-worth; thoughts of suicide and suicidal behavior.
HP:0000494	Downslanted palpebral fissures	The palpebral fissure inclination is more than two standard deviations below the mean.
HP:0001508	Failure to thrive	Failure to thrive (FTT) refers to a child whose physical growth is substantially below the norm.
HP:0008872	Feeding difficulties in infancy	Impaired feeding performance of an infant as manifested by difficulties such as weak and ineffective sucking, brief bursts of sucking, and falling asleep during sucking. There may be difficulties with chewing or maintaining attention.
HP:0001829	Foot polydactyly	A kind of polydactyly characterized by the presence of a supernumerary toe or toes.
HP:0002020	Gastroesophageal reflux	A condition in which the stomach contents leak backwards from the stomach into the esophagus through the lower esophageal sphincter.
HP:0002239	Gastrointestinal hemorrhage	Hemorrhage affecting the gastrointestinal tract.
HP:0000501	Glaucoma	Glaucoma refers loss of retinal ganglion cells in a characteristic pattern of optic neuropathy usually associated with increased intraocular pressure.
HP:0001161	Hand polydactyly	A kind of polydactyly characterized by the presence of a supernumerary finger or fingers.
HP:0000238	Hydrocephalus	Hydrocephalus is an active distension of the ventricular system of the brain resulting from inadequate passage of CSF from its point of production within the cerebral ventricles to its point of absorption into the systemic circulation.
HP:0000316	Hypertelorism	Interpupillary distance more than 2 SD above the mean (alternatively, the appearance of an increased interpupillary distance or widely spaced eyes).

HP:0100735	Hypertensive crisis	
HP:0000836	Hyperthyroidism	An abnormality of thyroid physiology characterized by excessive secretion of the thyroid hormones thyroxine (i.e., T4) and/or 3,3',5-triiodo-L-thyronine zwitterion (i.e., triiodothyronine or T3).
HP:0000821	Hypothyroidism	Deficiency of thyroid hormone.
HP:0001053	Hypopigmented skin patches	
HP:0000047	Hypospadias	Abnormal position of urethral meatus on the ventral penile shaft (underside) characterized by displacement of the urethral meatus from the tip of the glans penis to the ventral surface of the penis, scrotum, or perineum.
HP:0000023	Inguinal hernia	Protrusion of the contents of the abdominal cavity through the inguinal canal.
HP:0001249	Intellectual disability	Subnormal intellectual functioning which originates during the developmental period. Intellectual disability, previously referred to as mental retardation, has been defined as an IQ score below 70.
HP:0002566	Intestinal malrotation	An abnormality of the intestinal rotation and fixation that normally occurs during the development of the gut. This can lead to volvulus, or twisting of the intestine that causes obstruction and necrosis.
HP:0001511	Intrauterine growth retardation	An abnormal restriction of fetal growth with fetal weight below the tenth percentile for gestational age.
HP:0005692	Joint hyperflexibility	Increased mobility and flexibility in the joint due to the tension in tissues such as ligaments and muscles.
HP:0001601	Laryngomalacia	Laryngomalacia is a congenital abnormality of the laryngeal cartilage in which the cartilage is floppy and prolapses over the larynx during inspiration.
HP:0000252	Microcephaly	Head circumference below 2 standard deviations below the mean for age and gender.
HP:0000347	Micrognathia	Developmental hypoplasia of the mandible.
HP:0000568	Microphthalmia	A developmental anomaly characterized by abnormal smallness of one or both eyes.
HP:0005562	Multiple renal cysts	The presence of many cysts in the kidney.
HP:0011324	Multiple suture craniosynostosis	Craniosynostosis involving at least 2 cranial sutures, where the exact pattern of sutures fused has not been precisely specified.
HP:0000160	Narrow mouth	Distance between the commissures of the mouth more than 2 SD below the mean.

		Alternatively, an apparently decreased width of the oral aperture (subjective).
HP:0001513	Obesity	Accumulation of substantial excess body fat.
HP:0000648	Optic atrophy	Atrophy of the optic nerve. Optic atrophy results from the death of the retinal ganglion cell axons that comprise the optic nerve and manifesting as a pale optic nerve on fundoscopy.
HP:0002999	Patellar dislocation	The kneecap normally is located within the groove termed trochlea on the distal femur and can slide up and down in it. Patellar dislocation occurs if the patella fully dislocates out of the groove.
HP:0001643	Patent ductus arteriosus	In utero, the ductus arteriosus (DA) serves to divert ventricular output away from the lungs and toward the placenta by connecting the main pulmonary artery to the descending aorta. A patent ductus arteriosus (PDA) in the first 3 days of life is a physiologic shunt in healthy term and preterm newborn infants, and normally is substantially closed within about 24 hours after birth and completely closed after about three weeks. Failure of physiological closure is referred to a persistent or patent ductus arteriosus (PDA). Depending on the degree of left-to-right shunting, PDA can have clinical consequences.
HP:0000113	Polycystic kidney dysplasia	The presence of multiple cysts in both kidneys.
HP:0001561	Polyhydramnios	The presence of excess amniotic fluid in the uterus during pregnancy.
HP:0000979	Purpura	Purpura (from Latin: purpura, meaning "purple") is the appearance of red or purple discolorations on the skin that do not blanch on applying pressure. They are caused by bleeding underneath the skin. This term refers to an abnormally increased susceptibility to developing purpura. Purpura are larger than petechiae.
HP:0001136	Retinal arteriolar tortuosity	The presence of an increased number of twists and turns of the retinal arterioles.
HP:0100753	Schizophrenia	A mental disorder characterized by a disintegration of thought processes and of emotional responsiveness. It most commonly manifests as auditory hallucinations, paranoid or bizarre delusions, or disorganized speech and

		thinking, and it is accompanied by significant social or occupational dysfunction. The onset of symptoms typically occurs in young adulthood, with a global lifetime prevalence of about 0.3-0.7%.
HP:0002650	Scoliosis	The presence of an abnormal lateral curvature of the spine.
HP:0001250	Seizures	Seizures are an intermittent abnormality of the central nervous system due to a sudden, excessive, disorderly discharge of cerebral neurons and characterized clinically by some combination of disturbance of sensation, loss of consciousness, impairment of psychic function, or convulsive movements. The term epilepsy is used to describe chronic, recurrent seizures.
HP:0000322	Short philtrum	Distance between nasal base and midline upper lip vermilion border more than 2 SD below the mean. Alternatively, an apparently decreased distance between nasal base and midline upper lip vermilion border.
HP:0002414	Spina bifida	Incomplete closure of the embryonic neural tube, whereby some vertebral arches remain unfused and open. The mildest form is spina bifida occulta, followed by meningocele and meningomyelocele.
HP:0001744	Splenomegaly	Abnormal increased size of the spleen.
HP:0000486	Strabismus	A misalignment of the eyes so that the visual axes deviate from bifoveal fixation. The classification of strabismus may be based on a number of features including the relative position of the eyes, whether the deviation is latent or manifest, intermittent or constant, concomitant or otherwise and according to the age of onset and the relevance of any associated refractive error.
HP:0001762	Talipes equinovarus	Talipes equinovarus (also called clubfoot) typically has four main components: inversion and adduction of the forefoot; inversion of the heel and hindfoot; equinus (limitation of extension) of the ankle and subtalar joint; and internal rotation of the leg.
HP:0001873	Thrombocytopenia	A reduction in the number of circulating thrombocytes.

HP:0011662	Tricuspid atresia	Failure to develop of the tricuspid valve and thus lack of the normal connection between the right atrium and the right ventricle.
HP:0000262	Turricephaly	Tall head relative to width and length.
HP:0001537	Umbilical hernia	Protrusion of abdominal contents through a defect in the abdominal wall musculature around the umbilicus. Skin and subcutaneous tissue overlie the defect.
HP:0002619	Varicose veins	Enlarged and tortuous veins.
HP:0000076	Vesicoureteral reflux	Abnormal (retrograde) movement of urine from the bladder into ureters or kidneys related to inadequacy of the valvular mechanism at the ureterovesicular junction or other causes.

Source: HPO-ORDO Ontological Module (21) - Validation association date: 01.06.2016

4.34 *Dyskeratosis congenita*

4.34.1.1 Very frequent

Term Identifier	Term Name	Definition
HP:0008066	Abnormal blistering of the skin	The presence of one or more bullae on the skin, defined as fluid-filled blisters more than 5 mm in diameter with thin walls.
HP:0001874	Abnormality of neutrophils	A neutrophil abnormality.
HP:0001231	Abnormal fingernail morphology	An abnormality of the fingernails.
HP:0001903	Anemia	A reduction in erythrocytes volume or hemoglobin concentration.
HP:0001034	Hypermelanotic macule	A hyperpigmented circumscribed area of change in normal skin color without elevation or depression of any size.
HP:0012733	Macule	A flat, distinct, discolored area of skin less than 1 cm wide that does not involve any change in the thickness or texture of the skin.
HP:0008404	Nail dystrophy	Onychodystrophy (nail dystrophy) refers to nail changes apart from changes of the color (nail dyschromia) and involves partial or complete disruption of the various keratinous layers of the nail plate.
HP:0002745	Oral leukoplakia	A thickened white patch on the oral mucosa that cannot be rubbed off.
HP:0001873	Thrombocytopenia	A reduction in the number of circulating thrombocytes.

4.34.1.2 Frequent

Term Identifier	Term Name	Definition
HP:0001928	Abnormality of coagulation	An abnormality of the process of blood coagulation. That is, altered ability or inability of the blood to clot.
HP:0000008	Abnormality of female internal genitalia	An abnormality of the female internal genitalia.
HP:0000164	Abnormality of the dentition	Any abnormality of the teeth.
HP:0000600	Abnormality of the pharynx	An anomaly of the pharynx, i.e., of the tubular structure extending from the base of the skull superiorly to the esophageal inlet inferiorly.
HP:0012732	Anorectal anomaly	An abnormality of the anus or rectum.
HP:0008065	Aplasia/Hypoplasia of the skin	
HP:0010624	Aplastic/hypoplastic toenail	Absence or underdevelopment of the toenail.
HP:0005528	Bone marrow hypocellularity	A reduced number of hematopoietic cells present in the bone marrow relative to marrow fat.
HP:0000670	Carious teeth	Caries is a multifactorial bacterial infection affecting the structure of the tooth. This term has been used to describe the presence of more than expected dental caries.
HP:0005374	Cellular immunodeficiency	An immunodeficiency characterized by defective cell-mediated immunity or humoral immunity.
HP:0010450	Esophageal stenosis	An abnormal narrowing of the lumen of the esophagus.
HP:0001263	Global developmental delay	A delay in the achievement of motor or mental milestones in the domains of development of a child, including motor skills, speech and language, cognitive skills, and social and emotional skills. This term should only be used to describe children younger than five years of age.
HP:0000975	Hyperhidrosis	Abnormal excessive perspiration (sweating) despite the lack of appropriate stimuli like hot and humid weather.
HP:0001053	Hypopigmented skin patches	
HP:0001511	Intrauterine growth retardation	An abnormal restriction of fetal growth with fetal weight below the tenth percentile for gestational age.

HP:0000668	Hypodontia	A developmental anomaly characterized by a reduced number of teeth, whereby up to 6 teeth are missing.
HP:0002024	Malabsorption	Impaired ability to absorb one or more nutrients from the intestine.
HP:0000704	Periodontitis	Inflammation of the periodontium.
HP:0002757	Recurrent fractures	The repeated occurrence of bone fractures (implying an abnormally increased tendency for fracture).
HP:0002205	Recurrent respiratory infections	An increased susceptibility to respiratory infections as manifested by a history of recurrent respiratory infections.
HP:0100670	Rough bone trabeculation	
HP:0004322	Short stature	A height below that which is expected according to age and gender norms. Although there is no universally accepted definition of short stature, many refer to "short stature" as height more than 2 standard deviations below the mean for age and gender (or below the 3rd percentile for age and gender dependent norms).
HP:0008070	Sparse hair	Reduced density of hairs.
HP:0200042	Skin ulcer	A discontinuity of the skin exhibiting complete loss of the epidermis and often portions of the dermis and even subcutaneous fat.
HP:0000679	Taurodontia	Increased volume of dental pulp of permanent molar.
HP:0100585	Telangiectasia of the skin	Presence of small, permanently dilated blood vessels near the surface of the skin, visible as small focal red lesions.
HP:0002575	Tracheoesophageal fistula	An abnormal connection (fistula) between the esophagus and the trachea.
HP:0008661	Urethral stenosis	Abnormal narrowing of the urethra.

4.34.1.3 Occasional

Term Identifier	Term Name	Definition
HP:0000499	Abnormal eyelash morphology	An abnormality of the eyelashes.
HP:0000534	Abnormal eyebrow morphology	An abnormality of the eyebrow.
HP:0000035	Abnormal testis morphology	An anomaly of the testicle (the male gonad).

HP:0001596	Alopecia	Loss of hair from the head or body.
HP:0010885	Avascular necrosis	A disease where there is cellular death (necrosis) of bone components due to interruption of the blood supply.
HP:0000498	Blepharitis	Inflammation of the eyelids.
HP:0000518	Cataract	A cataract is an opacity or clouding that develops in the crystalline lens of the eye or in its capsule.
HP:0002514	Cerebral calcification	The presence of calcium deposition within brain structures.
HP:0001394	Cirrhosis	A chronic disorder of the liver in which liver tissue becomes scarred and is partially replaced by regenerative nodules and fibrotic tissue resulting in loss of liver function.
HP:0000819	Diabetes mellitus	A group of abnormalities characterized by hyperglycemia and glucose intolerance.
HP:0100627	Displacement of the urethral meatus	A displacement of the external urethral orifice from its normal position (in males normally placed at the tip of glans penis, in females normally placed about 2.5 cm behind the glans clitoridis and immediately in front of that of the vagina).
HP:0000365	Hearing impairment	A decreased magnitude of the sensory perception of sound.
HP:0001399	Hepatic failure	
HP:0002240	Hepatomegaly	Abnormally increased size of the liver.
HP:0000327	Hypoplasia of the maxilla	Abnormally small dimension of the Maxilla. Usually creating a malocclusion or malalignment between the upper and lower teeth or resulting in a deficient amount of projection of the base of the nose and lower midface region.
HP:0002665	Lymphoma	A cancer originating in lymphocytes and presenting as a solid tumor of lymphoid cells.
HP:0002894	Neoplasm of the pancreas	A tumor (abnormal growth of tissue) of the pancreas.
HP:0000939	Osteoporosis	Osteoporosis is a systemic skeletal disease characterized by low bone density and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility. According to the WHO criteria, osteoporosis is defined as a BMD that lies 2.5 standard deviations or more below the average value for young healthy adults (a T-score below -2.5 SD).
HP:0000982	Palmoplantar keratoderma	Abnormal thickening of the skin of the palms of the hands and the soles of the feet.
HP:0002216	Premature graying of hair	Development of gray hair at a younger than normal age.

HP:0200037	Skin vesicle	A circumscribed, fluid-containing, epidermal elevation generally considered less than 10mm in diameter at the widest point.
HP:0002650	Scoliosis	The presence of an abnormal lateral curvature of the spine.
HP:0001744	Splenomegaly	Abnormal increased size of the spleen.
HP:0011364	White hair	Hypopigmented hair that appears white.

Source: HPO-ORDO Ontological Module (21) - Validation association date: 01.06.2016

4.35 Early-onset inflammatory bowel disease

4.35.1.1 No frequency available

Term Identifier	Term Name	Definition
HP:0025084	Folliculitis	Inflammatory cells within the wall and ostia of the hair follicle, creating a follicular-based pustule.
HP:0004387	Enterocolitis	An inflammation of the colon and small intestine. However, most conditions are either categorized as Enteritis (inflammation of the small intestine) or Colitis (inflammation of the large intestine).
HP:0009789	Perianal abscess	The presence of an abscess located around the anus.
HP:0000007	Autosomal recessive inheritance	A mode of inheritance that is observed for traits related to a gene encoded on one of the autosomes (i.e., the human chromosomes 1-22) in which a trait manifests in individuals with two pathogenic alleles, either homozygotes (two copies of the same mutant allele) or compound heterozygotes (whereby each copy of a gene has a distinct mutant allele).
HP:0005224	Rectal abscess	A collection of pus in the area of the rectum.
HP:0000143	Rectovaginal fistula	The presence of a fistula between the vagina and the rectum.

OMIM Clinical synopsis #612567 – Creation date: 26.02.2015, Marla J.F. O’Neill

OMIM Clinical synopsis #613148 – Creation date: 06.05.2013, Marla J.F. O’Neill

4.36 Early-onset multi-organ autoimmune disease

4.36.1.1 No frequency available

Term Identifier	Term Name	Definition
HP:0000964	Eczema	Eczema is a form of dermatitis. The term eczema is broadly applied to a range of persistent skin conditions and can be related to a number of underlying

		conditions. Manifestations of eczema can include dryness and recurring skin rashes with redness, skin edema, itching and dryness, crusting, flaking, blistering, cracking, oozing, or bleeding.
HP:0002960	Autoimmunity	The occurrence of an immune reaction against the organism's own cells or tissues.
HP:0002608	Celiac disease	Celiac disease (CD) is an autoimmune condition affecting the small intestine, triggered by the ingestion of gluten, the protein fraction of wheat, barley, and rye. Clinical manifestations of CD are highly variable and include both gastrointestinal and non-gastrointestinal features. The hallmark of CD is an immune-mediated enteropathy. This term is included because the occurrence of CD is seen as a feature of a number of other diseases.
HP:0001890	Autoimmune hemolytic anemia	An autoimmune form of hemolytic anemia.
HP:0004313	Decreased antibody level in blood	An abnormally decreased level of immunoglobulin in blood.
HP:0002719	Recurrent infections	Increased susceptibility to infections.
HP:0000821	Hypothyroidism	Deficiency of thyroid hormone.
HP:0000819	Diabetes mellitus	A group of abnormalities characterized by hyperglycemia and glucose intolerance.
HP:0000823	Delayed puberty	Passing the age when puberty normally occurs with no physical or hormonal signs of the onset of puberty.
HP:0004322	Short stature	A height below that which is expected according to age and gender norms. Although there is no universally accepted definition of short stature, many refer to "short stature" as height more than 2 standard deviations below the mean for age and gender (or below the 3rd percentile for age and gender dependent norms).
HP:0000006	Autosomal dominant inheritance	A mode of inheritance that is observed for traits related to a gene encoded on one of the autosomes (i.e., the human chromosomes 1-22) in which a trait manifests in heterozygotes. In the context of medical genetics, an autosomal dominant disorder is caused when a single copy of the mutant allele is present. Males and females are affected equally, and can both transmit the disorder with a risk of

		50% for each child of inheriting the mutant allele.
HP:0001973	Autoimmune thrombocytopenia	The presence of thrombocytopenia in combination with detection of antiplatelet antibodies.
HP:0000164	Abnormality of the dentition	Any abnormality of the teeth.
HP:0006515	Interstitial pneumonitis	
HP:0001369	Arthritis	Inflammation of a joint.
HP:0000100	Nephrotic syndrome	Nephrotic syndrome is a collection of findings resulting from glomerular dysfunction with an increase in glomerular capillary wall permeability associated with pronounced proteinuria. Nephrotic syndrome refers to the constellation of clinical findings that result from severe renal loss of protein, with Proteinuria and hypoalbuminemia, edema, and hyperlipidemia.
HP:0012579	Minimal change glomerulonephritis	The presence of minimal changes visible by light microscopy but flattened and fused podocyte foot processes on electron microscopy in a person with nephrotic range proteinuria.
HP:0000093	Proteinuria	Increased levels of protein in the urine.

OMIM Clinical synopsis #615952 – Creation date: 20.08.2014, Cassandra L. Kniffin; updated: 23.05.2016, Cassandra L. Kniffin

OMIM Clinical synopsis #617006 – Creation date: 27.06.2016, Cassandra L. Kniffin

4.37 Epidermodysplasia verruciformis

4.37.1.1 Very frequent

Term Identifier	Term Name	Definition
HP:0200034	Papule	A circumscribed, solid elevation of skin with no visible fluid, varying in size from a pinhead to less than 10mm in diameter at the widest point.
HP:0200039	Pustule	A small elevation of the skin containing cloudy or purulent material usually consisting of necrotic inflammatory cells.
HP:0001581	Recurrent skin infections	Infections of the skin that happen multiple times.
HP:0001051	Seborrheic dermatitis	Seborrheic dermatitis is a form of eczema which is closely related to dandruff. It causes dry or greasy peeling of the scalp, eyebrows, and face, and sometimes trunk.

HP:0200035	Skin plaque	A plaque is a solid, raised, plateau-like (flat-topped) lesion greater than 1 cm in diameter.
HP:0200043	Verrucae	Warts, benign growths on the skin or mucous membranes that cause cosmetic problems as well as pain and discomfort. Warts most often occur on the hands, feet, and genital areas.
HP:0002715	Abnormality of the immune system	An abnormality of the immune system.

4.37.1.2 Frequent

Term Identifier	Term Name	Definition
HP:0001053	Hypopigmented skin patches	
HP:0007565	Multiple cafe-au-lait spots	The presence of six or more cafe-au-lait spots.

4.37.1.3 Occasional

Term Identifier	Term Name	Definition
HP:0002860	Squamous cell carcinoma	The presence of squamous cell carcinoma of the skin.
HP:0100585	Telangiectasia of the skin	Presence of small, permanently dilated blood vessels near the surface of the skin, visible as small focal red lesions.

Source: HPO-ORDO Ontological Module (21) - Validation association date: 01.06.2016

4.38 Factor B deficiency

4.38.1.1 No frequency available

Term Identifier	Term Name	Definition
HP:0002090	Pneumonia	Inflammation of any part of the lung parenchyma.
HP:0002718	Recurrent bacterial infections	Increased susceptibility to bacterial infections, as manifested by recurrent episodes of bacterial infection.
HP:0005381	Recurrent meningococcal disease	Recurrent infections by <i>Neisseria meningitidis</i> (one of the most common causes of bacterial meningitis), which is also known as meningococcus.
HP:0005416	Decreased serum complement factor B	A reduced level of the complement component factor B in circulation.
HP:0002586	Peritonitis	Inflammation of the peritoneum.

Source: OMIM #615561; Creation date: 12.12.2013, Cassandra L. Kniffin

4.39 Factor D Deficiency

4.39.1.1 No frequency available

Term Identifier	Term Name	Definition
HP:0002718	Recurrent bacterial infections	Increased susceptibility to bacterial infections, as manifested by recurrent episodes of bacterial infection.
HP:0004431	Complement deficiency	An immunodeficiency defined by the absent or suboptimal functioning of one of the complement system proteins.
HP:0000007	Autosomal recessive inheritance	A mode of inheritance that is observed for traits related to a gene encoded on one of the autosomes (i.e., the human chromosomes 1-22) in which a trait manifests in individuals with two pathogenic alleles, either homozygotes (two copies of the same mutant allele) or compound heterozygotes (whereby each copy of a gene has a distinct mutant allele).
HP:0005430	Recurrent Neisserial infections	Recurrent infections by bacteria of the genus Neisseria, including N. meningitidis (one of the most common causes of bacterial meningitis).

OMIM Clinical synopsis #613912 – Creation date: 15.06.1995, John F. Jackson; updated: 20.04.2011, Cassandra L. Kniffin

4.40 Factor H deficiency

4.40.1.1 No frequency available

Term Identifier	Term Name	Definition
HP:0004722	Thickening of the glomerular basement membrane	Increase in thickness of the basal lamina of the glomerulus of the kidney.
HP:0012622	Chronic kidney disease	Functional anomaly of the kidney persisting for at least three months.
HP:0004746	Glomerular subendothelial electron-dense deposits	Electron dense deposits at the glomerular basement membrane,
HP:0002718	Recurrent bacterial infections	Increased susceptibility to bacterial infections, as manifested by recurrent episodes of bacterial infection.

HP:0005369	Decreased serum complement factor H	A reduced level of the complement component Factor H in circulation.
HP:0005389	Depletion of components of the alternative complement pathway	An abnormal reduction in the components of the alternative complement pathway, such as the C3 protein or its cleavage products.
HP:0000007	Autosomal recessive inheritance	A mode of inheritance that is observed for traits related to a gene encoded on one of the autosomes (i.e., the human chromosomes 1-22) in which a trait manifests in individuals with two pathogenic alleles, either homozygotes (two copies of the same mutant allele) or compound heterozygotes (whereby each copy of a gene has a distinct mutant allele).
HP:0000006	Autosomal dominant inheritance	A mode of inheritance that is observed for traits related to a gene encoded on one of the autosomes (i.e., the human chromosomes 1-22) in which a trait manifests in heterozygotes. In the context of medical genetics, an autosomal dominant disorder is caused when a single copy of the mutant allele is present. Males and females are affected equally, and can both transmit the disorder with a risk of 50% for each child of inheriting the mutant allele.
HP:0000790	Hematuria	The presence of blood in the urine. Hematuria may be gross hematuria (visible to the naked eye) or microscopic hematuria (detected by dipstick or microscopic examination of the urine).

OMIM Clinical synopsis #609814 – Creation date: 27.09.2006, Cassandra L. Kniffin

4.41 Factor H related protein deficiency

4.41.1 aHUS1

4.41.1.1 No frequency available

Term Identifier	Term Name	Definition
HP:0100543	Cognitive impairment	Abnormality in the process of thought including the ability to process information.
HP:0001259	Coma	Complete absence of wakefulness and content of conscience, which manifests itself as a lack of response to any kind of external stimuli.

HP:0001269	Hemiparesis	Loss of strength in the arm, leg, and sometimes face on one side of the body. Hemiplegia refers to a complete loss of strength, whereas hemiparesis refers to an incomplete loss of strength.
HP:0001250	Seizures	Seizures are an intermittent abnormality of the central nervous system due to a sudden, excessive, disorderly discharge of cerebral neurons and characterized clinically by some combination of disturbance of sensation, loss of consciousness, impairment of psychic function, or convulsive movements. The term epilepsy is used to describe chronic, recurrent seizures.
HP:0002357	Dysphasia	
HP:0001873	Thrombocytopenia	A reduction in the number of circulating thrombocytes.
HP:0001981	Schistocytosis	The presence of an abnormal number of fragmented red blood cells (schistocytes) in the blood.
HP:0001923	Reticulocytosis	An elevation in the number of reticulocytes (immature erythrocytes) in the peripheral blood circulation.
HP:0001937	Microangiopathic hemolytic anemia	
HP:0003259	Elevated serum creatinine	An increased amount of creatinine in the blood.
HP:0003077	Hyperlipidemia	An elevated lipid concentration in the blood.
HP:0003138	Increased blood urea nitrogen	An increased amount of nitrogen in the form of urea in the blood.
HP:0001945	Fever	Elevated body temperature due to failed thermoregulation.
HP:0005356	Decreased serum complement factor I	A reduced level of the complement component Factor I in circulation.
HP:0005369	Decreased serum complement factor H	A reduced level of the complement component Factor H in circulation.
HP:0005416	Decreased serum complement factor B	A reduced level of the complement component factor B in circulation.
HP:0005421	Decreased serum complement C3	A reduced level of the complement component C3 in circulation.
HP:0100519	Anuria	Absence of urine, clinically classified as below 50ml/day.
HP:0005575	Hemolytic-uremic syndrome	
HP:0001919	Acute kidney injury	Sudden loss of renal function, as manifested by decreased urine production,

		and a rise in serum creatinine or blood urea nitrogen concentration (azotemia).
HP:0000007	Autosomal recessive inheritance	A mode of inheritance that is observed for traits related to a gene encoded on one of the autosomes (i.e., the human chromosomes 1-22) in which a trait manifests in individuals with two pathogenic alleles, either homozygotes (two copies of the same mutant allele) or compound heterozygotes (whereby each copy of a gene has a distinct mutant allele).
HP:0000006	Autosomal dominant inheritance	A mode of inheritance that is observed for traits related to a gene encoded on one of the autosomes (i.e., the human chromosomes 1-22) in which a trait manifests in heterozygotes. In the context of medical genetics, an autosomal dominant disorder is caused when a single copy of the mutant allele is present. Males and females are affected equally, and can both transmit the disorder with a risk of 50% for each child of inheriting the mutant allele.
HP:0000822	Hypertension	The presence of chronic increased pressure in the systemic arterial system.
HP:0000979	Purpura	Purpura (from Latin: purpura, meaning "purple") is the appearance of red or purple discolorations on the skin that do not blanch on applying pressure. They are caused by bleeding underneath the skin. This term refers to an abnormally increased susceptibility to developing purpura. Purpura are larger than petechiae.
HP:0002014	Diarrhea	Abnormally increased frequency of loose or watery bowel movements.

OMIM Clinical synopsis #235400 – Creation date: 15.06.1995, John F. Jackson; updated: 27.07.2009, Cassandra L. Kniffin

4.41.2 Cfhr5 Deficiency

4.41.2.1 No frequency available

Term Identifier	Term Name	Definition
HP:0000099	Glomerulonephritis	Inflammation of the renal glomeruli.
HP:0003774	Stage 5 chronic kidney disease	A degree of kidney failure severe enough to require dialysis or kidney transplantation for survival characterized by a severe

		reduction in glomerular filtration rate (less than 15 ml/min/1.73 m ²) and other manifestations including increased serum creatinine.
HP:0000083	Renal insufficiency	A reduction in the level of performance of the kidneys in areas of function comprising the concentration of urine, removal of wastes, the maintenance of electrolyte balance, homeostasis of blood pressure, and calcium metabolism.
HP:0000006	Autosomal dominant inheritance	A mode of inheritance that is observed for traits related to a gene encoded on one of the autosomes (i.e., the human chromosomes 1-22) in which a trait manifests in heterozygotes. In the context of medical genetics, an autosomal dominant disorder is caused when a single copy of the mutant allele is present. Males and females are affected equally, and can both transmit the disorder with a risk of 50% for each child of inheriting the mutant allele.
HP:0000790	Hematuria	The presence of blood in the urine. Hematuria may be gross hematuria (visible to the naked eye) or microscopic hematuria (detected by dipstick or microscopic examination of the urine).

OMIM Clinical synopsis #235400 – Creation date: 09.09.2012, Cassandra L. Kniffin

4.42 Factor I deficiency

4.42.1.1 No frequency available

Term Identifier	Term Name	Definition
HP:0005356	Decreased serum complement factor I	A reduced level of the complement component Factor I in circulation.
HP:0005376	Recurrent Haemophilus influenzae infections	Increased susceptibility to Haemophilus influenzae infections as manifested by recurrent episodes of infection by Haemophilus influenzae.
HP:0000403	Recurrent otitis media	Increased susceptibility to otitis media, as manifested by recurrent episodes of otitis media.
HP:0005381	Recurrent meningococcal disease	Recurrent infections by Neisseria meningitidis (one of the most common causes of bacterial meningitis), which is also known as meningococcus.
HP:0005369	Decreased serum complement factor H	A reduced level of the complement component Factor H in circulation.

HP:0005366	Recurrent streptococcus pneumoniae infections	Increased susceptibility to streptococcus pneumoniae infections as manifested by a history of recurrent infections by streptococcus pneumoniae.
HP:0000246	Sinusitis	Inflammation of the paranasal sinuses owing to a viral, bacterial, or fungal infection, allergy, or an autoimmune reaction.
HP:0005416	Decreased serum complement factor B	A reduced level of the complement component factor B in circulation.
HP:0001581	Recurrent skin infections	Infections of the skin that happen multiple times.
HP:0005421	Decreased serum complement C3	A reduced level of the complement component C3 in circulation.
HP:0011108	Recurrent sinusitis	A recurrent form of sinusitis.
HP:0000010	Recurrent urinary tract infections	Repeated infections of the urinary tract.
HP:0000083	Renal insufficiency	A reduction in the level of performance of the kidneys in areas of function comprising the concentration of urine, removal of wastes, the maintenance of electrolyte balance, homeostasis of blood pressure, and calcium metabolism.
HP:0012330	Pyelonephritis	An inflammation of the kidney involving the parenchyma of kidney, the renal pelvis and the kidney calices.
HP:0000099	Glomerulonephritis	Inflammation of the renal glomeruli.
HP:0000007	Autosomal recessive inheritance	A mode of inheritance that is observed for traits related to a gene encoded on one of the autosomes (i.e., the human chromosomes 1-22) in which a trait manifests in individuals with two pathogenic alleles, either homozygotes (two copies of the same mutant allele) or compound heterozygotes (whereby each copy of a gene has a distinct mutant allele).
HP:0002633	Vasculitis	Inflammation of blood vessel.
HP:0006946	Recurrent meningitis	An increased susceptibility to meningitis as manifested by a medical history of recurrent episodes of meningitis.
HP:0001369	Arthritis	Inflammation of a joint.

OMIM Clinical synopsis #610984 – Creation date: 30.04.2007, Cassandra L. Kniffin

4.43 Ficolin 3 Deficiency (FC3RN)

4.43.1.1 No frequency available

Term Identifier	Term Name	Definition
HP:0002722	Recurrent abscess formation	An increased susceptibility to abscess formation, as manifested by a medical history of recurrent abscesses.
HP:0002721	Immunodeficiency	Failure of the immune system to protect the body adequately from infection, due to the absence or insufficiency of some component process or substance.
HP:0002783	Recurrent lower respiratory tract infections	An increased susceptibility to lower respiratory tract infections as manifested by a history of recurrent lower respiratory tract infections.
HP:0000007	Autosomal recessive inheritance	A mode of inheritance that is observed for traits related to a gene encoded on one of the autosomes (i.e., the human chromosomes 1-22) in which a trait manifests in individuals with two pathogenic alleles, either homozygotes (two copies of the same mutant allele) or compound heterozygotes (whereby each copy of a gene has a distinct mutant allele).
HP:0200043	Verrucae	Warts, benign growths on the skin or mucous membranes that cause cosmetic problems as well as pain and discomfort. Warts most often occur on the hands, feet, and genital areas.

OMIM Clinical synopsis #613860 – Creation date: 02.06.2016, Cassandra L. Kniffin

4.44 Familial hemophagocytic lymphohistiocytosis syndromes (FHLH)

4.44.1 FHLH 1

4.44.1.1 No frequency available

Term Identifier	Term Name	Definition
HP:0002516	Increased intracranial pressure	An increase of the pressure inside the cranium (skull) and thereby in the brain tissue and cerebrospinal fluid.
HP:0000737	Irritability	
HP:0001263	Global developmental delay	A delay in the achievement of motor or mental milestones in the domains of development of a child, including motor

		<p>skills, speech and language, cognitive skills, and social and emotional skills.</p> <p>This term should only be used to describe children younger than five years of age.</p>
HP:0002301	Hemiplegia	Paralysis (complete loss of muscle function) in the arm, leg, and in some cases the face on one side of the body.
HP:0002445	Tetraplegia	Paralysis of all four limbs, and trunk of the body below the level of an associated injury to the spinal cord. The etiology of quadriplegia is similar to that of paraplegia except that the lesion is in the cervical spinal cord rather than in the thoracic or lumbar segments of the spinal cord.
HP:0002383	Encephalitis	
HP:0001251	Ataxia	Cerebellar ataxia refers to ataxia due to dysfunction of the cerebellum. This causes a variety of elementary neurological deficits including asynergy (lack of coordination between muscles, limbs and joints), dysmetria (lack of ability to judge distances that can lead to under- or overshoot in grasping movements), and dysdiadochokinesia (inability to perform rapid movements requiring antagonizing muscle groups to be switched on and off repeatedly).
HP:0002922	Increased CSF protein	Increased concentration of protein in the cerebrospinal fluid.
HP:0001250	Seizures	Seizures are an intermittent abnormality of the central nervous system due to a sudden, excessive, disorderly discharge of cerebral neurons and characterized clinically by some combination of disturbance of sensation, loss of consciousness, impairment of psychic function, or convulsive movements. The term epilepsy is used to describe chronic, recurrent seizures.
HP:0001287	Meningitis	Inflammation of the meninges.
HP:0001259	Coma	Complete absence of wakefulness and content of conscience, which manifests itself as a lack of response to any kind of external stimuli.
HP:0012229	CSF pleocytosis	An increased white blood cell count in the cerebrospinal fluid.

HP:0007430	Generalized edema	Generalized abnormal accumulation of fluid beneath the skin, or in one or more cavities of the body.
HP:0003141	Increased LDL cholesterol concentration	An elevated concentration of low-density lipoprotein cholesterol in the blood.
HP:0002155	Hypertriglyceridemia	An abnormal increase in the level of triglycerides in the blood.
HP:0003573	Increased total bilirubin	Increased concentration of total (conjugated and unconjugated) bilirubin in the blood.
HP:0003233	Decreased HDL cholesterol concentration	A decreased concentration of high-density lipoprotein cholesterol in the blood.
HP:0003281	Increased serum ferritin	Abnormal raised concentration of ferritin, a ubiquitous intracellular protein that stores iron, in the blood.
HP:0003075	Hypoproteinemia	A decreased concentration of protein in the blood.
HP:0002902	Hyponatremia	An abnormally decreased sodium concentration in the blood.
HP:0003362	Increased VLDL cholesterol concentration	An increase in the amount of very-low-density lipoprotein cholesterol in the blood.
HP:0003073	Hypoalbuminemia	Reduction in the concentration of albumin in the blood.
HP:0011900	Hypofibrinogenemia	Decreased concentration of fibrinogen in the blood.
HP:0012156	Hemophagocytosis	Phagocytosis by macrophages of erythrocytes, leukocytes, platelets, and their precursors in bone marrow and other tissues.
HP:0008151	Prolonged prothrombin time	Increased time to coagulation in the prothrombin time test, which is a measure of the extrinsic pathway of coagulation. The results of the prothrombin time test are often expressed in terms of the International normalized ratio (INR), which is calculated as a ratio of the patient's prothrombin time (PT) to a control PT standardized for the potency of the thromboplastin reagent developed by the World Health Organization (WHO) using the formula: INR is equal to Patient PT divided by Control PT.
HP:0001882	Leukopenia	An abnormal decreased number of leukocytes in the blood.
HP:0003645	Prolonged partial thromboplastin time	Increased time to coagulation in the partial thromboplastin time (PTT) test, a

		measure of the intrinsic and common coagulation pathways. Phospholipid, and activator, and calcium are mixed into an anticoagulated plasma sample, and the time is measured until a thrombus forms.
HP:0001873	Thrombocytopenia	A reduction in the number of circulating thrombocytes.
HP:0001903	Anemia	A reduction in erythrocytes volume or hemoglobin concentration.
HP:0000952	Jaundice	Yellow pigmentation of the skin due to bilirubin, which in turn is the result of increased bilirubin concentration in the bloodstream.
HP:0002240	Hepatomegaly	Abnormally increased size of the liver.
HP:0001744	Splenomegaly	Abnormal increased size of the spleen.
HP:0001276	Hypertonia	A condition in which there is increased muscle tone so that arms or legs, for example, are stiff and difficult to move.
HP:0001252	Muscular hypotonia	Muscular hypotonia is an abnormally low muscle tone (the amount of tension or resistance to movement in a muscle), often involving reduced muscle strength. Hypotonia is characterized by a diminished resistance to passive stretching.
HP:0001290	Generalized hypotonia	Generalized muscular hypotonia (abnormally low muscle tone).
HP:0000007	Autosomal recessive inheritance	A mode of inheritance that is observed for traits related to a gene encoded on one of the autosomes (i.e., the human chromosomes 1-22) in which a trait manifests in individuals with two pathogenic alleles, either homozygotes (two copies of the same mutant allele) or compound heterozygotes (whereby each copy of a gene has a distinct mutant allele).
HP:0002716	Lymphadenopathy	Enlargement (swelling) of a lymph node.
HP:0001508	Failure to thrive	Failure to thrive (FTT) refers to a child whose physical growth is substantially below the norm.

OMIM Clinical synopsis %267700 – Creation date: 15.06.1995, John F. Jackson; reviewed: 04.01.2001, Ada Hamosh

4.44.2 FHLH 2

4.44.2.1 No frequency available

Term Identifier	Term Name	Definition
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HP:0002516	Increased intracranial pressure	An increase of the pressure inside the cranium (skull) and thereby in the brain tissue and cerebrospinal fluid.
HP:0001263	Global developmental delay	A delay in the achievement of motor or mental milestones in the domains of development of a child, including motor skills, speech and language, cognitive skills, and social and emotional skills. This term should only be used to describe children younger than five years of age.
HP:0012229	CSF pleocytosis	An increased white blood cell count in the cerebrospinal fluid.
HP:0002301	Hemiplegia	Paralysis (complete loss of muscle function) in the arm, leg, and in some cases the face on one side of the body.
HP:0001287	Meningitis	Inflammation of the meninges.
HP:0002922	Increased CSF protein	Increased concentration of protein in the cerebrospinal fluid.
HP:0001259	Coma	Complete absence of wakefulness and content of conscience, which manifests itself as a lack of response to any kind of external stimuli.
HP:0002445	Tetraplegia	Paralysis of all four limbs, and trunk of the body below the level of an associated injury to the spinal cord. The etiology of quadriplegia is similar to that of paraplegia except that the lesion is in the cervical spinal cord rather than in the thoracic or lumbar segments of the spinal cord.
HP:0002383	Encephalitis	
HP:0001250	Seizures	Seizures are an intermittent abnormality of the central nervous system due to a sudden, excessive, disorderly discharge of cerebral neurons and characterized clinically by some combination of disturbance of sensation, loss of consciousness, impairment of psychic function, or convulsive movements. The term epilepsy is used to describe chronic, recurrent seizures.
HP:0000737	Irritability	
HP:0001251	Ataxia	Cerebellar ataxia refers to ataxia due to dysfunction of the cerebellum. This causes a variety of elementary neurological deficits including asynergy (lack of coordination between muscles, limbs and joints), dysmetria (lack of ability to judge distances that can lead to under- or overshoot in grasping movements),

		and dysdiadochokinesia (inability to perform rapid movements requiring antagonizing muscle groups to be switched on and off repeatedly).
HP:0003075	Hypoproteinemia	A decreased concentration of protein in the blood.
HP:0002902	Hyponatremia	An abnormally decreased sodium concentration in the blood.
HP:0002155	Hypertriglyceridemia	An abnormal increase in the level of triglycerides in the blood.
HP:0003073	Hypoalbuminemia	Reduction in the concentration of albumin in the blood.
HP:0003281	Increased serum ferritin	Abnormal raised concentration of ferritin, a ubiquitous intracellular protein that stores iron, in the blood.
HP:0007430	Generalized edema	Generalized abnormal accumulation of fluid beneath the skin, or in one or more cavities of the body.
HP:0003573	Increased total bilirubin	Increased concentration of total (conjugated and unconjugated) bilirubin in the blood.
HP:0001873	Thrombocytopenia	A reduction in the number of circulating thrombocytes.
HP:0011900	Hypofibrinogenemia	Decreased concentration of fibrinogen in the blood.
HP:0001882	Leukopenia	An abnormal decreased number of leukocytes in the blood.
HP:0012156	Hemophagocytosis	Phagocytosis by macrophages of erythrocytes, leukocytes, platelets, and their precursors in bone marrow and other tissues.
HP:0008151	Prolonged prothrombin time	Increased time to coagulation in the prothrombin time test, which is a measure of the extrinsic pathway of coagulation. The results of the prothrombin time test are often expressed in terms of the International normalized ratio (INR), which is calculated as a ratio of the patient's prothrombin time (PT) to a control PT standardized for the potency of the thromboplastin reagent developed by the World Health Organization (WHO) using the formula: INR is equal to Patient PT divided by Control PT.
HP:0001903	Anemia	A reduction in erythrocytes volume or hemoglobin concentration.
HP:0000952	Jaundice	Yellow pigmentation of the skin due to bilirubin, which in turn is the result of increased bilirubin concentration in the bloodstream.

HP:0001744	Splenomegaly	Abnormal increased size of the spleen.
HP:0002240	Hepatomegaly	Abnormally increased size of the liver.
HP:0001276	Hypertonia	A condition in which there is increased muscle tone so that arms or legs, for example, are stiff and difficult to move.
HP:0001290	Generalized hypotonia	Generalized muscular hypotonia (abnormally low muscle tone).
HP:0001252	Muscular hypotonia	Muscular hypotonia is an abnormally low muscle tone (the amount of tension or resistance to movement in a muscle), often involving reduced muscle strength. Hypotonia is characterized by a diminished resistance to passive stretching.
HP:0000007	Autosomal recessive inheritance	A mode of inheritance that is observed for traits related to a gene encoded on one of the autosomes (i.e., the human chromosomes 1-22) in which a trait manifests in individuals with two pathogenic alleles, either homozygotes (two copies of the same mutant allele) or compound heterozygotes (whereby each copy of a gene has a distinct mutant allele).
HP:0002716	Lymphadenopathy	Enlargement (swelling) of a lymph node.
HP:0001508	Failure to thrive	Failure to thrive (FTT) refers to a child whose physical growth is substantially below the norm.

OMIM Clinical synopsis #603553– Creation date: 15.06.1995, John F. Jackson; reviewed: 04.01.2001, Ada Hamosh

4.44.3 FHLH 3

4.44.3.1 No frequency available

Term Identifier	Term Name	Definition
HP:0001913	Granulocytopenia	An abnormally reduced number of granulocytes in the blood.
HP:0012156	Hemophagocytosis	Phagocytosis by macrophages of erythrocytes, leukocytes, platelets, and their precursors in bone marrow and other tissues.
HP:0011900	Hypofibrinogenemia	Decreased concentration of fibrinogen in the blood.
HP:0001903	Anemia	A reduction in erythrocytes volume or hemoglobin concentration.
HP:0001945	Fever	Elevated body temperature due to failed thermoregulation.

HP:0002155	Hypertriglyceridemia	An abnormal increase in the level of triglycerides in the blood.
HP:0000007	Autosomal recessive inheritance	A mode of inheritance that is observed for traits related to a gene encoded on one of the autosomes (i.e., the human chromosomes 1-22) in which a trait manifests in individuals with two pathogenic alleles, either homozygotes (two copies of the same mutant allele) or compound heterozygotes (whereby each copy of a gene has a distinct mutant allele).
HP:0001433	Hepatosplenomegaly	Simultaneous enlargement of the liver and spleen.
HP:0012178	Reduced natural killer cell activity	Reduced ability of the natural killer cell to function in the adaptive immune response.

Source: OMIM #608898; Creation date: 03.09.2004, Stylianos E. Antonarakis; updated: 12.11.2008 Marla J.F. O'Neill

4.44.4 FHLH 4

4.44.4.1 No frequency available

Term Identifier	Term Name	Definition
HP:0001875	Neutropenia	An abnormally low number of neutrophils in the peripheral blood.
HP:0001873	Thrombocytopenia	A reduction in the number of circulating thrombocytes.
HP:0011900	Hypofibrinogenemia	Decreased concentration of fibrinogen in the blood.
HP:0001903	Anemia	A reduction in erythrocytes volume or hemoglobin concentration.
HP:0012156	Hemophagocytosis	Phagocytosis by macrophages of erythrocytes, leukocytes, platelets, and their precursors in bone marrow and other tissues.
HP:0002155	Hypertriglyceridemia	An abnormal increase in the level of triglycerides in the blood.
HP:0003281	Increased serum ferritin	Abnormal raised concentration of ferritin, a ubiquitous intracellular protein that stores iron, in the blood.
HP:0001945	Fever	Elevated body temperature due to failed thermoregulation.
HP:0001744	Splenomegaly	Abnormal increased size of the spleen.
HP:0002240	Hepatomegaly	Abnormally increased size of the liver.
HP:0001252	Muscular hypotonia	Muscular hypotonia is an abnormally low muscle tone (the amount of tension or

		resistance to movement in a muscle), often involving reduced muscle strength. Hypotonia is characterized by a diminished resistance to passive stretching.
HP:0001290	Generalized hypotonia	Generalized muscular hypotonia (abnormally low muscle tone).
HP:0001263	Global developmental delay	A delay in the achievement of motor or mental milestones in the domains of development of a child, including motor skills, speech and language, cognitive skills, and social and emotional skills. This term should only be used to describe children younger than five years of age.
HP:0001250	Seizures	Seizures are an intermittent abnormality of the central nervous system due to a sudden, excessive, disorderly discharge of cerebral neurons and characterized clinically by some combination of disturbance of sensation, loss of consciousness, impairment of psychic function, or convulsive movements. The term epilepsy is used to describe chronic, recurrent seizures.
HP:0000007	Autosomal recessive inheritance	A mode of inheritance that is observed for traits related to a gene encoded on one of the autosomes (i.e., the human chromosomes 1-22) in which a trait manifests in individuals with two pathogenic alleles, either homozygotes (two copies of the same mutant allele) or compound heterozygotes (whereby each copy of a gene has a distinct mutant allele).

OMIM Clinical synopsis #603552– Creation date: 03.02.2014, Cassandra L. Kniffin

4.44.5 FHLH 5

4.44.5.1 No frequency available

Term Identifier	Term Name	Definition
HP:0002155	Hypertriglyceridemia	An abnormal increase in the level of triglycerides in the blood.
HP:0003281	Increased serum ferritin	Abnormal raised concentration of ferritin, a ubiquitous intracellular protein that stores iron, in the blood.
HP:0001954	Recurrent fever	Periodic (episodic or recurrent) bouts of fever.

HP:0000007	Autosomal recessive inheritance	A mode of inheritance that is observed for traits related to a gene encoded on one of the autosomes (i.e., the human chromosomes 1-22) in which a trait manifests in individuals with two pathogenic alleles, either homozygotes (two copies of the same mutant allele) or compound heterozygotes (whereby each copy of a gene has a distinct mutant allele).
HP:0012156	Hemophagocytosis	Phagocytosis by macrophages of erythrocytes, leukocytes, platelets, and their precursors in bone marrow and other tissues.
HP:0001433	Hepatosplenomegaly	Simultaneous enlargement of the liver and spleen.
HP:0012177	Abnormal natural killer cell physiology	A functional anomaly of the natural killer cell.

Source: OMIM #613101; Creation date: 22.10.2009, Marla J.F. O'Neill; updated: 05.01.2011 Marla J.F. O'Neill

4.45 *FOXP3* deficiency (IPEX)

4.45.1.1 Very frequent

Term Identifier	Term Name	Definition
HP:0002960	Autoimmunity	The occurrence of an immune reaction against the organism's own cells or tissues.

4.45.1.2 Frequent

Term Identifier	Term Name	Definition
HP:0002242	Abnormal intestine morphology	An abnormality of the intestine. The closely related term enteropathy is used to refer to any disease of the intestine.
HP:0003111	Abnormal blood ion concentration	Abnormality of the homeostasis (concentration) of a monoatomic ion.
HP:0012393	Allergy	An allergy is an immune response or reaction to substances that are usually not harmful.
HP:0025379	Anti-thyroid peroxidase antibody positivity	The presence of autoantibodies (immunoglobulins) in the serum that react against thyroid peroxidase.
HP:0007473	Crusting erythematous dermatitis	

HP:0000964	Eczema	Eczema is a form of dermatitis. The term eczema is broadly applied to a range of persistent skin conditions and can be related to a number of underlying conditions. Manifestations of eczema can include dryness and recurring skin rashes with redness, skin edema, itching and dryness, crusting, flaking, blistering, cracking, oozing, or bleeding.
HP:0000976	Ecematoid dermatitis	
HP:0001531	Failure to thrive in infancy	
HP:0031401	Reduced proportion of CD4-negative, CD8-negative, alpha-beta regulatory T cells	An abnormally decreased proportion of CD4-negative, CD8-negative (double negative or DN) alpha-beta regulatory T cells (Tregs) as compared to total number of T cells.
HP:0003212	Increased circulating total IgE level	An abnormally increased overall level of immunoglobulin E in blood.
HP:0011123	Inflammatory abnormality of the skin	The presence of inflammation of the skin. That is, an abnormality of the skin resulting from the local accumulation of fluid, plasma proteins, and leukocytes.
HP:0001891	Iron deficiency anemia	
HP:0005208	Secretory diarrhea	Watery voluminous diarrhea resulting from an imbalance between ion and water secretion and absorption.
HP:0100646	Thyroiditis	Inflammation of the thyroid gland.
HP:0100651	Type I diabetes mellitus	A chronic condition in which the pancreas produces little or no insulin. Type I diabetes mellitus is manifested by the sudden onset of severe hyperglycemia with rapid progression to diabetic ketoacidosis unless treated with insulin.

4.45.1.3 Occasional

Term Identifier	Term Name	Definition
HP:0008066	Abnormal blistering of the skin	The presence of one or more bullae on the skin, defined as fluid-filled blisters more than 5 mm in diameter with thin walls.
HP:0030909	Anti-liver cytosolic antigen type 1 antibody positivity	The presence of autoantibodies (immunoglobulins) in the serum that react against a 60-kd peptide contained in the liver cytosolic fraction.

HP:0001890	Autoimmune hemolytic anemia	An autoimmune form of hemolytic anemia.
HP:0001973	Autoimmune thrombocytopenia	The presence of thrombocytopenia in combination with detection of antiplatelet antibodies.
HP:0004326	Cachexia	Severe weight loss, wasting of muscle, loss of appetite, and general debility related to a chronic disease.
HP:0031085	Decreased prealbumin level	A reduced concentration of prealbumin in the blood. Prealbumin, also known as transthyretin, has a half-life in plasma of about 2 days, much shorter than that of albumin. Prealbumin is therefore more sensitive to changes in protein-energy status than albumin, and its concentration closely reflects recent dietary intake rather than overall nutritional status.
HP:0003073	Hypoalbuminemia	Reduction in the concentration of albumin in the blood.
HP:0002901	Hypocalcemia	An abnormally decreased calcium concentration in the blood.
HP:0002917	Hypomagnesemia	An abnormally decreased magnesium concentration in the blood.
HP:0000821	Hypothyroidism	Deficiency of thyroid hormone.
HP:0031104	Insulin receptor antibody positivity	The presence of autoantibodies (immunoglobulins) in the serum that react against the insulin receptor.
HP:0006515	Interstitial pneumonitis	
HP:0002024	Malabsorption	Impaired ability to absorb one or more nutrients from the intestine.
HP:0012578	Membranous nephropathy	A type of glomerulonephropathy characterized by thickening of the basement membrane and deposition of immune complexes in the subepithelial space.
HP:0008404	Nail dystrophy	Onychodystrophy (nail dystrophy) refers to nail changes apart from changes of the color (nail dyschromia) and involves partial or complete disruption of the various keratinous layers of the nail plate.
HP:0001875	Neutropenia	An abnormally low number of neutrophils in the peripheral blood.
HP:0001904	Neutropenia in presence of anti-neutropil antibodies	A type of neutropenia that is observed in the presence of granulocyte-specific antibodies.
HP:0003765	Psoriasiform dermatitis	A skin abnormality characterized by redness and irritation, with thick, red skin that displays flaky, silver-white patches (scales).

HP:0031123	Recurrent gastroenteritis	Increased susceptibility to gastroenteritis, an infectious inflammation of the stomach and small intestines manifested by signs and symptoms such as diarrheas and abdominal pain, as manifested by recurrent episodes of gastroenteritis.
HP:0002719	Recurrent infections	Increased susceptibility to infections.
HP:0002205	Recurrent respiratory infections	An increased susceptibility to respiratory infections as manifested by a history of recurrent respiratory infections.
HP:0001581	Recurrent skin infections	Infections of the skin that happen multiple times.
HP:0002098	Respiratory distress	Difficulty in breathing. The physical presentation of respiratory distress is generally referred to as labored breathing, while the sensation of respiratory distress is called shortness of breath or dyspnea.
HP:0001970	Tubulointerstitial nephritis	A form of inflammation of the kidney affecting the interstitium of the kidneys surrounding the tubules.
HP:0001025	Urticaria	Raised, well-circumscribed areas of erythema and edema involving the dermis and epidermis. Urticaria is intensely pruritic, and blanches completely with pressure.
HP:0002013	Vomiting	Forceful ejection of the contents of the stomach through the mouth by means of a series of involuntary spasmic contractions.
HP:0002910	Elevated hepatic transaminase	Elevations of the levels of SGOT and SGPT in the serum. SGOT (serum glutamic oxaloacetic transaminase) and SGPT (serum glutamic pyruvic transaminase) are transaminases primarily found in the liver and heart and are released into the bloodstream as the result of liver or heart damage. SGOT and SGPT are used clinically mainly as markers of liver damage.
HP:0012115	Hepatitis	Inflammation of the liver.

4.45.1.4 Rare

Term Identifier	Term Name	Definition
HP:0001596	Alopecia	A noncongenital process of hair loss, which may progress to partial or complete baldness.
HP:0002583	Colitis	Colitis refers to an inflammation of the colon and is often used to describe an

		inflammation of the large intestine (colon, cecum and rectum). Colitides may be acute and self-limited or chronic, and broadly fit into the category of digestive diseases.
HP:0025156	Dependency on intravenous nutrition	Inability to be weaned from intravenous (parenteral) nutrition, as judged by the hydration status (urine output, blood urea nitrogen, creatinine, urine sodium concentration), ability to maintain weight, stool output, and serum electrolyte status.
HP:0005263	Gastritis	The presence of inflammation of the gastric mucous membrane.
HP:0000836	Hyperthyroidism	An abnormality of thyroid physiology characterized by excessive secretion of the thyroid hormones thyroxine (i.e., T4) and/or 3,3',5-triiodo-L-thyronine zwitterion (i.e., triiodothyronine or T3).
HP:0002595	Ileus	Acute obstruction of the intestines preventing passage of the contents of the intestines.
HP:0002716	Lymphadenopathy	Enlargement (swelling) of a lymph node.
HP:0001287	Meningitis	Inflammation of the meninges.
HP:0040288	Nasogastric tube feeding	
HP:0000100	Nephrotic syndrome	Nephrotic syndrome is a collection of findings resulting from glomerular dysfunction with an increase in glomerular capillary wall permeability associated with pronounced proteinuria. Nephrotic syndrome refers to the constellation of clinical findings that result from severe renal loss of protein, with Proteinuria and hypoalbuminemia, edema, and hyperlipidemia.
HP:0002754	Osteomyelitis	Osteomyelitis is an inflammatory process accompanied by bone destruction and caused by an infecting microorganism.
HP:0002090	Pneumonia	Inflammation of any part of the lung parenchyma.
HP:0100806	Sepsis	Systemic inflammatory response to infection.
HP:0001744	Splenomegaly	Abnormal increased size of the spleen.

Source: HPO-ORDO Ontological Module (21) - Validation association date: 23.05.2019 - PMID: 30805323 (42), PMID: 24240290 (43), PMID: 20301297 (44)

4.46 Glycogen storage disease type 1b (GS1b)

4.46.1.1 No frequency available

Term Identifier	Term Name	Definition
HP:0000093	Proteinuria	Increased levels of protein in the urine.
HP:0003077	Hyperlipidemia	An elevated lipid concentration in the blood.
HP:0002149	Hyperuricemia	An abnormally high level of uric acid in the blood.
HP:0003128	Lactic acidosis	An abnormal buildup of lactic acid in the body, leading to acidification of the blood and other bodily fluids.
HP:0002149	Hyperuricemia	An abnormally high level of uric acid in the blood.
HP:0002910	Elevated hepatic transaminase	Elevations of the levels of SGOT and SGPT in the serum. SGOT (serum glutamic oxaloacetic transaminase) and SGPT (serum glutamic pyruvic transaminase) are transaminases primarily found in the liver and heart and are released into the bloodstream as the result of liver or heart damage. SGOT and SGPT are used clinically mainly as markers of liver damage.
HP:0001538	Protuberant abdomen	A thrusting or bulging out of the abdomen.
HP:0001733	Pancreatitis	The presence of inflammation in the pancreas.
HP:0002240	Hepatomegaly	Abnormally increased size of the liver.
HP:0000097	Focal segmental glomerulosclerosis	Segmental accumulation of scar tissue in individual (but not all) glomeruli.
HP:0000787	Nephrolithiasis	The presence of calculi (stones) in the kidneys.
HP:0000105	Enlarged kidney	An abnormal increase in the size of the kidney.
HP:0012213	Decreased glomerular filtration rate	An abnormal reduction in the volume of fluid filtered out of plasma through glomerular capillary walls into Bowman's capsules per unit of time.
HP:0000295	Doll-like facies	A characteristic facial appearance with a round facial form, full cheeks, a short nose, and a relatively small chin.
HP:0000155	Oral ulcer	Erosion of the mucous membrane of the mouth with local excavation of the surface, resulting from the sloughing of inflammatory necrotic tissue.
HP:0000991	Xanthomatosis	The presence of multiple xanthomas (xanthomata) in the skin. Xanthomas are

		yellowish, firm, lipid-laden nodules in the skin.
HP:0001114	Xanthelasma	The presence of xanthomata in the skin of the eyelid.
HP:0000939	Osteoporosis	Osteoporosis is a systemic skeletal disease characterized by low bone density and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility. According to the WHO criteria, osteoporosis is defined as a BMD that lies 2.5 standard deviations or more below the average value for young healthy adults (a T-score below -2.5 SD).
HP:0001997	Gout	Recurrent attacks of acute inflammatory arthritis of a joint or set of joints caused by elevated levels of uric acid in the blood which crystallize and are deposited in joints, tendons, and surrounding tissues.
HP:0000823	Delayed puberty	Passing the age when puberty normally occurs with no physical or hormonal signs of the onset of puberty.
HP:0004322	Short stature	A height below that which is expected according to age and gender norms. Although there is no universally accepted definition of short stature, many refer to "short stature" as height more than 2 standard deviations below the mean for age and gender (or below the 3rd percentile for age and gender dependent norms).
HP:0000007	Autosomal recessive inheritance	A mode of inheritance that is observed for traits related to a gene encoded on one of the autosomes (i.e., the human chromosomes 1-22) in which a trait manifests in individuals with two pathogenic alleles, either homozygotes (two copies of the same mutant allele) or compound heterozygotes (whereby each copy of a gene has a distinct mutant allele).
HP:0001875	Neutropenia	An abnormally low number of neutrophils in the peripheral blood.
HP:0000822	Hypertension	The presence of chronic increased pressure in the systemic arterial system.
HP:0000660	Lipemia retinalis	A creamy appearance of the retinal blood vessels that occurs when the concentration of lipids in the blood are extremely increased, with pale pink to milky white retinal vessels and altered pale reflexes from choroidal vasculature.

HP:0002718	Recurrent bacterial infections	Increased susceptibility to bacterial infections, as manifested by recurrent episodes of bacterial infection.
HP:0001402	Hepatocellular carcinoma	A kind of neoplasm of the liver that originates in hepatocytes and presents macroscopically as a soft and hemorrhagic tan mass in the liver.

OMIM Clinical synopsis #232220– Creation date: 15.06.1995, John F. Jackson; revised: 20.09.2000, Kelly A. Przylepa

4.47 Griscelli syndrome type 2

4.47.1.1 Very frequent

Term Identifier	Term Name	Definition
HP:0012156	Hemophagocytosis	Phagocytosis by macrophages of erythrocytes, leukocytes, platelets, and their precursors in bone marrow and other tissues.
HP:0002240	Hepatomegaly	Abnormally increased size of the liver.
HP:0005599	Hypopigmentation of hair	
HP:0002721	Immunodeficiency	Failure of the immune system to protect the body adequately from infection, due to the absence or insufficiency of some component process or substance.
HP:0001876	Pancytopenia	An abnormal reduction in numbers of all blood cell types (red blood cells, white blood cells, and platelets).
HP:0007443	Partial albinism	Absence of melanin pigment in various areas, which is found at birth and is permanent. The lesions are known as leucoderma and are often found on the face, trunk, or limbs.
HP:0002216	Premature graying of hair	Development of gray hair at a younger than normal age.
HP:0001744	Splenomegaly	Abnormal increased size of the spleen.

4.47.1.2 Frequent

Term Identifier	Term Name	Definition
HP:0003077	Hyperlipidemia	An elevated lipid concentration in the blood.
HP:0000952	Jaundice	Yellow pigmentation of the skin due to bilirubin, which in turn is the result of

		increased bilirubin concentration in the bloodstream.
HP:0002716	Lymphadenopathy	Enlargement (swelling) of a lymph node.
HP:0001875	Neutropenia	An abnormally low number of neutrophils in the peripheral blood.

4.47.1.3 Occasional

Term Identifier	Term Name	Definition
HP:0001945	Fever	Elevated body temperature due to failed thermoregulation.
HP:0001276	Hypertonia	A condition in which there is increased muscle tone so that arms or legs, for example, are stiff and difficult to move.
HP:0007730	Iris hypopigmentation	An abnormal reduction in the amount of pigmentation of the iris.
HP:0002017	Nausea and vomiting	
HP:0000967	Petechiae	Petechiae are pinpoint-sized reddish/purple spots, resembling a rash, that appear just under the skin or a mucous membrane when capillaries have ruptured and some superficial bleeding into the skin has happened. This term refers to an abnormally increased susceptibility to developing petechiae.
HP:0002113	Pulmonary infiltrates	
HP:0001250	Seizures	Seizures are an intermittent abnormality of the central nervous system due to a sudden, excessive, disorderly discharge of cerebral neurons and characterized clinically by some combination of disturbance of sensation, loss of consciousness, impairment of psychic function, or convulsive movements. The term epilepsy is used to describe chronic, recurrent seizures.

Source: HPO-ORDO Ontological Module (21) - Validation association date: 01.06.2016 - PMID: 25315806 (45)

4.48 Hereditary angioedema (C1Inh)

4.48.1.1 Very Frequent

Term Identifier	Term Name	Definition
HP:0002027	Abdominal pain	An unpleasant sensation characterized by physical discomfort (such as pricking,

		throbbing, or aching) and perceived to originate in the abdomen.
HP:0012252	Abnormal respiratory system morphology	A structural anomaly of the respiratory system.
HP:0011971	Dermatographic urticaria	An exaggerated whealing tendency when the skin is stroked, that is, formation of red, itchy bumps and lines on the skin as a result of pressure on the skin (for instance, stroking the skin with a pen or tongue depressor).
HP:0007514	Edema of the dorsum of hands	An abnormal accumulation of fluid beneath the skin on the back of the hands.
HP:0000282	Facial edema	
HP:0005225	Intestinal edema	Accumulation of cell free, noninflammatory fluid within the wall of the intestinal tract producing uniform thickening of the mucosal folds.
HP:0025349	Limbal edema	Swelling of the margin of the cornea overlapped by the sclera.
HP:0003401	Paresthesia	Abnormal sensations such as tingling, pricking, or numbness of the skin with no apparent physical cause.
HP:0040315	Tongue edema	
HP:0001025	Urticaria	Raised, well-circumscribed areas of erythema and edema involving the dermis and epidermis. Urticaria is intensely pruritic, and blanches completely with pressure.

4.48.1.2 Frequent

Term Identifier	Term Name	Definition
HP:0100755	Abnormality of salivation	
HP:0002014	Diarrhea	Abnormally increased frequency of loose or watery bowel movements.
HP:0002015	Dysphagia	Difficulty in swallowing.
HP:0002094	Dyspnea	Difficult or labored breathing.
HP:0002018	Nausea	A sensation of unease in the stomach together with an urge to vomit.
HP:0002013	Vomiting	Forceful ejection of the contents of the stomach through the mouth by means of a series of involuntary spasmic contractions.

4.48.1.3 Occasional

Term Identifier	Term Name	Definition
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HP:0005483	Abnormal epiglottis morphology	An abnormality of the epiglottis.
HP:0100736	Abnormal soft palate morphology	An abnormality of the soft palate.
HP:0000172	Abnormality of the uvula	Abnormality of the uvula, the conic projection from the posterior edge of the middle of the soft palate.
HP:0001609	Hoarse voice	Hoarseness refers to a change in the pitch or quality of the voice, with the voice sounding weak, very breathy, scratchy, or husky.
HP:0002615	Hypotension	Low Blood Pressure, vascular hypotension.
HP:0005348	Inspiratory stridor	Inspiratory stridor is a high pitched sound upon inspiration that is generally related to laryngeal abnormalities.
HP:0011855	Pharyngeal edema	Abnormal accumulation of fluid leading to swelling of the pharynx.
HP:0002098	Respiratory distress	Difficulty in breathing. The physical presentation of respiratory distress is generally referred to as labored breathing, while the sensation of respiratory distress is called shortness of breath or dyspnea.

Source: HPO-ORDO Ontological Module (21) - Validation association date: 04.07.2017 - PMID: 26661330 (46), PMID: 22299312 (47), PMID: 23283143 (48)

*applies only to HAE1

4.49 Herpetic encephalitis (HSE)

4.49.1.1 No frequency available

Term Identifier	Term Name	Definition
HP:0001269	Hemiparesis	Loss of strength in the arm, leg, and sometimes face on one side of the body. Hemiplegia refers to a complete loss of strength, whereas hemiparesis refers to an incomplete loss of strength.
HP:0002171	Gliosis	Gliosis is the focal proliferation of glial cells in the central nervous system.
HP:0001254	Lethargy	A state of disinterestedness, listlessness, and indifference, resulting in difficulty performing simple tasks or concentrating.
HP:0001287	Meningitis	Inflammation of the meninges.
HP:0002353	EEG abnormality	Abnormality observed by electroencephalogram (EEG), which is used to record of the brain's spontaneous electrical activity from multiple electrodes placed on the scalp.

HP:0001289	Confusion	Lack of clarity and coherence of thought, perception, understanding, or action.
HP:0001250	Seizures	Seizures are an intermittent abnormality of the central nervous system due to a sudden, excessive, disorderly discharge of cerebral neurons and characterized clinically by some combination of disturbance of sensation, loss of consciousness, impairment of psychic function, or convulsive movements. The term epilepsy is used to describe chronic, recurrent seizures.
HP:0001249	Intellectual disability	Subnormal intellectual functioning which originates during the developmental period. Intellectual disability, previously referred to as mental retardation, has been defined as an IQ score below 70.
HP:0001268	Mental deterioration	Loss of previously present mental abilities, generally in adults.
HP:0012302	Herpes simplex encephalitis	A severe virus infection of the central nervous system by the herpes simplex virus (HSV).
HP:0005353	Recurrent herpes	Increased susceptibility to herpesvirus, as manifested by recurrent episodes of herpesvirus.

OMIM Clinical synopsis #613002– Creation date: 08.03.2018, Cassandra L. Kniffin
OMIM #610551 – Creation date: 07.11.2006, Ada Hamosh; updated: 09.01.2013, Ada Hamosh

4.50 Hermansky-Pudlak syndrome (type 2)

4.50.1.1 No frequency available

Term Identifier	Term Name	Definition
HP:0000280	Coarse facial features	Absence of fine and sharp appearance of brows, nose, lips, mouth, and chin, usually because of rounded and heavy features or thickened skin with or without thickening of subcutaneous and bony tissues.
HP:0000343	Long philtrum	Distance between nasal base and midline upper lip vermilion border more than 2 SD above the mean. Alternatively, an apparently increased distance between nasal base and midline upper lip vermilion border.
HP:0000431	Wide nasal bridge	Increased breadth of the nasal bridge (and with it, the nasal root).
HP:0000319	Smooth philtrum	Flat skin surface, with no ridge formation in the central region of the upper lip between the nasal base and upper vermilion border.
HP:0000219	Thin upper lip vermilion	Height of the vermilion of the upper lip in the midline more than 2 SD below the

		mean. Alternatively, an apparently reduced height of the vermilion of the upper lip in the frontal view (subjective).
HP:0000252	Microcephaly	Head circumference below 2 standard deviations below the mean for age and gender.
HP:0000582	Upslanted palpebral fissure	The palpebral fissure inclination is more than two standard deviations above the mean for age (objective); or, the inclination of the palpebral fissure is greater than typical for age.
HP:0000670	Carious teeth	Caries is a multifactorial bacterial infection affecting the structure of the tooth. This term has been used to describe the presence of more than expected dental caries.
HP:0000486	Strabismus	A misalignment of the eyes so that the visual axes deviate from bifoveal fixation. The classification of strabismus may be based on a number of features including the relative position of the eyes, whether the deviation is latent or manifest, intermittent or constant, concomitant or otherwise and according to the age of onset and the relevance of any associated refractive error.
HP:0000639	Nystagmus	Rhythmic, involuntary oscillations of one or both eyes related to abnormality in fixation, conjugate gaze, or vestibular mechanisms.
HP:0000505	Visual impairment	Visual impairment (or vision impairment) is vision loss (of a person) to such a degree as to qualify as an additional support need through a significant limitation of visual capability resulting from either disease, trauma, or congenital or degenerative conditions that cannot be corrected by conventional means, such as refractive correction, medication, or surgery.
HP:0007663	Reduced visual acuity	
HP:0001107	Ocular albinism	An abnormal reduction in the amount of pigmentation (reduced or absent) of the iris and retina.
HP:0007513	Generalized hypopigmentation	
HP:0001022	Albinism	An abnormal reduction in the amount of pigmentation (reduced or absent) of skin, hair and eye (iris and retina).

HP:0007384	Aberrant melanosome maturation	
HP:0002286	Fair hair	A lesser degree of hair pigmentation than would otherwise be expected.
HP:0000613	Photophobia	Excessive sensitivity to light with the sensation of discomfort or pain in the eyes due to exposure to bright light.
HP:0001256	Intellectual disability, mild	Mild intellectual disability is defined as an intelligence quotient (IQ) in the range of 50-69.
HP:0001270	Motor delay	A type of Developmental delay characterized by a delay in acquiring motor skills.
HP:0001873	Thrombocytopenia	A reduction in the number of circulating thrombocytes.
HP:0001875	Neutropenia	An abnormally low number of neutrophils in the peripheral blood.
HP:0002240	Hepatomegaly	Abnormally increased size of the liver.
HP:0001744	Splenomegaly	Abnormal increased size of the spleen.
HP:0000358	Posteriorly rotated ears	A type of abnormal location of the ears in which the position of the ears is characterized by posterior rotation (the superior part of the ears is rotated towards the back of the head, and the inferior part of the ears towards the front).
HP:0000369	Low-set ears	Upper insertion of the ear to the scalp below an imaginary horizontal line drawn between the inner canthi of the eye and extending posteriorly to the ear.
HP:0002718	Recurrent bacterial infections	Increased susceptibility to bacterial infections, as manifested by recurrent episodes of bacterial infection.
HP:0000704	Periodontitis	Inflammation of the periodontium.
HP:0001385	Hip dysplasia	The presence of developmental dysplasia of the hip.
HP:0008807	Acetabular dysplasia	The presence of developmental dysplasia of the acetabular part of hip bone.
HP:0002206	Pulmonary fibrosis	Replacement of normal lung tissues by fibroblasts and collagen.

OMIM Clinical synopsis #608233– Creation date: 03.10.2006, Cassandra L. Kniffin

4.51 HLA class I deficiency

4.51.1.1 No frequency available

Term Identifier	Term Name	Definition
HP:0011109	Chronic sinusitis	A chronic form of sinusitis.

HP:0011950	Bronchiolitis	Inflammation of the bronchioles.
HP:0000389	Chronic otitis media	Chronic otitis media refers to fluid, swelling, or infection of the middle ear that does not heal and may cause permanent damage to the ear.
HP:0002097	Emphysema	
HP:0002110	Bronchiectasis	Persistent abnormal dilatation of the bronchi owing to localized and irreversible destruction and widening of the large airways.
HP:0002837	Recurrent bronchitis	An increased susceptibility to bronchitis as manifested by a history of recurrent bronchitis.
HP:0100582	Nasal polyposis	Polypoidal masses arising mainly from the mucous membranes of the nose and paranasal sinuses. They are freely movable and nontender overgrowths of the mucosa that frequently accompany allergic rhinitis.
HP:0001083	Ectopia lentis	Dislocation or malposition of the crystalline lens of the eye. A partial displacement (or dislocation) of the lens is described as a subluxation of the lens, while a complete displacement is termed luxation of the lens. A complete displacement occurs if the lens is completely outside the patellar fossa of the lens, either in the anterior chamber, in the vitreous, or directly on the retina. If the lens is partially displaced but still contained within the lens space, then it is termed subluxation.
HP:0200042	Skin ulcer	A discontinuity of the skin exhibiting complete loss of the epidermis and often portions of the dermis and even subcutaneous fat.
HP:0001000	Abnormality of skin pigmentation	An abnormality of the pigmentation of the skin.
HP:0031949	Recurrent bacterial upper respiratory tract infections	An increased susceptibility to bacterial upper respiratory tract infections as manifested by a history of recurrent bacterial upper respiratory tract infections (running ears - otitis, sinusitis, pharyngitis, tonsillitis).

OMIM Clinical synopsis #604571– Creation date: 07.04.2000, Assil Saleh; reviewed: 19.04.2000, Ada Hamosh

4.52 HLA class II deficiency (MHC2)

4.52.1.1 Always present

Term Identifier	Term Name	Definition
HP:0031390	Reduced MHC II surface expression	A reduction from the normal level of major histocompatibility complex class II molecules expressed at the cell surface.

4.52.1.2 Very frequent

Term Identifier	Term Name	Definition
HP:0005354	Lack of T cell function	Complete inability of T cells to perform their functions in cell-mediated immunity.
HP:0004798	Recurrent infection of the gastrointestinal tract	Recurrent infection of the gastrointestinal tract.
HP:0002205	Recurrent respiratory infections	An increased susceptibility to respiratory infections as manifested by a history of recurrent respiratory infections.

4.52.1.3 Frequent

Term Identifier	Term Name	Definition
HP:0005368	Abnormality of humoral immunity	An abnormality of the humoral immune system, which comprises antibodies produced by B cells as well as the complement system.
HP:0200124	Chronic hepatitis due to cryptosporidium infection	Chronic hepatitis associated with infection by cryptosporidia, as demonstrated (for example) by immunohistochemistry of liver tissue.
HP:0002728	Chronic mucocutaneous candidiasis	Recurrent or persistent superficial Candida infections of the skin, mucous membranes, and nails.
HP:0004313	Decreased antibody level in blood	An abnormally decreased level of immunoglobulin in blood.
HP:0025347	Decreased circulating beta-2-microglobulin level	Reduced concentration of beta-2-microglobulin in the blood.
HP:0005407	Decreased proportion of CD4-positive T cells	A decreased proportion of circulating CD4-positive helper T cells relative to total T cell count.

HP:0002014	Diarrhea	Abnormally increased frequency of loose or watery bowel movements.
HP:0001508	Failure to thrive	Failure to thrive (FTT) refers to a child whose physical growth is substantially below the norm.
HP:0004385	Protracted diarrhea	
HP:0002726	Recurrent Staphylococcus aureus infections	Increased susceptibility to Staphylococcus aureus infections, as manifested by recurrent episodes of Staphylococcus aureus infection.
HP:0002718	Recurrent bacterial infections	Increased susceptibility to bacterial infections, as manifested by recurrent episodes of bacterial infection.
HP:0005401	Recurrent candida infections	An increased susceptibility to candida infections, as manifested by a history of recurrent episodes of candida infections.
HP:0002841	Recurrent fungal infections	Increased susceptibility to fungal infections, as manifested by multiple episodes of fungal infection.
HP:0005353	Recurrent herpes	Increased susceptibility to herpesvirus, as manifested by recurrent episodes of herpesvirus.
HP:0005386	Recurrent protozoan infections	Increased susceptibility to protozoan infections, as manifested by recurrent episodes of protozoan infection.
HP:0004429	Recurrent viral infections	Increased susceptibility to viral infections, as manifested by recurrent episodes of viral infection.
HP:0000246	Sinusitis	Inflammation of the paranasal sinuses owing to a viral, bacterial, or fungal infection, allergy, or an autoimmune reaction.
HP:0030991	Sclerosing cholangitis	Cholangitis associated with evident ductal fibrosis that develops as a consequence of long-standing bile duct inflammatory, obstruction, or ischemic injury; it can be obliterative or nonobliterative.
HP:0012384	Rhinitis	Inflammation of the nasal mucosa with nasal congestion.

4.52.1.4 Occasional

Term Identifier	Term Name	Definition
HP:0031394	Abnormal CD4:CD8 ratio	Any abnormality in the relative amount of CD4+ and CD8+ T lymphocytes.

HP:0000371	Acute otitis media	Acute otitis media is a short and generally painful infection of the middle ear.
HP:0001890	Autoimmune hemolytic anemia	An autoimmune form of hemolytic anemia.
HP:0001973	Autoimmune thrombocytopenia	The presence of thrombocytopenia in combination with detection of antiplatelet antibodies.
HP:0002960	Autoimmunity	The occurrence of an immune reaction against the organism's own cells or tissues.
HP:0005403	Decrease in T cell count	An abnormally low count of T cells.
HP:0001904	Neutropenia in presence of anti-neutropil antibodies	A type of neutropenia that is observed in the presence of granulocyte-specific antibodies.
HP:0031381	Decreased lymphocyte proliferation in response to mitogen	A decreased proliferative response of lymphocytes in vitro or in vivo, when stimulated with mitogens, such as phytohemagglutinin (PHA).
HP:0001875	Neutropenia	An abnormally low number of neutrophils in the peripheral blood.
HP:0001876	Pancytopenia	An abnormal reduction in numbers of all blood cell types (red blood cells, white blood cells, and platelets).
HP:0003139	Panhypogammaglobulinemia	A reduction in the circulating levels of all the major classes of immunoglobulin. is characterized by profound decreases in all classes of immunoglobulin with an absence of circulating B lymphocytes.
HP:0000988	Skin rash	A red eruption of the skin.

4.52.1.5 Rare

Term Identifier	Term Name	Definition
HP:0001999	Abnormal facial shape	An abnormal morphology (form) of the face or its components.
HP:0002066	Gait ataxia	A type of ataxia characterized by the impairment of the ability to coordinate the movements required for normal walking. Gait ataxia is characterized by

		a wide-based staggering gait with a tendency to fall.
HP:0001260	Dysarthria	Dysarthric speech is a general description referring to a neurological speech disorder characterized by poor articulation. Depending on the involved neurological structures, dysarthria may be further classified as spastic, flaccid, ataxic, hyperkinetic and hypokinetic, or mixed.

Source: HPO-ORDO Ontological Module (21) - Validation association date: 18.04.2019 - PMID: 25001848 (49), PMID: 28676232 (50), PMID: 26634365 (51)

4.53 Hoyeraal-Hreidarsson syndrome

4.53.1.1 Very frequent

Term Identifier	Term Name	Definition
HP:0001321	Cerebellar hypoplasia	Underdevelopment of the cerebellum.
HP:0001263	Global developmental delay	A delay in the achievement of motor or mental milestones in the domains of development of a child, including motor skills, speech and language, cognitive skills, and social and emotional skills. This term should only be used to describe children younger than five years of age.
HP:0001249	Intellectual disability	Subnormal intellectual functioning which originates during the developmental period. Intellectual disability, previously referred to as mental retardation, has been defined as an IQ score below 70.
HP:0004334	Dermal atrophy	Partial or complete wasting (atrophy) of the skin.
HP:0001873	Thrombocytopenia	A reduction in the number of circulating thrombocytes.
HP:0000252	Microcephaly	Occipito-frontal (head) circumference (OFC) less than -3 standard deviations compared to appropriate, age matched, normal standards (Ross JJ, Frias JL 1977, PMID:9683597). Alternatively, decreased size of the cranium.
HP:0001508	Failure to thrive	Failure to thrive (FTT) refers to a child whose physical growth is substantially below the norm.
HP:0001511	Intrauterine growth retardation	An abnormal restriction of fetal growth with fetal weight below the tenth percentile for gestational age.
HP:0004322	Short stature	A height below that which is expected according to age and gender norms. Although there is no universally accepted

		definition of short stature, many refer to "short stature" as height more than 2 standard deviations below the mean for age and gender (or below the 3rd percentile for age and gender dependent norms).
HP:0002721	Immunodeficiency	Failure of the immune system to protect the body adequately from infection, due to the absence or insufficiency of some component process or substance.

4.53.1.2 Frequent

Term Identifier	Term Name	Definition
HP:0002120	Cerebral cortical atrophy	Atrophy of the cortex of the cerebrum.
HP:0002119	Ventriculomegaly	An increase in size of the ventricular system of the brain.
HP:0011358	Generalized hypopigmentation of hair	Reduced pigmentation of hair diffusely.
HP:0008404	Nail dystrophy	Onychodystrophy (nail dystrophy) refers to nail changes apart from changes of the color (nail dyschromia) and involves partial or complete disruption of the various keratinous layers of the nail plate.
HP:0007392	Excessive wrinkled skin	
HP:0007440	Generalized hyperpigmentation	
HP:0002216	Premature graying of hair	Development of gray hair at a younger than normal age.
HP:0001928	Abnormality of coagulation	An abnormality of the process of blood coagulation. That is, altered ability or inability of the blood to clot.
HP:0001903	Anemia	A reduction in erythrocytes volume or hemoglobin concentration.
HP:0002209	Sparse scalp hair	Decreased number of head hairs per unit area.
HP:0002745	Oral leukoplakia	A thickened white patch on the oral mucosa that cannot be rubbed off.
HP:0001276	Hypertonia	A condition in which there is increased muscle tone so that arms or legs, for example, are stiff and difficult to move.

4.53.1.3 Occasional

Term Identifier	Term Name	Definition
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HP:0001251	Ataxia	Cerebellar ataxia refers to ataxia due to dysfunction of the cerebellum. This causes a variety of elementary neurological deficits including asynergy (lack of coordination between muscles, limbs and joints), dysmetria (lack of ability to judge distances that can lead to under- oder overshoot in grasping movements), and dysdiadochokinesia (inability to perform rapid movements requiring antagonizing muscle groups to be switched on and off repeatedly).
HP:0001265	Hyporeflexia	Reduction of neurologic reflexes such as the knee-jerk reaction.
HP:0005528	Bone marrow hypocellularity	A reduced number of hematopoietic cells present in the bone marrow relative to marrow fat.
HP:0001881	Abnormal leukocyte morphology	An abnormality of leukocytes.
HP:0002514	Cerebral calcification	The presence of calcium deposition within brain structures.
HP:0002664	Neoplasm	An organ or organ-system abnormality that consists of uncontrolled autonomous cell-proliferation which can occur in any part of the body as a benign or malignant neoplasm (tumour).

Source: HPO-ORDO Ontological Module (21)- Validation association date: 01.06.2016

4.54 Hyper IgE syndrome (HIES)

4.54.1.1 Very frequent

Term Identifier	Term Name	Definition
HP:0000989	Pruritus	Pruritus is an itch or a sensation that makes a person want to scratch. This term refers to an abnormally increased disposition to experience pruritus.
HP:0200042	Skin ulcer	A discontinuity of the skin exhibiting complete loss of the epidermis and often portions of the dermis and even subcutaneous fat.
HP:0011354	Generalized abnormality of skin	An abnormality of the skin that is not localized to any one particular region.
HP:0000988	Skin rash	A red eruption of the skin.
HP:0002719	Recurrent infections	Increased susceptibility to infections.
HP:0003212	Increased IgE level	An abnormally increased level of immunoglobulin E in blood.

HP:0000964	Eczema	Eczema is a form of dermatitis. The term eczema is broadly applied to a range of persistent skin conditions and can be related to a number of underlying conditions. Manifestations of eczema can include dryness and recurring skin rashes with redness, skin edema, itching and dryness, crusting, flaking, blistering, cracking, oozing, or bleeding.
HP:0002205	Recurrent respiratory infections	An increased susceptibility to respiratory infections as manifested by a history of recurrent respiratory infections.
HP:0100750	Atelectasis	Collapse of part of a lung associated with absence of inflation (air) of that part.

4.54.1.2 Frequent

Term Identifier	Term Name	Definition
HP:0000175	Cleft palate	Cleft palate is a developmental defect of the palate resulting from a failure of fusion of the palatine processes and manifesting as a separation of the roof of the mouth (soft and hard palate).
HP:0000271	Abnormality of the face	An abnormality of the face.
HP:0000230	Gingivitis	Inflammation of the gingiva.
HP:0000431	Wide nasal bridge	Increased breadth of the nasal bridge (and with it, the nasal root).
HP:0011220	Prominent forehead	Forward prominence of the entire forehead, due to protrusion of the frontal bone.
HP:0000684	Delayed eruption of teeth	Delayed tooth eruption, which can be defined as tooth eruption more than 2 SD beyond the mean eruption age.
HP:0000164	Abnormality of the dentition	Any abnormality of the teeth.
HP:0001818	Paronychia	The nail disease paronychia is an often-tender bacterial or fungal hand infection or foot infection where the nail and skin meet at the side or the base of a finger or toenail. The infection can start suddenly (acute paronychia) or gradually (chronic paronychia).
HP:0200034	Papule	A circumscribed, solid elevation of skin with no visible fluid, varying in size from a pinhead to less than 10mm in diameter at the widest point.
HP:0001595	Abnormality of the hair	An abnormality of the hair.
HP:0008391	Dystrophic fingernails	The presence of misshapen or partially destroyed nail plates, often with accumulation of soft, yellow keratin between the dystrophic

		nail plate and nail bed, resulting in elevation of the nail plate.
HP:0000389	Chronic otitis media	Chronic otitis media refers to fluid, swelling, or infection of the middle ear that does not heal and may cause permanent damage to the ear.
HP:0005692	Joint hyperflexibility	Increased mobility and flexibility in the joint due to the tension in tissues such as ligaments and muscles.
HP:0002757	Recurrent fractures	The repeated occurrence of bone fractures (implying an abnormally increased tendency for fracture).
HP:0002650	Scoliosis	The presence of an abnormal lateral curvature of the spine.
HP:0012735	Cough	A sudden, audible expulsion of air from the lungs through a partially closed glottis, preceded by inhalation.
HP:0001880	Eosinophilia	Increased count of eosinophils in the blood.
HP:0000490	Deeply set eye	An eye that is more deeply recessed into the plane of the face than is typical.

4.54.1.3 Occasional

Term Identifier	Term Name	Definition
HP:0001363	Craniosynostosis	Craniosynostosis refers to the premature closure of the cranial sutures. Primary craniosynostosis refers to the closure of one or more sutures due to abnormalities in skull development, and secondary craniosynostosis results from failure of brain growth.
HP:0200037	Skin vesicle	A circumscribed, fluid-containing, epidermal elevation generally considered less than 10mm in diameter at the widest point.
HP:0002754	Osteomyelitis	Osteomyelitis is an inflammatory process accompanied by bone destruction and caused by an infecting microorganism.
HP:0100658	Cellulitis	A bacterial infection and inflammation of the skin and subcutaneous tissues.
HP:0001945	Fever	Elevated body temperature due to failed thermoregulation.
HP:0002617	Dilatation	Abnormal outpouching or sac-like dilatation in the wall of an artery, vein or the heart.
HP:0002665	Lymphoma	A cancer originating in lymphocytes and presenting as a solid tumor of lymphoid cells.

Source: HPO-ORDO Ontological Module (21) - Validation association date: 01.06.2016

*applies only to autosomal dominant Hyper IgE syndrome

4.55 Immunodeficiency-centromeric instability-facial anomalies syndrome (ICF)

4.55.1.1 Very frequent

Term Identifier	Term Name	Definition
HP:0000347	Micrognathia	Developmental hypoplasia of the mandible.
HP:0002721	Immunodeficiency	Failure of the immune system to protect the body adequately from infection, due to the absence or insufficiency of some component process or substance.
HP:0004313	Decreased antibody level in blood	An abnormally decreased level of immunoglobulin in blood.
HP:0002205	Recurrent respiratory infections	An increased susceptibility to respiratory infections as manifested by a history of recurrent respiratory infections.
HP:0003220	Abnormality of chromosome stability	A type of chromosomal aberration characterised by reduced resistance of chromosomes to change or deterioration.
HP:0004322	Short stature	A height below that which is expected according to age and gender norms. Although there is no universally accepted definition of short stature, many refer to "short stature" as height more than 2 standard deviations below the mean for age and gender (or below the 3rd percentile for age and gender dependent norms).

4.55.1.2 Frequent

Term Identifier	Term Name	Definition
HP:0005280	Depressed nasal bridge	Posterior positioning of the nasal root in relation to the overall facial profile for age.
HP:0000256	Macrocephaly	Occipitofrontal (head) circumference greater than 97th centile compared to appropriate, age matched, sex-matched normal standards. Alternatively, a apparently increased size of the cranium.
HP:0005374	Cellular immunodeficiency	An immunodeficiency characterized by defective cell-mediated immunity or humoral immunity.
HP:0001888	Lymphopenia	A reduced number of lymphocytes in the blood.
HP:0001903	Anemia	A reduction in erythrocytes volume or hemoglobin concentration.

HP:0001874	Abnormality of neutrophils	A neutrophil abnormality.
HP:0001334	Communicating hydrocephalus	A form of hydrocephalus in which there is no visible obstruction to the flow of the cerebrospinal fluid between the ventricles and subarachnoid space.
HP:0001263	Global developmental delay	A delay in the achievement of motor or mental milestones in the domains of development of a child, including motor skills, speech and language, cognitive skills, and social and emotional skills. This term should only be used to describe children younger than five years of age.
HP:0001249	Intellectual disability	Subnormal intellectual functioning which originates during the developmental period. Intellectual disability, previously referred to as mental retardation, has been defined as an IQ score below 70.
HP:0002024	Malabsorption	Impaired ability to absorb one or more nutrients from the intestine.

4.55.1.3 Occasional

Term Identifier	Term Name	Definition
HP:0000286	Epicanthus	A fold of skin starting above the medial aspect of the upper eyelid and arching downward to cover, pass in front of and lateral to the medial canthus.
HP:0010808	Protruding tongue	Tongue extending beyond the alveolar ridges or teeth at rest.
HP:0012368	Flat face	Absence of concavity or convexity of the face when viewed in profile.
HP:0001537	Umbilical hernia	Protrusion of abdominal contents through a defect in the abdominal wall musculature around the umbilicus. Skin and subcutaneous tissue overlie the defect.
HP:0000369	Low-set ears	Upper insertion of the ear to the scalp below an imaginary horizontal line drawn between the inner canthi of the eye and extending posteriorly to the ear.
HP:0000316	Hypertelorism	Interpupillary distance more than 2 SD above the mean (alternatively, the appearance of an increased interpupillary distance or widely spaced eyes).
HP:0000158	Macroglossia	Increased length and width of the tongue.

Source: HPO-ORDO Ontological Module (21) - Validation association date: 01.06.2016

4.56 IPEX-like disease

4.56.1.1 Very frequent

Term Identifier	Term Name	Definition
HP:0002728	Chronic mucocutaneous candidiasis	Recurrent or persistent superficial <i>Candida</i> infections of the skin, mucous membranes, and nails.
HP:0002788	Recurrent upper respiratory tract infections	An increased susceptibility to upper respiratory tract infections as manifested by a history of recurrent upper respiratory tract infections (running ears - otitis, sinusitis, pharyngitis, tonsillitis).
HP:0002242	Abnormal intestine morphology	An abnormality of the intestine. The closely related term enteropathy is used to refer to any disease of the intestine.
HP:0002750	Delayed skeletal maturation	A decreased rate of skeletal maturation. Delayed skeletal maturation can be diagnosed on the basis of an estimation of the bone age from radiographs of specific bones in the human body.
HP:0001510	Growth delay	A deficiency or slowing down of growth pre- and postnatally.
HP:0004322	Short stature	A height below that which is expected according to age and gender norms. Although there is no universally accepted definition of short stature, many refer to "short stature" as height more than 2 standard deviations below the mean for age and gender (or below the 3rd percentile for age and gender dependent norms).
HP:0000009	Functional abnormality of the bladder	Dysfunction of the urinary bladder.

4.56.1.2 Frequent

Term Identifier	Term Name	Definition
HP:0005353	Recurrent herpes	Increased susceptibility to herpesvirus, as manifested by recurrent episodes of herpesvirus.
HP:0004387	Enterocolitis	An inflammation of the colon and small intestine. However, most conditions are either categorized as Enteritis (inflammation of the small intestine) or Colitis (inflammation of the large intestine).

HP:0000964	Eczema	Eczema is a form of dermatitis. The term eczema is broadly applied to a range of persistent skin conditions and can be related to a number of underlying conditions. Manifestations of eczema can include dryness and recurring skin rashes with redness, skin edema, itching and dryness, crusting, flaking, blistering, cracking, oozing, or bleeding.
HP:0002958	Immune dysregulation	Altered immune function characterized by lymphoid proliferation, immune activation, and excessive autoreactivity often leading to autoimmune/inflammatory complications.
HP:0002721	Immunodeficiency	Failure of the immune system to protect the body adequately from infection, due to the absence or insufficiency of some component process or substance.
HP:0001890	Autoimmune hemolytic anemia	An autoimmune form of hemolytic anemia.
HP:0002719	Recurrent infections	Increased susceptibility to infections.
HP:0011123	Inflammatory abnormality of the skin	The presence of inflammation of the skin. That is, an abnormality of the skin resulting from the local accumulation of fluid, plasma proteins, and leukocytes.
HP:0004944	Dilatation of the cerebral artery	The presence of a localized dilatation or ballooning of a cerebral artery.
HP:0001920	Renal artery stenosis	The presence of stenosis of the renal artery.
HP:0012163	Carotid artery dilatation	A dilatation (ballooning or bulging out of the vessel wall) of a carotid artery.
HP:0100817	Renovascular hypertension	The presence of hypertension related to stenosis of the renal artery.
HP:0001888	Lymphopenia	A reduced number of lymphocytes in the blood.
HP:0010976	B lymphocytopenia	An abnormal decrease from the normal count of B cells.
HP:0002014	Diarrhea	Abnormally increased frequency of loose or watery bowel movements.
HP:0001433	Hepatosplenomegaly	Simultaneous enlargement of the liver and spleen.
HP:0011473	Villous atrophy	The enteric villi are atrophic or absent.
HP:0100646	Thyroiditis	Inflammation of the thyroid gland.
HP:0100651	Type I diabetes mellitus	A chronic condition in which the pancreas produces little or no insulin. Type I diabetes mellitus is manifested by the sudden onset of severe hyperglycemia with rapid progression to diabetic ketoacidosis unless treated with insulin.

HP:0000832	Primary hypothyroidism	A type of hypothyroidism that results from a defect in the thyroid gland.
HP:0000938	Osteopenia	Osteopenia is a term to define bone density that is not normal but also not as low as osteoporosis. By definition from the World Health Organization osteopenia is defined by bone densitometry as a T score -1 to -2.5.
HP:0040160	Generalized osteoporosis	
HP:0000823	Delayed puberty	Passing the age when puberty normally occurs with no physical or hormonal signs of the onset of puberty.
HP:0002110	Bronchiectasis	Persistent abnormal dilatation of the bronchi owing to localized and irreversible destruction and widening of the large airways.
HP:0000818	Abnormality of the endocrine system	An abnormality of the endocrine system.

4.56.1.3 Occasional

Term Identifier	Term Name	Definition
HP:0012115	Hepatitis	Inflammation of the liver.
HP:0003613	Antiphospholipid antibody positivity	The presence of circulating autoantibodies to phospholipids.
HP:0002724	Recurrent Aspergillus infections	An increased susceptibility to Aspergillus infections, as manifested by a history of recurrent episodes of Aspergillus infections.
HP:0030355	Abnormal serum interferon-gamma level	Abnormal levels of interferon gamma measured in the blood circulation.
HP:0004966	Medial calcification of large arteries	Calcification, that is, pathological deposition of calcium salts in the tunica media of large (conduit) arteries.
HP:0001635	Congestive heart failure	The presence of an abnormality of cardiac function that is responsible for the failure of the heart to pump blood at a rate that is commensurate with the needs of the tissues or a state in which abnormally elevated filling pressures are required for the heart to do so. Heart failure is frequently related to a defect in myocardial contraction.
HP:0001655	Patent foramen ovale	Failure of the foramen ovale to seal postnatally, leaving a potential conduit between the left and right cardiac atria.

HP:0001904	Neutropenia in presence of anti-neutropil antibodies	A type of neutropenia that is observed in the presence of granulocyte-specific antibodies.
HP:0001973	Autoimmune thrombocytopenia	The presence of thrombocytopenia in combination with detection of antiplatelet antibodies.
HP:0001873	Thrombocytopenia	A reduction in the number of circulating thrombocytes.
HP:0002092	Pulmonary arterial hypertension	Pulmonary hypertension is defined mean pulmonary artery pressure of 25mmHg or more and pulmonary capillary wedge pressure of 15mmHg or less when measured by right heart catheterisation at rest and in a supine position.
HP:0011459	Esophageal carcinoma	The presence of a carcinoma of the esophagus.
HP:0012182	Oropharyngeal squamous cell carcinoma	A squamous cell carcinoma that originates in the oropharynx.
HP:0002383	Encephalitis	

4.56.1.4 Exclusion criteria

Term Identifier	Term Name	Definition
HP:0005403	Decrease in T cell count	An abnormally low count of T cells.

Source: HPO-ORDO Ontological Module - Validation association date: 25.04.2016 - PMID: 21714643 (52), PMID: 23541320 (53), PMID: 23534974 (54)

4.57 Isolated congenital asplenia

4.57.1.1 No frequency available

Term Identifier	Term Name	Definition
HP:0000006	Autosomal dominant inheritance	A mode of inheritance that is observed for traits related to a gene encoded on one of the autosomes (i.e., the human chromosomes 1-22) in which a trait manifests in heterozygotes. In the context of medical genetics, an autosomal dominant disorder is caused when a single copy of the mutant allele is present. Males and females are affected equally, and can both transmit the disorder with a risk of 50% for each child of inheriting the mutant allele.
HP:0001746	Asplenia	Absence (aplasia) of the spleen.
HP:0001438	Abnormality of abdomen morphology	A structural abnormality of the abdomen ('belly'), that is, the part of the body between the pelvis and the thorax.

HP:0001894	Thrombocytosis	Increased numbers of platelets in the peripheral blood.
HP:0002718	Recurrent bacterial infections	Increased susceptibility to bacterial infections, as manifested by recurrent episodes of bacterial infection.
HP:0005366	Recurrent streptococcus pneumoniae infections	Increased susceptibility to streptococcus pneumoniae infections as manifested by a history of recurrent infections by streptococcus pneumoniae.

Source: OMIM #271400 – Creation date: 04.06.1986, Victor A. McKusick; updated: 08.10.2013, Marla J.F. O'Neill

4.58 Mannose-binding Lectin Deficiency

4.58.1.1 No frequency available

Term Identifier	Term Name	Definition
HP:0031699	Disseminated cryptosporidium infection	Failure to contain infection by a protozoan of the genus <i>Cryptosporidium</i> , leading to spread to many parts of the body.
HP:0001581	Recurrent skin infections	Infections of the skin that happen multiple times.
HP:0005353	Recurrent herpes	Increased susceptibility to herpesvirus, as manifested by recurrent episodes of herpesvirus.
HP:0002742	Recurrent Klebsiella infections	Increased susceptibility to <i>Klebsiella</i> infections, as manifested by recurrent episodes of <i>Klebsiella</i> infection.
HP:0005381	Recurrent meningococcal disease	Recurrent infections by <i>Neisseria meningitidis</i> (one of the most common causes of bacterial meningitis), which is also known as meningococcus.
HP:0001508	Failure to thrive	Failure to thrive (FTT) refers to a child whose physical growth is substantially below the norm.
HP:0000006	Autosomal dominant inheritance	A mode of inheritance that is observed for traits related to a gene encoded on one of the autosomes (i.e., the human chromosomes 1-22) in which a trait manifests in heterozygotes. In the context of medical genetics, an autosomal dominant disorder is caused when a single copy of the mutant allele is present. Males and females are affected equally, and can both transmit the disorder with a risk of 50% for each child of inheriting the mutant allele.

Source: OMIM #614372 – Creation date: 02.12.2011, Matthew B. Gross; updated: 28.11.2016, Cassandra L. Kniffin

4.59 MonoMAC

4.59.1.1 No frequency available

Term Identifier	Term Name	Definition
HP:0032283	Disseminated nontuberculous mycobacterial infection	An infection with nontuberculous mycobacteria that affects multiple body sites. Such infections can occur in individuals with immune disease.
HP:0004429	Recurrent viral infections	Increased susceptibility to viral infections, as manifested by recurrent episodes of viral infection.
HP:0001915	Aplastic anemia	Aplastic anemia is defined as pancytopenia with a hypocellular marrow.
HP:0001875	Neutropenia	An abnormally low number of neutrophils in the peripheral blood.
HP:0012312	Monocytopenia	An decreased number of circulating monocytes.
HP:0012176	Abnormal natural killer cell morphology	An anomaly of the natural killer cell, which is a lymphocyte that can spontaneously kill a variety of target cells without prior antigenic activation via germline encoded activation receptors and also regulate immune responses via cytokine release and direct contact with other cells.
HP:0001888	Lymphopenia	A reduced number of lymphocytes in the blood.
HP:0002721	Immunodeficiency	Failure of the immune system to protect the body adequately from infection, due to the absence or insufficiency of some component process or substance.
HP:0002841	Recurrent fungal infections	Increased susceptibility to fungal infections, as manifested by multiple episodes of fungal infection.
HP:0011275	Recurrent mycobacterium avium complex infections	Increased susceptibility to mycobacterial avium complex infections, as manifested by recurrent episodes of mycobacterial infection.
HP:0002863	Myelodysplasia	Clonal hematopoietic stem cell disorders characterized by dysplasia (ineffective production) in one or more hematopoietic cell lineages, leading to anemia and cytopenia.
HP:0012324	Myeloid leukemia	A leukemia that originates from a myeloid cell, that is the blood forming cells of the bone marrow.

HP:0006517	Alveolar proteinosis	Abnormal accumulation of surfactant-like, periodic acid-schiff-positive lipoproteinaceous material in macrophages within the alveolar spaces and distal bronchioles. This results in gas exchange impairment leading to dyspnea and alveolar infiltrates.
HP:0012219	Erythema nodosum	An erythematous eruption commonly associated with drug reactions or infection and characterized by inflammatory nodules that are usually tender, multiple, and bilateral.
HP:0001004	Lymphedema	Localized fluid retention and tissue swelling caused by a compromised lymphatic system.

Source: OMIM #614172 – Creation date: 17.08.2011, Paul J. Converse; updated: 25.11.2014, Ada Hamosh

4.60 Netherton syndrome

4.60.1.1 Very frequent

Term Identifier	Term Name	Definition
HP:0003212	Increased IgE level	An abnormally increased level of immunoglobulin E in blood.
HP:0100326	Immunologic hypersensitivity	Immunological states where the immune system produces harmful responses upon reexposure to sensitising antigens.
HP:0000964	Eczema	Eczema is a form of dermatitis. The term eczema is broadly applied to a range of persistent skin conditions and can be related to a number of underlying conditions. Manifestations of eczema can include dryness and recurring skin rashes with redness, skin edema, itching and dryness, crusting, flaking, blistering, cracking, oozing, or bleeding.
HP:0000956	Acanthosis	A dermatosis characterized by thickened, hyperpigmented plaques, typically on the intertriginous surfaces and neck.
HP:0008064	Ichthyosis	An abnormality of the skin characterized the presence of excessive amounts of dry surface scales on the skin resulting from an abnormality of keratinization.
HP:0002213	Fine hair	Hair that is fine or thin to the touch.
HP:0007479	Congenital nonbullous ichthyosiform erythroderma	The term collodion baby applies to newborns who appear to have an extra layer of skin (known as a collodion membrane) that has a collodion-like

		quality. It is a descriptive term, not a specific diagnosis or disorder (as such, it is a syndrome). Affected babies are born in a collodion membrane, a shiny waxy outer layer to the skin. This is shed 10-14 days after birth, revealing the main symptom of the disease, extensive scaling of the skin caused by hyperkeratosis. With increasing age, the scaling tends to be concentrated around joints in areas such as the groin, the armpits, the inside of the elbow and the neck. The scales often tile the skin and may resemble fish scales.
HP:0001595	Abnormality of the hair	An abnormality of the hair.
HP:0009886	Trichorrhexis nodosa	Trichorrhexis nodosa is the formation of nodes along the hair shaft through which breakage readily occurs. It is thus a focal defect in the hair fiber that is characterized by thickening or weak points (nodes) that cause the hair to break off easily. The result is defective, abnormally fragile hair.
HP:0007400	Irregular hyperpigmentation	
HP:0002209	Sparse scalp hair	Decreased number of head hairs per unit area.
HP:0002099	Asthma	Asthma is characterized by increased responsiveness of the tracheobronchial tree to multiple stimuli, leading to narrowing of the air passages with resultant dyspnea, cough, and wheezing.
HP:0001025	Urticaria	Raised, well-circumscribed areas of erythema and edema involving the dermis and epidermis. Urticaria is intensely pruritic, and blanches completely with pressure.
HP:0002024	Malabsorption	Impaired ability to absorb one or more nutrients from the intestine.

4.60.1.2 Frequent

Term Identifier	Term Name	Definition
HP:0002205	Recurrent respiratory infections	An increased susceptibility to respiratory infections as manifested by a history of recurrent respiratory infections.

HP:0004313	Decreased antibody level in blood	An abnormally decreased level of immunoglobulin in blood.
HP:0001263	Global developmental delay	A delay in the achievement of motor or mental milestones in the domains of development of a child, including motor skills, speech and language, cognitive skills, and social and emotional skills. This term should only be used to describe children younger than five years of age.
HP:0001250	Seizures	Seizures are an intermittent abnormality of the central nervous system due to a sudden, excessive, disorderly discharge of cerebral neurons and characterized clinically by some combination of disturbance of sensation, loss of consciousness, impairment of psychic function, or convulsive movements. The term epilepsy is used to describe chronic, recurrent seizures.
HP:0001249	Intellectual disability	Subnormal intellectual functioning which originates during the developmental period. Intellectual disability, previously referred to as mental retardation, has been defined as an IQ score below 70.
HP:0002097	Emphysema	

4.60.1.3 Occasional

Term Identifier	Term Name	Definition
HP:0002719	Recurrent infections	Increased susceptibility to infections.
HP:0000988	Skin rash	A red eruption of the skin.
HP:0001019	Erythroderma	An inflammatory exfoliative dermatosis involving nearly all of the surface of the skin. Erythroderma develops suddenly. A patchy erythema may generalize and spread to affect most of the skin. Scaling may appear in 2-6 days and be accompanied by hot, red, dry skin, malaise, and fever.
HP:0000958	Dry skin	Skin characterized by the lack of natural or normal moisture.
HP:0000535	Sparse and thin eyebrow	Decreased density/number and/or decreased diameter of eyebrow hairs.
HP:0000653	Sparse eyelashes	Decreased density/number of eyelashes.
HP:0003355	Aminoaciduria	An increased concentration of an amino acid in the urine.
HP:0001944	Dehydration	

HP:0000126	Hydronephrosis	Severe distention of the kidney with dilation of the renal pelvis and calices.
HP:0000086	Ectopic kidney	A developmental defect in which a kidney is located in an abnormal anatomic position.
HP:0004322	Short stature	A height below that which is expected according to age and gender norms. Although there is no universally accepted definition of short stature, many refer to "short stature" as height more than 2 standard deviations below the mean for age and gender (or below the 3rd percentile for age and gender dependent norms).

Source: HPO-ORDO Ontological Module (21) - Validation association date: 01.06.2016

4.61 Nijmegen breakage syndrome

4.61.1.1 Very frequent

Term Identifier	Term Name	Definition
HP:0000252	Microcephaly	Occipito-frontal (head) circumference (OFC) less than -3 standard deviations compared to appropriate, age matched, normal standards (Ross JJ, Frias JL 1977, PMID:9683597). Alternatively, decreased size of the cranium.
HP:0002002	Deep philtrum	Accentuated, prominent philtral ridges giving rise to an exaggerated groove in the midline between the nasal base and upper vermillion border.
HP:0000278	Retrognathia	An abnormality in which the mandible is mislocalised posteriorly.
HP:0000444	Convex nasal ridge	Nasal ridge curving anteriorly to an imaginary line that connects the nasal root and tip. The nose appears often also prominent, and the columella low.
HP:0000294	Low anterior hairline	Distance between the hairline (trichion) and the glabella (the most prominent point on the frontal bone above the root of the nose), in the midline, more than two SD below the mean. Alternatively, an apparently decreased distance between the hairline and the glabella.
HP:0005280	Depressed nasal bridge	Posterior positioning of the nasal root in relation to the overall facial profile for age.
HP:0000340	Sloping forehead	Inclination of the anterior surface of the forehead from the vertical more than two standard deviations above the mean (objective); or apparently excessive

		posterior sloping of the forehead in a lateral view.
HP:0000470	Short neck	Diminished length of the neck.
HP:0000426	Prominent nasal bridge	Anterior positioning of the nasal root in comparison to the usual positioning for age.
HP:0000271	Abnormality of the face	An abnormality of the face.
HP:0000582	Upslanted palpebral fissure	The palpebral fissure inclination is more than two standard deviations above the mean for age (objective); or, the inclination of the palpebral fissure is greater than typical for age.
HP:0000448	Prominent nose	Distance between subnasale and pronasale more than two standard deviations above the mean, or alternatively, an apparently increased anterior protrusion of the nasal tip.
HP:0002025	Anal stenosis	Abnormal narrowing of the anal opening.
HP:0002023	Anal atresia	Congenital absence of the anus, i.e., the opening at the bottom end of the intestinal tract.
HP:0012732	Anorectal anomaly	An abnormality of the anus or rectum.
HP:0002028	Chronic diarrhea	The presence of chronic diarrhea, which is usually taken to mean diarrhea that has persisted for over 4 weeks.
HP:0006532	Recurrent pneumonia	An increased susceptibility to pneumonia as manifested by a history of recurrent episodes of pneumonia.
HP:0005425	Recurrent sinopulmonary infections	An increased susceptibility to infections involving both the paranasal sinuses and the lungs, as manifested by a history of recurrent sinopulmonary infections.
HP:0002205	Recurrent respiratory infections	An increased susceptibility to respiratory infections as manifested by a history of recurrent respiratory infections.
HP:0001890	Autoimmune hemolytic anemia	An autoimmune form of hemolytic anemia.
HP:0001595	Abnormality of the hair	An abnormality of the hair.
HP:0011362	Abnormal hair quantity	An abnormal amount of hair.
HP:0001268	Mental deterioration	Loss of previously present mental abilities, generally in adults.
HP:0007018	Attention deficit hyperactivity disorder	Attention deficit hyperactivity disorder (ADHD) manifests at age 2-3 years or by first grade at the latest. The main symptoms are distractibility, impulsivity, hyperactivity, and often trouble organizing tasks and projects, difficulty going to sleep,

		and social problems from being aggressive, loud, or impatient.
HP:0001873	Thrombocytopenia	A reduction in the number of circulating thrombocytes.
HP:0001878	Hemolytic anemia	A type of anemia caused by premature destruction of red blood cells (hemolysis).
HP:0000400	Macrotia	Median longitudinal ear length greater than two standard deviations above the mean and median ear width greater than two standard deviations above the mean (objective); or, apparent increase in length and width of the pinna (subjective).
HP:0000364	Hearing abnormality	An abnormality of the sensory perception of sound.
HP:0004326	Cachexia	Severe weight loss, wasting of muscle, loss of appetite, and general debility related to a chronic disease.
HP:0004322	Short stature	A height below that which is expected according to age and gender norms. Although there is no universally accepted definition of short stature, many refer to "short stature" as height more than 2 standard deviations below the mean for age and gender (or below the 3rd percentile for age and gender dependent norms).
HP:0003220	Abnormality of chromosome stability	A type of chromosomal aberration characterised by reduced resistance of chromosomes to change or deterioration.

4.61.1.2 Frequent

Term Identifier	Term Name	Definition
HP:0100515	Pollakisuria	Increased frequency of urination.
HP:0002664	Neoplasm	An organ or organ-system abnormality that consists of uncontrolled autonomous cell-proliferation which can occur in any part of the body as a benign or malignant neoplasm (tumour).

4.61.1.3 Occasional

Term Identifier	Term Name	Definition
HP:0100335	Non-midline cleft lip	Clefting of the upper lip affecting the lateral portions of the upper lip rather than the midline/median region.
HP:0000492	Abnormal eyelid morphology	An abnormality of the eyelids.

HP:0000175	Cleft palate	Cleft palate is a developmental defect of the palate resulting from a failure of fusion of the palatine processes and manifesting as a separation of the roof of the mouth (soft and hard palate).
HP:0002859	Rhabdomyosarcoma	
HP:0009733	Glioma	The presence of a glioma, which is a neoplasm of the central nervous system originating from a glial cell (astrocytes or oligodendrocytes).
HP:0002488	Acute leukemia	A clonal (malignant) hematopoietic disorder with an acute onset, affecting the bone marrow and the peripheral blood. The malignant cells show minimal differentiation and are called blasts, either myeloid blasts (myeloblasts) or lymphoid blasts (lymphoblasts).
HP:0002665	Lymphoma	A cancer originating in lymphocytes and presenting as a solid tumor of lymphoid cells.
HP:0012191	B-cell lymphoma	A type of lymphoma that originates in B-cells.
HP:0012190	T-cell lymphoma	A type of lymphoma that originates in T-cells.
HP:0001480	Freckling	The presence of an increased number of freckles, small circular spots on the skin that are darker than the surrounding skin because of deposits of melanin.
HP:0000992	Cutaneous photosensitivity	An increased sensitivity of the skin to light. Photosensitivity may result in a rash upon exposure to the sun (which is known as photodermatitis). Photosensitivity can be diagnosed by phototests in which light is shone on small areas of skin.
HP:0002269	Abnormality of neuronal migration	An abnormality resulting from an anomaly of neuronal migration, i.e., of the process by which neurons travel from their origin to their final position in the brain.
HP:0001324	Muscle weakness	Reduced strength of muscles.
HP:0003202	Skeletal muscle atrophy	The presence of skeletal muscular atrophy (which is also known as amyotrophy).
HP:0002878	Respiratory failure	A severe form of respiratory insufficiency characterized by inadequate gas exchange such that the levels of oxygen or carbon dioxide cannot be maintained within normal limits.

HP:0003011	Abnormality of the musculature	Abnormality originating in one or more muscles, i.e., of the set of muscles of body.
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Source: HPO-ORDO Ontological Module (21) - Validation association date: 01.06.2016

4.62 Omenn syndrome

4.62.1.1 Very frequent

Term Identifier	Term Name	Definition
HP:0004430	Severe combined immunodeficiency	A combined immunodeficiency primary immune deficiency that is characterized by a more severe defect in both the T- and B-lymphocyte systems.
HP:0001019	Erythroderma	An inflammatory exfoliative dermatosis involving nearly all of the surface of the skin. Erythroderma develops suddenly. A patchy erythema may generalize and spread to affect most of the skin. Scaling may appear in 2-6 days and be accompanied by hot, red, dry skin, malaise, and fever.
HP:0002716	Lymphadenopathy	Enlargment (swelling) of a lymph node.
HP:0001596	Alopecia	Loss of hair from the head or body.
HP:0004332	Abnormal lymphocyte morphology	An abnormality of lymphocytes.
HP:0002240	Hepatomegaly	Abnormally increased size of the liver.
HP:0002028	Chronic diarrhea	The presence of chronic diarrhea, which is usually taken to mean diarrhea that has persisted for over 4 weeks.
HP:0001508	Failure to thrive	Failure to thrive (FTT) refers to a child whose physical growth is substantially below the norm.

4.62.1.2 Frequent

Term Identifier	Term Name	Definition
HP:0002090	Pneumonia	Inflammation of any part of the lung parenchyma.
HP:0001072	Thickened skin	Laminar thickening of skin.
HP:0000958	Dry skin	Skin characterized by the lack of natural or normal moisture.
HP:0000989	Pruritus	Pruritus is an itch or a sensation that makes a person want to scratch. This term refers to an abnormally increased disposition to experience pruritus.

HP:0007549	Desquamation of skin soon after birth	
HP:0001880	Eosinophilia	Increased count of eosinophils in the blood.
HP:0001974	Leukocytosis	An abnormal increase in the number of leukocytes in the blood.
HP:0001744	Splenomegaly	Abnormal increased size of the spleen.
HP:0000969	Edema	An abnormal accumulation of fluid beneath the skin, or in one or more cavities of the body.
HP:0001945	Fever	Elevated body temperature due to failed thermoregulation.
HP:0100840	Aplasia/Hypoplasia of the eyebrow	Absence or underdevelopment of the eyebrow.

4.62.1.3 Occasional

Term Identifier	Term Name	Definition
HP:0100806	Sepsis	Systemic inflammatory response to infection.
HP:0002960	Autoimmunity	The occurrence of an immune reaction against the organism's own cells or tissues.
HP:0001903	Anemia	A reduction in erythrocytes volume or hemoglobin concentration.
HP:0100646	Thyroiditis	Inflammation of the thyroid gland.
HP:0000821	Hypothyroidism	Deficiency of thyroid hormone.
HP:0001831	Short toe	A toe that appears disproportionately short compared to the foot.
HP:0000100	Nephrotic syndrome	Nephrotic syndrome is a collection of findings resulting from glomerular dysfunction with an increase in glomerular capillary wall permeability associated with pronounced proteinuria. Nephrotic syndrome refers to the constellation of clinical findings that result from severe renal loss of protein, with Proteinuria and hypoalbuminemia, edema, and hyperlipidemia.
HP:0000944	Abnormality of the metaphysis	An abnormality of one or more metaphysis, i.e., of the somewhat wider portion of a long bone that is adjacent to the epiphyseal growth plate and grows during childhood.
HP:0002665	Lymphoma	A cancer originating in lymphocytes and presenting as a solid tumor of lymphoid cells.

Source: HPO-ORDO Ontological Module (21) - Validation association date: 01.06.2016

4.63 Papillon-Lefèvre syndrome

4.63.1.1 Very frequent

Term Identifier	Term Name	Definition
HP:0000982	Palmoplantar keratoderma	Abnormal thickening of the skin of the palms of the hands and the soles of the feet.
HP:0001231	Abnormality of the fingernails	An abnormality of the fingernails.
HP:0000972	Palmoplantar hyperkeratosis	Hyperkeratosis affecting the palm of the hand and the sole of the foot.
HP:0000166	Severe periodontitis	A severe form of periodontitis.
HP:0000704	Periodontitis	Inflammation of the periodontium.
HP:0200039	Pustule	A small elevation of the skin containing cloudy or purulent material usually consisting of necrotic inflammatory cells.
HP:0009804	Reduced number of teeth	The presence of a reduced number of teeth as in Hypodontia or as in Anodontia.
HP:0000164	Abnormality of the dentition	Any abnormality of the teeth.
HP:0000230	Gingivitis	Inflammation of the gingiva.
HP:0006308	Atrophy of alveolar ridges	
HP:0006323	Premature loss of primary teeth	Loss of the primary (also known as deciduous) teeth before the usual age.

4.63.1.2 Frequent

Term Identifier	Term Name	Definition
HP:0001597	Abnormality of the nail	Abnormality of the nail.
HP:0008404	Nail dystrophy	Onychodystrophy (nail dystrophy) refers to nail changes apart from changes of the color (nail dyschromia) and involves partial or complete disruption of the various keratinous layers of the nail plate.
HP:0100838	Recurrent cutaneous abscess formation	An increased susceptibility to cutaneous abscess formation, as manifested by a medical history of recurrent cutaneous abscesses.
HP:0002205	Recurrent respiratory infections	An increased susceptibility to respiratory infections as manifested by a history of recurrent respiratory infections.
HP:0001581	Recurrent skin infections	Infections of the skin that happen multiple times.

HP:0011132	Chronic furunculosis	A furuncle (boil) is a skin infection involving an entire hair follicle and nearby skin tissue. Chronic furunculosis refers to recurrent episodes of furuncles, often caused by recurrent staphylococcus infection.
HP:0002514	Cerebral calcification	The presence of calcium deposition within brain structures.

4.63.1.3 Occasional

Term Identifier	Term Name	Definition
HP:0002231	Sparse body hair	Sparseness of the body hair.
HP:0001073	Cigarette-paper scars	Thin (atrophic) and wide scars.
HP:0000998	Hypertrichosis	Hypertrichosis is increased hair growth that is abnormal in quantity or location.
HP:0001053	Hypopigmented skin patches	
HP:0002230	Generalized hirsutism	Abnormally increased hair growth over much of the entire body.
HP:0002861	Melanoma	The presence of a melanoma, a malignant cancer originating from pigment producing melanocytes. Melanoma can originate from the skin or the pigmented layers of the eye (the uvea).
HP:0008069	Neoplasm of the skin	A tumor (abnormal growth of tissue) of the skin.
HP:0002860	Squamous cell carcinoma	The presence of squamous cell carcinoma of the skin.
HP:0002797	Osteolysis	Osteolysis refers to the destruction of bone through bone resorption with removal or loss of calcium.
HP:0001166	Arachnodactyly	Abnormally long and slender fingers ("spider fingers").
HP:0100523	Liver abscess	The presence of an abscess of the liver.

Source: HPO-ORDO Ontological Module (21) - Validation association date: 01.06.2016

4.64 Properdin P factor complement deficiency (PFC)

4.64.1.1 No frequency available

Term Identifier	Term Name	Definition
HP:0001419	X-linked recessive inheritance	A mode of inheritance that is observed for recessive traits related to a gene encoded on the X chromosome. In the context of medical genetics, X-linked recessive disorders manifest in males (who have one copy of the

		X chromosome and are thus hemizygotes), but generally not in female heterozygotes who have one mutant and one normal allele.
HP:0005423	Dysfunctional alternative complement pathway	An abnormality of the functioning of any aspect of the alternative complement pathway.
HP:0005381	Recurrent meningococcal disease	Recurrent infections by Neisseria meningitidis (one of the most common causes of bacterial meningitis), which is also known as meningococcus.

Source: OMIM #312060 – Creation date: 04.06.1986, Victor A. McKusick; updated: 14.01.2014, Cassandra L. Kniffin

4.65 Schimke disease

4.65.1.1 Very frequent

Term Identifier	Term Name	Definition
HP:0000926	Platyspondyly	A flattened vertebral body shape with reduced distance between the vertebral endplates.
HP:0005930	Abnormality of epiphysis morphology	An anomaly of epiphysis, which is the expanded articular end of a long bone that develops from a secondary ossification center, and which during the period of growth is either entirely cartilaginous or is separated from the shaft by a cartilaginous disk.
HP:0003300	Ovoid vertebral bodies	When viewed in lateral radiographs, vertebral bodies have a roughly rectangular configuration. This term applies if the vertebral body appears rounded or oval.
HP:0003312	Abnormal form of the vertebral bodies	Abnormal morphology of vertebral body.
HP:0002827	Hip dislocation	Displacement of the femur from its normal location in the hip joint.
HP:0003307	Hyperlordosis	Abnormally increased curvature (anterior concavity) of the lumbar or cervical spine.
HP:0002843	Abnormal T cell morphology	An abnormality of T cells.
HP:0001903	Anemia	A reduction in erythrocytes volume or hemoglobin concentration.
HP:0001873	Thrombocytopenia	A reduction in the number of circulating thrombocytes.
HP:0001888	Lymphopenia	A reduced number of lymphocytes in the blood.

HP:0000691	Microdontia	Decreased size of the teeth, which can be defined as a mesiodistal tooth diameter (width) more than 2 SD below mean. Alternatively, an apparently decreased maximum width of tooth.
HP:0005280	Depressed nasal bridge	Posterior positioning of the nasal root in relation to the overall facial profile for age.
HP:0000470	Short neck	Diminished length of the neck.
HP:0000414	Bulbous nose	Increased volume and globular shape of the anteroinferior aspect of the nose.
HP:0100820	Glomerulopathy	Inflammatory or noninflammatory diseases affecting the glomeruli of the nephron.
HP:0000100	Nephrotic syndrome	Nephrotic syndrome is a collection of findings resulting from glomerular dysfunction with an increase in glomerular capillary wall permeability associated with pronounced proteinuria. Nephrotic syndrome refers to the constellation of clinical findings that result from severe renal loss of protein, with Proteinuria and hypoalbuminemia, edema, and hyperlipidemia.
HP:0000995	Melanocytic nevus	A oval and round, colored (usually medium-to dark brown, reddish brown, or flesh colored) lesion. Typically, a melanocytic nevus is less than 6 mm in diameter, but may be much smaller or larger.
HP:0003521	Disproportionate short-trunk short stature	A type of disproportionate short stature characterized by a short trunk but a average-sized limbs.
HP:0001511	Intrauterine growth retardation	An abnormal restriction of fetal growth with fetal weight below the tenth percentile for gestational age.
HP:0000093	Proteinuria	Increased levels of protein in the urine.
HP:0005374	Cellular immunodeficiency	An immunodeficiency characterized by defective cell-mediated immunity or humoral immunity.

4.65.1.2 Frequent

Term Identifier	Term Name	Definition
HP:0007565	Multiple cafe-au-lait spots	The presence of six or more cafe-au-lait spots.

Source: HPO-ORDO Ontological Module (21) - Validation association date: 01.06.2016

4.66 Seckel syndrome

4.66.1.1 Very frequent

Term Identifier	Term Name	Definition
HP:0000252	Microcephaly	Occipito-frontal (head) circumference (OFC) less than -3 standard deviations compared to appropriate, age matched, normal standards (Ross JJ, Frias JL 1977, PMID:9683597). Alternatively, decreased size of the cranium.
HP:0000444	Convex nasal ridge	Nasal ridge curving anteriorly to an imaginary line that connects the nasal root and tip. The nose appears often also prominent, and the columella low.
HP:0000347	Micrognathia	Developmental hypoplasia of the mandible.
HP:0001363	Craniosynostosis	Craniosynostosis refers to the premature closure of the cranial sutures. Primary craniosynostosis refers to the closure of one or more sutures due to abnormalities in skull development, and secondary craniosynostosis results from failure of brain growth.
HP:0000275	Narrow face	Bizygomatic (upper face) and bigonial (lower face) width are both more than 2 standard deviations below the mean (objective); or, an apparent reduction in the width of the upper and lower face (subjective).
HP:0002750	Delayed skeletal maturation	A decreased rate of skeletal maturation. Delayed skeletal maturation can be diagnosed on the basis of an estimation of the bone age from radiographs of specific bones in the human body.
HP:0100543	Cognitive impairment	Abnormality in the process of thought including the ability to process information.
HP:0001249	Intellectual disability	Subnormal intellectual functioning which originates during the developmental period. Intellectual disability, previously referred to as mental retardation, has been defined as an IQ score below 70.
HP:0011342	Mild global developmental delay	Mild global developmental delay
HP:0004322	Short stature	A height below that which is expected according to age and gender norms. Although there is no universally accepted definition of short stature, many refer to "short stature" as height more than 2 standard deviations below the mean for age

		and gender (or below the 3rd percentile for age and gender dependent norms).
HP:0004326	Cachexia	Severe weight loss, wasting of muscle, loss of appetite, and general debility related to a chronic disease.
HP:0001511	Intrauterine growth retardation	An abnormal restriction of fetal growth with fetal weight below the tenth percentile for gestational age.
HP:0004209	Clinodactyly of the 5th finger	Clinodactyly refers to a bending or curvature of the fifth finger in the radial direction (i.e., towards the 4th finger).
HP:0001852	Sandal gap	A widely spaced gap between the first toe (the great toe) and the second toe.
HP:0007495	Prematurely aged appearance	

4.66.1.2 Frequent

Term Identifier	Term Name	Definition
HP:0000494	Downslanted palpebral fissures	The palpebral fissure inclination is more than two standard deviations below the mean.
HP:0002209	Sparse scalp hair	Decreased number of head hairs per unit area.
HP:0009804	Reduced number of teeth	The presence of a reduced number of teeth as in Hypodontia or as in Anodontia.
HP:0010579	Cone-shaped epiphysis	Cone-shaped epiphyses (also known as coned epiphyses) are epiphyses that invaginate into cupped metaphyses. That is, the epiphysis has a cone-shaped distal extension resulting from increased growth of the central portion of the epiphysis relative to its periphery.
HP:0000682	Abnormality of dental enamel	An abnormality of the dental enamel.
HP:0001385	Hip dysplasia	The presence of developmental dysplasia of the hip.
HP:0005692	Joint hyperflexibility	Increased mobility and flexibility in the joint due to the tension in tissues such as ligaments and muscles.
HP:0000387	Absent earlobe	Absence of fleshy non-cartilaginous tissue inferior to the tragus and incisura.
HP:0000363	Abnormality of earlobe	An abnormality of the lobule of pinna.
HP:0000501	Glaucoma	Glaucoma refers loss of retinal ganglion cells in a characteristic pattern of optic neuropathy usually associated with increased intraocular pressure.

4.66.1.3 Occasional

Term Identifier	Term Name	Definition
HP:0002650	Scoliosis	The presence of an abnormal lateral curvature of the spine.

Source: HPO-ORDO Ontological Module (21) - Validation association date: 01.06.2016

4.67 Selective CD4 cell deficiency

4.67.1.1 No frequency available

Term Identifier	Term Name	Definition
HP:0004429	Recurrent viral infections	Increased susceptibility to viral infections, as manifested by recurrent episodes of viral infection.
HP:0002718	Recurrent bacterial infections	Increased susceptibility to bacterial infections, as manifested by recurrent episodes of bacterial infection.
HP:0002841	Recurrent fungal infections	Increased susceptibility to fungal infections, as manifested by multiple episodes of fungal infection.
HP:0410018	Recurrent ear infections	Increased susceptibility to ear infections, as manifested by recurrent episodes of ear infections.
HP:0002837	Recurrent bronchitis	An increased susceptibility to bronchitis as manifested by a history of recurrent bronchitis.
HP:0011108	Recurrent sinusitis	A recurrent form of sinusitis.
HP:0006532	Recurrent pneumonia	An increased susceptibility to pneumonia as manifested by a history of recurrent episodes of pneumonia.
HP:0030885	Recurrent parasitic infections	Increased susceptibility to parasitic infections, as manifested by recurrent episodes of parasitic infection.
HP:0001888	Lymphopenia	A reduced number of lymphocytes in the blood.
HP:0002721	Immunodeficiency	Failure of the immune system to protect the body adequately from infection, due to the absence or insufficiency of some component process or substance.
HP:0002725	Systemic lupus erythematosus	A chronic, relapsing, inflammatory, and often febrile multisystemic disorder of connective tissue, characterized principally by involvement of the skin, joints, kidneys, and serosal membranes.
HP:0001890	Autoimmune hemolytic anemia	An autoimmune form of hemolytic anemia.

HP:0002665	Lymphoma	A cancer originating in lymphocytes and presenting as a solid tumor of lymphoid cells.
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Source: OMIM #615518 – Creation date: 07.11.2013, Marla J.F. O'Neill

4.68 Selective IgA deficiency

4.68.1.1 No frequency available

Term Identifier	Term Name	Definition
HP:0002720	Decreased circulating IgA level	Decreased levels of immunoglobulin A (IgA).
HP:0005425	Recurrent sinopulmonary infections	An increased susceptibility to infections involving both the paranasal sinuses and the lungs, as manifested by a history of recurrent sinopulmonary infections.
HP:0007378	Neoplasm of the gastrointestinal tract	A tumor (abnormal growth of tissue) of the gastrointestinal tract.
HP:0004798	Recurrent infection of the gastrointestinal tract	Recurrent infection of the gastrointestinal tract.
HP:0012393	Allergy	An allergy is an immune response or reaction to substances that are usually not harmful.
HP:0002608	Celiac disease	Celiac disease (CD) is an autoimmune condition affecting the small intestine, triggered by the ingestion of gluten, the protein fraction of wheat, barley, and rye. Clinical manifestations of CD are highly variable and include both gastrointestinal and non-gastrointestinal features. The hallmark of CD is an immune-mediated enteropathy. This term is included because the occurrence of CD is seen as a feature of a number of other diseases.
HP:0100280	Crohn's disease	A chronic granulomatous inflammatory disease of the intestines that may affect any part of the gastrointestinal tract from mouth to anus, causing a wide variety of symptoms. It primarily causes abdominal pain, diarrhea which may be bloody, vomiting, or weight loss, but may also cause complications outside of the gastrointestinal tract such as skin rashes, arthritis, inflammation of the eye, tiredness, and lack of concentration. Crohn's disease is thought to be an

		autoimmune disease, in which the body's immune system attacks the gastrointestinal tract, causing inflammation.
HP:0100279	Ulcerative colitis	A chronic inflammatory bowel disease that includes characteristic ulcers, or open sores, in the colon. The main symptom of active disease is usually constant diarrhea mixed with blood, of gradual onset and intermittent periods of exacerbated symptoms contrasting with periods that are relatively symptom-free. In contrast to Crohn's disease this special form of colitis begins in the distal parts of the rectum, spreads continually upwards and affects only mucose and submucose tissue of the colon.
HP:0002725	Systemic lupus erythematosus	A chronic, relapsing, inflammatory, and often febrile multisystemic disorder of connective tissue, characterized principally by involvement of the skin, joints, kidneys, and serosal membranes.
HP:0001370	Rheumatoid arthritis	Inflammatory changes in the synovial membranes and articular structures with widespread fibrinoid degeneration of the collagen fibers in mesenchymal tissues, as well as atrophy and rarefaction of bony structures.
HP:0002665	Lymphoma	A cancer originating in lymphocytes and presenting as a solid tumor of lymphoid cells.
HP:0100522	Thymoma	A tumor originating from the epithelial cells of the thymus.
HP:0002099	Asthma	Asthma is characterized by increased responsiveness of the tracheobronchial tree to multiple stimuli, leading to narrowing of the air passages with resultant dyspnea, cough, and wheezing.

Source: OMIM #137100 – Creation date: 04.06.1986, Victor A. McKusick; updated: 24.09.2010, Marla J.F. O'Neill

OMIM #609529 – Creation date: 09.08.2005, Anna M. Stumpf; updated: 04.08.2004, Cassandra L. Kniffin

4.69 Selective IgM deficiency

4.69.1.1 No frequency available

Term Identifier	Term Name	Definition
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HP:0004429	Recurrent viral infections	Increased susceptibility to viral infections, as manifested by recurrent episodes of viral infection.
HP:0002718	Recurrent bacterial infections	Increased susceptibility to bacterial infections, as manifested by recurrent episodes of bacterial infection.
HP:0002841	Recurrent fungal infections	Increased susceptibility to fungal infections, as manifested by multiple episodes of fungal infection.
HP:0410018	Recurrent ear infections	Increased susceptibility to ear infections, as manifested by recurrent episodes of ear infections.
HP:0002837	Recurrent bronchitis	An increased susceptibility to bronchitis as manifested by a history of recurrent bronchitis.
HP:0011108	Recurrent sinusitis	A recurrent form of sinusitis.
HP:0006532	Recurrent pneumonia	An increased susceptibility to pneumonia as manifested by a history of recurrent episodes of pneumonia.
HP:0002014	Diarrhea	Abnormally increased frequency of loose or watery bowel movements.
HP:0000988	Skin rash	A red eruption of the skin.
HP:0032163	Molluscum contagiosum	<p>Molluscum contagiosum is a cutaneous viral infection that is commonly observed in both healthy and immunocompromised children. The infection is caused by a member of the Poxviridae family, the molluscum contagiosum virus. Molluscum contagiosum presents as single or multiple small white or flesh-colored papules that typically have a central umbilication. The central umbilication may be difficult to observe in young children and, instead, may bear an appearance similar to an acneiform eruption. The lesions vary in size (from 1 mm to 1 cm in diameter) and are painless, although a subset of patients report pruritus in the area of infection. On average, 11-20 papules appear on the body during the course of infection and generally remains a self-limiting disease. However, in immunosuppressed patients, molluscum contagiosum can be a severe infection with hundreds of lesions developing on the body. Extensive eruption is indicative of an advanced immunodeficiency state.</p>
HP:0001508	Failure to thrive	Failure to thrive (FTT) refers to a child whose physical growth is substantially below the norm.
HP:0004395	Malnutrition	
HP:0002850	Decreased circulating total IgM	An abnormally decreased level of immunoglobulin M (IgM) in blood.

Source: (28)

4.70 Severe combined immunodeficiency (SCID)

4.70.1.1 Very frequent

Term Identifier	Term Name	Definition
HP:0100806	Sepsis	Systemic inflammatory response to infection.
HP:0002721	Immunodeficiency	Failure of the immune system to protect the body adequately from infection, due to the absence or insufficiency of some component process or substance.
HP:0100763	Abnormality of the lymphatic system	An anomaly of the lymphatic system, a network of lymphatic vessels that carry a clear fluid called lymph unidirectionally towards either the right lymphatic duct or the thoracic duct, which in turn drain into the right and left subclavian veins respectively.
HP:0004430	Severe combined immunodeficiency	A combined immunodeficiency primary immune deficiency that is characterized by a more severe defect in both the T- and B-lymphocyte systems.
HP:0002205	Recurrent respiratory infections	An increased susceptibility to respiratory infections as manifested by a history of recurrent respiratory infections.
HP:0002028	Chronic diarrhea	The presence of chronic diarrhea, which is usually taken to mean diarrhea that has persisted for over 4 weeks.
HP:0001945	Fever	Elevated body temperature due to failed thermoregulation.
HP:0001508	Failure to thrive	Failure to thrive (FTT) refers to a child whose physical growth is substantially below the norm.

4.70.1.2 Frequent

Term Identifier	Term Name	Definition
HP:0000988	Skin rash	A red eruption of the skin.
HP:0001888	Lymphopenia	A reduced number of lymphocytes in the blood.
HP:0001596	Alopecia	Loss of hair from the head or body.

4.70.1.3 Occasional

Term Identifier	Term Name	Definition
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HP:0000389	Chronic otitis media	Chronic otitis media refers to fluid, swelling, or infection of the middle ear that does not heal and may cause permanent damage to the ear.
HP:0002240	Hepatomegaly	Abnormally increased size of the liver.
HP:0001744	Splenomegaly	Abnormal increased size of the spleen.
HP:0000164	Abnormality of the dentition	Any abnormality of the teeth.
HP:0000252	Microcephaly	Occipito-frontal (head) circumference (OFC) less than -3 standard deviations compared to appropriate, age matched, normal standards (Ross JJ, Frias JL 1977, PMID:9683597). Alternatively, decreased size of the cranium.
HP:0000407	Sensorineural hearing impairment	A type of hearing impairment in one or both ears related to an abnormal functionality of the cochlear nerve.
HP:0000010	Recurrent urinary tract infections	Repeated infections of the urinary tract.

Source: HPO-ORDO Ontological Module (21) - Validation association date: 01.06.2016

4.71 Shwachman-Diamond syndrome

4.71.1.1 Very frequent

Term Identifier	Term Name	Definition
HP:0001875	Neutropenia	An abnormally low number of neutrophils in the peripheral blood.
HP:0001738	Exocrine pancreatic insufficiency	Impaired function of the exocrine pancreas associated with a reduced ability to digest foods because of lack of digestive enzymes.
HP:0001290	Generalized hypotonia	Generalized muscular hypotonia (abnormally low muscle tone).

4.71.1.2 Frequent

Term Identifier	Term Name	Definition
HP:0000938	Osteopenia	Osteopenia is a term to define bone density that is not normal but also not as low as osteoporosis. By definition from the World Health Organization osteopenia is defined by bone densitometry as a T score -1 to -2.5.
HP:0002750	Delayed skeletal maturation	A decreased rate of skeletal maturation. Delayed skeletal maturation can be diagnosed on the basis of an estimation of

		the bone age from radiographs of specific bones in the human body.
HP:0000944	Abnormality of the metaphysis	An abnormality of one or more metaphysis, i.e., of the somewhat wider portion of a long bone that is adjacent to the epiphyseal growth plate and grows during childhood.
HP:0001903	Anemia	A reduction in erythrocytes volume or hemoglobin concentration.
HP:0001873	Thrombocytopenia	A reduction in the number of circulating thrombocytes.
HP:0002024	Malabsorption	Impaired ability to absorb one or more nutrients from the intestine.
HP:0001263	Global developmental delay	A delay in the achievement of motor or mental milestones in the domains of development of a child, including motor skills, speech and language, cognitive skills, and social and emotional skills. This term should only be used to describe children younger than five years of age.
HP:0001249	Intellectual disability	Subnormal intellectual functioning which originates during the developmental period. Intellectual disability, previously referred to as mental retardation, has been defined as an IQ score below 70.
HP:0001508	Failure to thrive	Failure to thrive (FTT) refers to a child whose physical growth is substantially below the norm.
HP:0004322	Short stature	A height below that which is expected according to age and gender norms. Although there is no universally accepted definition of short stature, many refer to "short stature" as height more than 2 standard deviations below the mean for age and gender (or below the 3rd percentile for age and gender dependent norms).
HP:0001510	Growth delay	A deficiency or slowing down of growth pre- and postnatally.
HP:0002719	Recurrent infections	Increased susceptibility to infections.
HP:0000964	Eczema	Eczema is a form of dermatitis. The term eczema is broadly applied to a range of persistent skin conditions and can be related to a number of underlying conditions. Manifestations of eczema can include dryness and recurring skin rashes with redness, skin edema, itching and dryness, crusting, flaking, blistering, cracking, oozing, or bleeding.

HP:0008064	Ichthyosis	An abnormality of the skin characterized the presence of excessive amounts of dry surface scales on the skin resulting from an abnormality of keratinization.
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4.71.1.3 Occasional

Term Identifier	Term Name	Definition
HP:0000768	Pectus carinatum	A deformity of the chest caused by overgrowth of the ribs and characterized by protrusion of the sternum.
HP:0002650	Scoliosis	The presence of an abnormal lateral curvature of the spine.
HP:0010306	Short thorax	Reduced inferior to superior extent of the thorax.
HP:0005528	Bone marrow hypocellularity	A reduced number of hematopoietic cells present in the bone marrow relative to marrow fat.
HP:0001915	Aplastic anemia	Aplastic anemia is defined as pancytopenia with a hypocellular marrow.
HP:0000691	Microdontia	Decreased size of the teeth, which can be defined as a mesiodistal tooth diameter (width) more than 2 SD below mean. Alternatively, an apparently decreased maximum width of tooth.
HP:0000670	Carious teeth	Caries is a multifactorial bacterial infection affecting the structure of the tooth. This term has been used to describe the presence of more than expected dental caries.
HP:0011107	Recurrent aphthous stomatitis	Recurrent episodes of ulceration of the oral mucosa, typically presenting as painful, sharply circumscribed fibrin-covered mucosal defects with a hyperemic border.
HP:0002240	Hepatomegaly	Abnormally increased size of the liver.
HP:0001288	Gait disturbance	The term gait disturbance can refer to any disruption of the ability to walk. In general, this can refer to neurological diseases but also fractures or other sources of pain that is triggered upon walking. However, in the current context gait disturbance refers to difficulty walking on the basis of a neurological or muscular disease.
HP:0004808	Acute myeloid leukemia	A form of leukemia characterized by overproduction of an early myeloid cell.
HP:0002863	Myelodysplasia	Clonal hematopoietic stem cell disorders characterized by dysplasia (ineffective production) in one or more hematopoietic cell lineages, leading to anemia and cytopenia.

HP:0001909	Leukemia	A cancer of the blood and bone marrow characterized by an abnormal proliferation of leukocytes.
HP:0100651	Type I diabetes mellitus	A chronic condition in which the pancreas produces little or no insulin. Type I diabetes mellitus is manifested by the sudden onset of severe hyperglycemia with rapid progression to diabetic ketoacidosis unless treated with insulin.

Source: HPO-ORDO Ontological Module (21) - Validation association date: 01.06.2016

4.72 *Thymoma with immunodeficiency*

4.72.1.1 Very frequent

Term Identifier	Term Name	Definition
HP:0004313	Decreased antibody level in blood	An abnormally decreased level of immunoglobulin in blood.
HP:0100721	Mediastinal lymphadenopathy	Swelling of lymph nodes within the mediastinum, the central compartment of the thoracic cavities that contains the heart and the great vessels, the esophagus, and trachea and other structures including lymph nodes.
HP:0100522	Thymoma	A tumor originating from the epithelial cells of the thymus.

4.72.1.2 Frequent

Term Identifier	Term Name	Definition
HP:0001581	Recurrent skin infections	Infections of the skin that happen multiple times.
HP:0000246	Sinusitis	Inflammation of the paranasal sinuses owing to a viral, bacterial, or fungal infection, allergy, or an autoimmune reaction.
HP:0001881	Abnormal leukocyte morphology	An abnormality of leukocytes.
HP:0012735	Cough	A sudden, audible expulsion of air from the lungs through a partially closed glottis, preceded by inhalation.
HP:0002094	Dyspnea	Difficult or labored breathing.
HP:0002110	Bronchiectasis	Persistent abnormal dilatation of the bronchi owing to localized and irreversible destruction and widening of the large airways.

HP:0003473	Fatigable weakness	A type of weakness that occurs after a muscle group is used and lessens if the muscle group has some rest. That is, there is diminution of strength with repetitive muscle actions.
HP:0002015	Dysphagia	Difficulty in swallowing.
HP:0000508	Ptosis	The upper eyelid margin is positioned 3 mm or more lower than usual and covers the superior portion of the iris (objective); or, the upper lid margin obscures at least part of the pupil (subjective).
HP:0000010	Recurrent urinary tract infections	Repeated infections of the urinary tract.
HP:0001618	Dysphonia	An impairment in the ability to produce voice sounds.

4.72.1.3 Occasional

Term Identifier	Term Name	Definition
HP:0002205	Recurrent respiratory infections	An increased susceptibility to respiratory infections as manifested by a history of recurrent respiratory infections.
HP:0001903	Anemia	A reduction in erythrocytes volume or hemoglobin concentration.
HP:0001873	Thrombocytopenia	A reduction in the number of circulating thrombocytes.
HP:0010515	Aplasia/Hypoplasia of the thymus	Absence or underdevelopment of the thymus.
HP:0000819	Diabetes mellitus	A group of abnormalities characterized by hyperglycemia and glucose intolerance.
HP:0002014	Diarrhea	Abnormally increased frequency of loose or watery bowel movements.

Source: HPO-ORDO Ontological Module (21) - Validation association date: 01.06.2016

4.73 Warts, hypogammaglobulinemia, infections and myelokathexis (WHIM)

4.73.1.1 No frequency available

Term Identifier	Term Name	Definition
HP:0005561	Abnormality of bone marrow cell morphology	An anomaly of the form or number of cells in the bone marrow.
HP:0031020	Bone marrow hypercellularity	A larger than normal amount or percentage of hematopoietic cells relative to marrow fat.

HP:0001875	Neutropenia	An abnormally low number of neutrophils in the peripheral blood.
HP:0031160	Myelokathexis	Impaired egress of mature neutrophils from bone marrow causing neutropenia.
HP:0002718	Recurrent bacterial infections	Increased susceptibility to bacterial infections, as manifested by recurrent episodes of bacterial infection.
HP:0004313	Decreased antibody level in blood	An abnormally decreased level of immunoglobulin in blood.
HP:0002788	Recurrent upper respiratory tract infections	An increased susceptibility to upper respiratory tract infections as manifested by a history of recurrent upper respiratory tract infections (running ears - otitis, sinusitis, pharyngitis, tonsillitis).
HP:0004315	Decreased circulating IgG level	An abnormally decreased level of immunoglobulin G (IgG) in blood.
HP:0000055	Abnormality of female external genitalia	An abnormality of the female external genitalia.
HP:0000008	Abnormality of female internal genitalia	An abnormality of the female internal genitalia.
HP:0000006	Autosomal dominant inheritance	A mode of inheritance that is observed for traits related to a gene encoded on one of the autosomes (i.e., the human chromosomes 1-22) in which a trait manifests in heterozygotes. In the context of medical genetics, an autosomal dominant disorder is caused when a single copy of the mutant allele is present. Males and females are affected equally, and can both transmit the disorder with a risk of 50% for each child of inheriting the mutant allele.
HP:0002110	Bronchiectasis	Persistent abnormal dilatation of the bronchi owing to localized and irreversible destruction and widening of the large airways.
HP:0200043	Verrucae	Warts, benign growths on the skin or mucous membranes that cause cosmetic problems as well as pain and discomfort. Warts most often occur on the hands, feet, and genital areas.

Source: OMIM #193670 – Creation date: 06.12.1990, Victor A. McKusick; updated: 06.02.2019, Ada Hamosh
PMID: 25662009 (57)

4.74 Wiskott-Aldrich-syndrome

4.74.1.1 Very Frequent

Term Identifier	Term Name	Definition
HP:0011875	Abnormal platelet morphology	An anomaly in platelet form, ultrastructure, or intracellular organelles.
HP:0003010	Prolonged bleeding time	Prolongation of the time taken for a standardized skin cut of fixed depth and length to stop bleeding.
HP:0011029	Internal hemorrhage	The presence of hemorrhage within the body.
HP:0001873	Thrombocytopenia	A reduction in the number of circulating thrombocytes.
HP:0001888	Lymphopenia	A reduced number of lymphocytes in the blood.
HP:0000389	Chronic otitis media	Chronic otitis media refers to fluid, swelling, or infection of the middle ear that does not heal and may cause permanent damage to the ear.
HP:0002205	Recurrent respiratory infections	An increased susceptibility to respiratory infections as manifested by a history of recurrent respiratory infections.
HP:0000246	Sinusitis	Inflammation of the paranasal sinuses owing to a viral, bacterial, or fungal infection, allergy, or an autoimmune reaction.
HP:0002721	Immunodeficiency	Failure of the immune system to protect the body adequately from infection, due to the absence or insufficiency of some component process or substance.
HP:0000388	Otitis media	Inflammation or infection of the middle ear.
HP:0007420	Spontaneous hematomas	Spontaneous development of hematomas (hematoma) or bruises without significant trauma.
HP:0000978	Bruising susceptibility	An ecchymosis (bruise) refers to the skin discoloration caused by the escape of blood into the tissues from ruptured blood vessels. This term refers to an abnormally increased susceptibility to bruising. The corresponding phenotypic abnormality is generally elicited on medical history as a report of frequent ecchymoses or bruising without adequate trauma.
HP:0001945	Fever	Elevated body temperature due to failed thermoregulation.
HP:0002028	Chronic diarrhea	The presence of chronic diarrhea, which is usually taken to mean diarrhea that has persisted for over 4 weeks.

4.74.1.2 Frequent

Term Identifier	Term Name	Definition
HP:0001879	Abnormal eosinophil morphology	An eosinophil abnormality.
HP:0002248	Hematemesis	The vomiting of blood.
HP:0001903	Anemia	A reduction in erythrocytes volume or hemoglobin concentration.
HP:0002573	Hematochezia	The passage of fresh (red) blood per anus, usually in or with stools. Most rectal bleeding comes from the colon, rectum, or anus.
HP:0001935	Microcytic anemia	A kind of anemia in which the volume of the red blood cells is reduced.
HP:0001878	Hemolytic anemia	A type of anemia caused by premature destruction of red blood cells (hemolysis).
HP:0002960	Autoimmunity	The occurrence of an immune reaction against the organism's own cells or tissues.
HP:0002037	Inflammation of the large intestine	Inflammation, or an inflammatory state in the large intestine.
HP:0000967	Petechiae	Petechiae are pinpoint-sized reddish/purple spots, resembling a rash, that appear just under the skin or a mucous membrane when capillaries have ruptured and some superficial bleeding into the skin has happened. This term refers to an abnormally increased susceptibility to developing petechiae.
HP:0011675	Arrhythmia	Any cardiac rhythm other than the normal sinus rhythm. Such a rhythm may be either of sinus or ectopic origin and either regular or irregular. An arrhythmia may be due to a disturbance in impulse formation or conduction or both.
HP:0001328	Specific learning disability	Impairment of certain skills such as reading or writing, coordination, self-control, or attention that interfere with the ability to learn. The impairment is not related to a global deficiency of intelligence.
HP:0002094	Dyspnea	Difficult or labored breathing.

4.74.1.3 Occasional

Term Identifier	Term Name	Definition
HP:0011869	Abnormal platelet function	Any anomaly in the function of thrombocytes.

HP:0002170	Intracranial hemorrhage	Hemorrhage occurring within the skull.
HP:0001875	Neutropenia	An abnormally low number of neutrophils in the peripheral blood.
HP:0100806	Sepsis	Systemic inflammatory response to infection.
HP:0001025	Urticaria	Raised, well-circumscribed areas of erythema and edema involving the dermis and epidermis. Urticaria is intensely pruritic, and blanches completely with pressure.
HP:0002633	Vasculitis	Inflammation of blood vessel.
HP:0001645	Sudden cardiac death	The heart suddenly and unexpectedly stops beating resulting in death within a short time period (generally within 1 h of symptom onset).
HP:0000509	Conjunctivitis	Inflammation of the conjunctiva.
HP:0000421	Epistaxis	Epistaxis, or nosebleed, refers to a hemorrhage localized in the nose.
HP:0000225	Gingival bleeding	Hemorrhage affecting the gingiva.
HP:0100820	Glomerulopathy	Inflammatory or noninflammatory diseases affecting the glomeruli of the nephron.
HP:0000140	Abnormality of the menstrual cycle	An abnormality of the ovulation cycle.
HP:0009830	Peripheral neuropathy	Peripheral neuropathy is a general term for any disorder of the peripheral nervous system. The main clinical features used to classify peripheral neuropathy are distribution, type (mainly demyelinating versus mainly axonal), duration, and course.
HP:0001287	Meningitis	Inflammation of the meninges.
HP:0006535	Recurrent intrapulmonary hemorrhage	A recurrent hemorrhage occurring within the lung.
HP:0100749	Chest pain	An unpleasant sensation characterized by physical discomfort (such as pricking, throbbing, or aching) localized to the chest.
HP:0100774	Hyperostosis	Excessive growth or abnormal thickening of bone tissue.
HP:0001369	Arthritis	Inflammation of a joint.
HP:0002665	Lymphoma	A cancer originating in lymphocytes and presenting as a solid tumor of lymphoid cells.
HP:0002488	Acute leukemia	A clonal (malignant) hematopoietic disorder with an acute onset, affecting the bone marrow and the peripheral blood. The malignant cells show minimal differentiation and are called blasts, either myeloid blasts (myeloblasts) or lymphoid blasts (lymphoblasts).

HP:0005558	Chronic leukemia	A slowly progressing leukemia characterized by a clonal (malignant) proliferation of maturing and mature myeloid cells or mature lymphocytes. When the clonal cellular population is composed of myeloid cells, the process is called chronic myelogenous leukemia. When the clonal cellular population is composed of lymphocytes, it is classified as chronic lymphocytic leukemia, hairy cell leukemia, or T-cell large granular lymphocyte leukemia.
HP:0000778	Hypoplasia of the thymus	Underdevelopment of the thymus.
HP:0000491	Keratitis	Inflammation of the cornea.
HP:0200042	Skin ulcer	A discontinuity of the skin exhibiting complete loss of the epidermis and often portions of the dermis and even subcutaneous fat.
HP:0002664	Neoplasm	An organ or organ-system abnormality that consists of uncontrolled autonomous cell-proliferation which can occur in any part of the body as a benign or malignant neoplasm (tumour).

Source: HPO-ORDO Ontological Module (21) - Validation association date: 01.06.2016

4.75X-linked lymphoproliferative syndrome (XLP)

4.75.1.1 Very frequent

Term Identifier	Term Name	Definition
HP:0005374	Cellular immunodeficiency	An immunodeficiency characterized by defective cell-mediated immunity or humoral immunity.

4.75.1.2 Frequent

Term Identifier	Term Name	Definition
HP:0004313	Decreased antibody level in blood	An abnormally decreased level of immunoglobulin in blood.
HP:0002665	Lymphoma	A cancer originating in lymphocytes and presenting as a solid tumor of lymphoid cells.
HP:0002240	Hepatomegaly	Abnormally increased size of the liver.
HP:0002716	Lymphadenopathy	Enlargment (swelling) of a lymph node.
HP:0001744	Splenomegaly	Abnormal increased size of the spleen.

4.75.1.3 Occasional

Term Identifier	Term Name	Definition
HP:0001903	Anemia	A reduction in erythrocytes volume or hemoglobin concentration.

Source: HPO-ORDO Ontological Module (21)- Validation association date: 01.06.2016

5 Discussion

Current technological developments in precision medicine increasingly rely on large-scale computational integration of laboratory data with clinical information. However, disease-associated clinical and laboratory features, and anatomical and functional phenotypes are often ill-defined in medical reports, being described with varying specificity and quality, mixing lay terms with professional jargon, using different languages across the world and a disease classification that is designed for billing purposes rather than for detailed phenotype definitions. The interpretation of results obtained from next-generation panels, whole exome, or whole genome sequencing (NGS) and other omics analyses used in the differential diagnostic work-up of a patient or for research purposes apply algorithm-based filtering of called variants to distinguish potentially disease-relevant from irrelevant changes. These algorithms are, not least, based on the available clinical information. The Human Phenotype Ontology (HPO) is widely used in the diagnostic genomics community for “deep phenotyping” to inform NGS-based diagnostics^{1, 2}. HPO-based algorithms help to narrow down candidate genes and variants by assessing phenotypic similarity of associated diseases with the phenotypic features of the patients being sequenced, which can increase the yield of phenotype-driven computer-assisted data interpretation. (58)

For this reason, this thesis tried to integrate a standardized terminology, namely the Human Phenotype Ontology, into the ESID Working Definitions for the Clinical Diagnosis of Inborn Errors of Immunity, where a non-standardised, inconsistent colloquial medical language is currently used to define the specific diseases. The in the course of this thesis newly created lists of HPO terms for each of the entities of the ESID Working Definitions for the Clinical Diagnosis of Inborn Errors of Immunity got attached to every IEI in the ESID Working Definitions for the Clinical Diagnosis of Inborn Errors of Immunity and can be reached within this document using hyperlinks. The updated document with added HPO terms can be found on the ESID registry website.

This integration of a standardized vocabulary into the ESID Working Definitions for the Clinical Diagnosis of Inborn Errors of Immunity enables a standardized, precise phenotypic description of patients entered into the ESID registry, which contains the data of more than 30000 patient with IEI. (58) Furthermore, it can be envisioned that in the future the selection of appropriate HPO terms for each patient entered into

the ESID registry becomes obligatory, which would allow an exact monitoring of phenotypic abnormalities occurring in each of the IEI of the ESID Working Definitions for the Clinical Diagnosis of Inborn Errors of Immunity. If this information is compiled at every annual follow-up, it will allow a longitudinal monitoring of symptoms, lab values and the disease course.

In addition, the application of a standardized vocabulary in the ESID registry allows and enables the use of computer-assisted data analysis. Up to the present day, one of the biggest problems in computer-assisted data analysis is the understanding of natural language. Finding the meaning of words and phrases, identifying different tenses and the recognition of synonyms are all tasks that are challenging for a computer-based algorithm. Furthermore, it is hardly possible for a Natural Language Processing-Algorithm to detect different intentions and emotions in texts. By using a standardized vocabulary, which is clear and precise and does not leave scope for interpretation, in the ESID registry, the contained data will become more accessible for computer-assisted analysis. This will ultimately help to maximize clinical and translational interoperability. (58)

As only 38 entities of the ESID Working Definitions for the Clinical Diagnosis of Inborn Errors of Immunity could be found in the HOOM, only these entities have a frequency information for the individual phenotypic abnormalities attached. For the other 37 entities, there was no frequency information available. Hence the significance of the individual phenotypic abnormalities is not always clear. Thus it is important that for the future, the ESID Working Definitions for the Clinical Diagnosis of Inborn Errors of Immunity get regularly updated and more entities are complemented with frequency information, as the HOOM is updated monthly and supplemented with new HPO annotations. Currently, there is an initiative from the ERN RITA (European Reference Network – Rare Immunodeficiency, Autoinflammatory and Autoimmune Disease Network) molecular testing working group and the ESID working party of genetics ongoing, which aim is to provide a complete and revised phenotype ontology for immunodeficiencies. To achieve this, computer-based algorithms are used to generate new terms to describe the phenotype of immune-mediated disorders in HPO. In the future, these newly generated terms could also be added to the ESID Working Definitions for the Clinical Diagnosis of Inborn Errors of Immunity.

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