

Heterogeneity in combined immunodeficiencies with associated or syndromic features (Review)

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Abstract. Primary immunodeficiencies are genetic diseases, mainly monogenic, that affect various components of the immune system and stages of the immune response. The category of combined immunodeficiencies with associated or syndromic features comprises over 70 clinical entities, characterized by heterogeneity of clinical presentation, mode of transmission, molecular, biological, mutational and immunological aspects. The mutational spectrum is wide, ranging from structural chromosomal abnormalities to gene mutations. The impact on the function of the proteins encoded by the genes involved is different; loss of function is most common, but situations with gain of function are also described. Most proteins have multiple functions and are components of several protein interaction networks. The pathophysiological mechanisms mainly involve: Missing enzymes, absent or non-functional proteins, abnormal DNA repair pathways, altered signal transduction, developmental arrest in immune differentiation, impairment of cell-to-cell and intracellular communications. Allelic heterogeneity, reduced penetrance and variable expressivity are genetic phenomena that cause diagnostic difficulties, especially since most are rare/very rare diseases, which is equivalent to delaying proper case management. Most primary immunodeficiencies are Mendelian diseases with X-linked or recessive inheritance, and molecular diagnosis allows the identification of family members at risk and the application of appropriate primary and secondary prevention measures in addition to the specific curative ones. In conclusion, recognizing heterogeneity and its sources is extremely important for

current medical practice, but also for the theoretical value of improving biological and biomedical applications.

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1. Introduction

Primary immunodeficiencies (PIDs) are rare, mostly monogenic genetic diseases that affect various components of the immune system and are characterized by pathological, clinical, and immunological diversity (1,2). The prevalence of PIDs is approximately 4-10 per 10⁵ live births (3).

The International Union of Immunological Societies (IUIS) recognizes the existence of 430 entities and 408 different genes involved. It classifies diseases into 9 categories: Immunodeficiencies affecting cellular and humoral immunity, combined immunodeficiencies with associated or syndromic features, predominantly antibody deficiencies, diseases of immune dysregulation, congenital defects of phagocyte number or function, defects in intrinsic and innate immunity, autoinflammatory disorders, complement deficiencies and phenocopies of inborn errors of immunity (4-6). Of these, combined immunodeficiencies with associated or syndromic features present high heterogeneity manifested at the molecular and mutational level. Biological processes involve different gene expression products, ‘extraimmune’ clinical symptoms characteristic of each syndrome, and many diseases present incomplete penetrance and variable expressivity. This combined immunodeficiencies are classified into 10 types: Immunodeficiency with congenital thrombocytopenia; DNA repair defects (immunodeficiencies affecting cellular and humoral immunity); thymic defects with additional congenital anomalies; immuno-osseous dysplasias; hyper

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IgE syndromes (hyperimmunoglobulin E syndromes or HIES); dyskeratosis congenita (DKC), myelodysplasia, short telomeres; defects of vitamin B12 and folate metabolism; ectodermal anhidrotic dysplasia with immunodeficiency (EDA-ID); and calcium channel defects (4).

Correct and early diagnosis is necessary to prevent complications and reduce mortality (7). The molecular diagnosis can be followed by early protective and curative interventions, but also by avoiding the usual interventions which in the case of certain PIDs can bring additional complications (for example use of DNA-radiomimetic drugs in radiosensitive PIDs) (8). It is estimated that 70-90% of patients with PID remain undiagnosed worldwide (9). The onset can be at any age, but early onset correlates negatively with the severity of the manifestations (7). In many cases, patients are consulted for recurrent infections, but the etiological diagnosis is delayed. There are studies that show that in the US the etiological diagnosis is delayed by up to 12.4 years (10). During all this time, negative consequences can appear in personal, social and professional life, so that the quality of life is profoundly altered (3,7,11). In some cases, patients also have a predisposition to autoimmune diseases, autoinflammatory diseases or lymphoproliferative phenomena (4,8,12-16).

2. Molecular heterogeneity and biological processes

The vast majority of genes involved are genes that encode proteins. In combined immunodeficiencies with syndromic features a double heterogeneity is present: A specific protein presents multiple and diverse molecular functions while several different proteins have the same molecular function. Table I summarizes the molecular functions of these proteins and the biological processes in which they intervene according to UniProt Knowledgebase <https://www.uniprot.org/> (4-6,17-23).

Some genes encode proteins that interact with chromatin, being implied in chromatin binding (*DNMT3B*, *RNF168*, *POLE*, *STAT5B* and *KDM6A*), chromatin DNA binding (*STAT3*, *KDM6A*) or chromatin regulation (*CHD7*, *MYSM1*, *KMT2D* and *KDM6A*) (23).

Other proteins interact with histones and allow histone binding (*RNF168*, *MYSM1*, *WRAP53* and *KMT2D*), histone deacetylase binding (*DNMT3B*), histone demethylase activity [H3-K27 specific] (*KDM6A*) or histone methyltransferase activity [H3-K4 specific] (*KMT2D* and *KMT2A*) (23).

A major category is represented by genes that encode proteins implied in interaction with DNA: DNA binding (*ZNF341*, *ATM*, *BLM*, *NFE2L2*, *DNMT3B*, *PMS2*, *POLE*, *POLE2*, *LIG1*, *ERCC6L2*, *TBX1*, *CHD7*, *FOXN1*, *MYSM1*, *STAT3*, *RTEL1*, *TERT*, *SPI10* and *KMT2D*), DNA replication origin binding (*MCM4*), single-stranded DNA binding (*BLM*, *MCM4*, *STN1* and *CTC1*), or damaged DNA binding (*NBN*, *DCLRE1B/SNM1/APOLLO*) (23).

Other genes encode transcription factors implied in RNA polymerase II activity (*TBX1*, *FOXN1*, *STAT3*, *STAT5B*, *NFE2L2*, *KMT2A* and *BCL11B*), DNA-binding transcription factor activity [*ZBTB24*, *FOXN1*, *MYSM1*, *STAT3*, *SPI10*, *STAT5B*, *KMT2D* (*MLL2*), *TBX1*, *ZNF341* and *NFE2L2*, *BCL11B*] or transcription factor binding (*NBN*, *TBX1*, *STAT3* and *NFKB1A*) (23).

The functions of telomeres are regulated by other genes that influence telomeric DNA binding (*TERT*, *TINF2*, *STN1* and *CTC1*), telomerase RNA binding (*DKC1*, *NHP2*, *NOP10*, *TERT*, *PARN* and *WRAP53*) or telomerase activity (*TERT* and *DKC1*) (23).

In addition, in immunodeficiencies different enzymatic activity may be disturbed: GTPase regulator activity (*WAS*), small GTPase binding (*WAS*), phospholipase binding (*WAS*), protein kinase binding (*WAS*, *ERCC6L2*, *STAT3*, *PARN* and *IKBKB*), DNA-dependent protein kinase activity (*ATM*), helicase (*BLM*, *HELLS*, *MCM4*, *ERCC6L2*, *CHD7*, *SMARCA1*, *RTEL1*, *SKIV2L*), hydrolase (*HELLS*, *PMS2*, *MCM4*, *POLE*, *ERCC6L2*, *CHD7*, *SMARCA1*, *MYSM1*, *RTEL1*, *TPP1*, *DCLRE1B/SNM1/APOLLO*, *PARN* and *MTHFD1*), nuclease (*PMS2*, *POLE*, *DCLRE1B/SNM1/APOLLO* and *PARN*), metalloprotease (*MYSM1*), phosphoglucomutase activity (*PGM3*), DNA polymerase binding (*RTEL1*) (23).

Another process that is perturbed in immunodeficiencies is ion binding and the main genes implied are *TGFB1*, *TGFB2*, *ZNF341*, *DNMT3B*, *ZBTB24*, *RNF168*, *LIG1*, *MYSM1*, *EXTL3*, *RTEL1*, *TERT*, *TPP1*, *PARN*, *TCN2*, *IKBKG* (*NEMO*), *SPI10*, *HOIL1* (*RBCK1*), *RNF31*, *KMT2D* (*MLL2*), *KMT2D* (*MLL2*), *KDM6A*, *BCL11B*, *STIM1*, *FAT4* and *CCBE1* (23).

The connection with RNA could be abnormal in immunodeficiencies because of an abnormal ribonucleoprotein (*DKC1*, *NHP2*, *NOP10*, *TERT*), RNA binding (*DKC1*, *NHP2*, *NOP10* and *WRAP53*) or box H/ACA snoRNA binding (*DKC1*, *NHP2* and *NOP10*) (23).

Other processes are disturbed because of gene mutations implied in protein binding (*WAS*, *ATM*, *BLM*, *STAT3*, *TERT*, *IKBKB*, *WRAP53*, *IKBKG* (*NEMO*), *NFKB1A*, *ORAI1*, *STIM1*, *PNP*, *HOIL1*, *KDM6A*, *KMT2A* and *IL6ST*), Rac GTPase (*WAS*), SH3 domain binding (*WAS*, *WIPF1*), profilin binding (*WIPF1*), ATP binding [*IKBKB*, *TGFB1*, *TGFB2*, *ATM*, *BLM* (*RECQL3*), *HELLS*, *PMS2*, *MCM4*, *LIG1*, *ERCC6L2*, *SKIV2L*, *CHD7*, *SMARCA1*, *RTEL1* and *MTHFD1*], chaperone binding (*TERT* and *WRAP53*), actin (actin filament) binding (*WAS*, *WIPF1* and *ARPC1B*) (23).

Other genes, such as *RMRP*, *RNU4ATAC* or *TERC*, encode noncoding RNA (part of RNase MRP), small nuclear RNA and telomerase RNA component (Table I). Mutations in these genes cause alterations in processing of ribosomal RNA. *RMRP* gene mutations disturb mitochondrial DNA replication and cell cycle control. *RNU4ATAC* gene mutations produce defects of spliceosome complex. Mutations in the *TERC* gene are implied in dysfunctions of telomere length (19,22,24-26).

Genes including *HELLS*, *TBX1*, *SEMA3E*, *FOXN1*, *CCBE1* or *KDM6A* encode proteins involved in development of one or more organs. The most illustrative example is the *TBX1* gene that is involved in multiple biological processes: Angiogenesis, morphogenesis of cranial region, heart, parathyroid gland, pharyngeal system, soft palate, thymus or thyroid gland (23). Thus, deficiency in the *TBX1* gene, characteristic to velo-cardio-facial syndrome, explains the association of abnormalities in multiple systems. The *TBX1* gene allows thymus epithelium morphogenesis, lymphoid lineage cell migration into the thymus, regulation of positive thymic T cell selection and T cell homeostasis. Other developmental proteins are also involved in the genesis of various organs/components of the immune system. For example, the *FOXN1* gene allows

Table I. Heterogeneity of molecular and biological processes in combined immunodeficiencies with associated or syndromic features (4-6,17,19-23).

Disease	Gene (MOI)	Molecular function	Biological process
Immunodeficiency with congenital thrombocytopenia			
Wiskott-Aldrich syndrome (WAS LOF)	<i>WAS</i> (XL)	GTPase regulator and binding activity; protein binding (actin, protein kinase); phospholipase binding	Fc-gamma receptor signaling pathway involved in phagocytosis; immune response; regulation of T cell antigen processing and presentation; T cell activation; T cell receptor signaling pathway
WIP deficiency	<i>WIPF1</i> (AR)	Actin binding; profilin binding; SH3 domain binding	Fc-gamma receptor signaling pathway involved in phagocytosis; regulation of cell shape, immune response against microorganisms
ARPC1B deficiency	<i>ARPC1B</i> (AR)	Actin filament and binding; structural constituent of cytoskeleton	Fc-gamma receptor signaling pathway involved in phagocytosis
DNA repair defects other than those listed in the 1st category			
Ataxia-telangiectasia	<i>ATM</i> (AR)	ATP, protein and DNA binding; DNA-dependent protein kinase activity	Cell cycle; DNA damage
Nijmegen breakage syndrome	<i>NBN</i> (AR)	Damaged DNA and protein binding;	Cell cycle; DNA damage; DNA repair; host-virus interaction;
Bloom syndrome	<i>BLM</i> (<i>RECQL3</i>) (AR)	3'-5' DNA helicase activity; DNA and ATP binding	DNA damage; DNA repair; DNA replication
ICF1	<i>DNMT3B</i> (AR)	Chromatin, DNA and metal binding; DNA-methyltransferase activity; histone deacetylase binding	DNA methylation; regulation of histone methylation and transcription
ICF2	<i>ZBTB24</i> (AR)	DNA-binding transcription factor activity	Transcription; transcription regulation
ICF3	<i>CDCA7</i> (AR)	MYC-mediated cell transformation and apoptosis	Apoptosis; transcription
ICF4	<i>HELLS</i> (AR)	Developmental protein; helicase activity; hydrolase; ATP binding	Cell cycle; transcription; multicellular organism development
PMS2 deficiency	<i>PMS2</i> (AR)	Endonuclease activity; ATPase activity; ATP and DNA binding	DNA damage; DNA repair
RNF168 deficiency (Riddle syndrome)	<i>RNF168</i> (AR)	Chromatin, histone and metal binding; ubiquitin-protein transferase activity	DNA damage; DNA repair; ubiquitin conjugation pathway
MCM4 deficiency	<i>MCM4</i> (AR)	ATP binding, DNA helicase activity	Cell cycle; DNA replication
POLE1 (polymerase ε subunit 1) deficiency (FILS syndrome)	<i>POLE</i> (AR)	DNA and metal binding; DNA-directed DNA polymerase	DNA damage; DNA repair; DNA replication
POLE2 (polymerase ε subunit 2) deficiency	<i>POLE2</i> (AR)	DNA-binding; DNA-directed DNA polymerase activity	DNA replication
Ligase I deficiency	<i>LIG1</i> (AR)	DNA ligase activity; ATP, DNA and metal binding	Cell cycle; DNA damage, recombination, repair and replication

Table I. Continued.

Disease	Gene (MOI)	Molecular function	Biological process
DNA repair defects other than those listed in the 1st category			
NSMCE3 deficiency	<i>NSMCE3</i> (AR)	Tumor antigen	DNA damage, recombination and repair; growth regulation
ERCC6L2 (Hebo deficiency)	<i>ERCC6L2</i> (AR)	DNA, ATP and protein kinase binding; helicase activity	DNA damage; DNA repair
GIN51 deficiency	<i>GIN51</i> (AR)	DNA-binding (single-stranded DNA)	DNA replication; inner cell mass cell proliferation
Thymic defects with additional congenital anomalies			
DiGeorge/velocardiofacial syndrome (22q11.2DS)	Deletion in chromosome 22 (AD)		
TBX1 deficiency	<i>TBX1</i> (AD)	Developmental protein; DNA and transcription activator binding; RNA polymerase II	Transcription; angiogenesis; thymus development; morphogenesis
CHARGE syndrome	<i>CHD7</i> (AD)	ATP and chromatin binding; DNA helicase activity;	rRNA processing; transcription
CHARGE syndrome	<i>SEMA3E</i> (AD)	Developmental protein;	Angiogenesis; differentiation; neurogenesis
Winged helix nude FOXN1 deficiency	<i>FOXN1</i> (AR)	Developmental protein; DNA-binding transcription activator	Differentiation; transcription; thymus epithelium morphogenesis; lymphoid lineage cell migration into thymus; regulation of thymic T cell selection; T cell homeostasis; T cell lineage commitment
Chromosome 10p13-p14 deletion	Del10p13-p14 (AD)		
Chromosome 11q deletion (Jacobsen syndrome)	Del11q23 (AD)		
Immuo-osseous dysplasias			
Cartilage hair hypoplasia (CHH)	<i>RMRP</i> (AR)	Noncoding RNA	Processing of ribosomal RNA; cell cycle control
Schimke immuno-osseous dysplasia	<i>SMARCAL1</i> (AR)	Helicase activity; ATP binding	Cellular response to DNA damage stimulus
MYSM1 deficiency	<i>MYSM1</i> (AR)	DNA histone and metal ion binding	Transcription
MOPD1 deficiency	<i>RNU4ATAC</i> (AR)	Small nuclear RNA (snRNA)	Part of spliceosome complex
EXTL3 deficiency	<i>EXTL3</i> (AR)	Metal ion binding; transferase activity	Proteoglycan biosynthetic process; regulation of cell growth
Hyper-IgE syndromes (HIES)			
STAT3 deficiency (Job syndrome)	<i>STAT3</i> (AD)	DNA, enzyme and chromatin binding; RNA polymerase activity	Host-virus interaction; transcription
IL6 receptor deficiency	<i>IL6R</i> (AR)	Cytokine and enzyme binding, cytokine receptor activity	Regulation of the immune response, acute-phase reactions and hematopoiesis

Table I. Continued.

Disease	Gene (MOI)	Molecular function	Biological process
Hyper-IgE syndromes (HIES)			
IL6 signal transducer (IL6ST) deficiency	<i>IL6ST</i> (AR)	Cytokine and growth factor binding, cytokine receptor activity, binding	Host-virus interaction
ZNF341 deficiency AR-HIES	<i>ZNF341</i> (AR)	DNA and metal ion binding; DNA-binding transcription activator activity	Transcription, transcription regulation
ERBIN deficiency	<i>ERBIN</i> (AD)	Signaling receptor binding; structural constituent of cytoskeleton	Cell adhesion; cellular response to tumor necrosis factor; epidermal growth factor receptor signaling pathway
Loeys-Dietz syndrome (TGFB1 deficiency)	<i>TGFB1</i> (AD)	Activin, ATP and metal ion binding; protein kinase activity	Apoptosis, differentiation, growth regulation
Loeys-Dietz syndrome (TGFB2 deficiency)	<i>TGFB2</i> (AD)	Activin-activated receptor activity; activin, ATP and metal ion binding	Apoptosis, differentiation, growth regulation
Comel-Netherton syndrome	<i>SPINK5</i> (AR)	Serine-type endopeptidase inhibitor activity	Cell differentiation; central nervous system development; regulation of T cell differentiation
PGM3 deficiency	<i>PGM3</i> (AR)	Magnesium binding; enzymatic activity	Carbohydrate metabolism; hemopoiesis
CARD11 deficiency (heterozygous)	<i>CARD11</i> (AD LOF dominant negative)	CARD domain binding, guanylate kinase activity	Costimulatory signal for T-cell receptor-mediated T-cell activation; NF- κ B activation in a T-cell receptor/CD3-dependent manner
Dyskeratosis congenita (DKC), myelodysplasia, short telomeres			
XL-DKC	<i>DKC1</i> (XL)	RNA-binding; telomerase RNA binding	Ribosome biogenesis; rRNA processing
AR-DKC with NHP2 deficiency	<i>NHP2</i> (AR)	RNA-binding; telomerase RNA binding	Ribosome biogenesis; rRNA processing
AR-DKC with NHP3 or NOP10 deficiency	<i>NOP10</i> (AR)	RNA-binding; telomerase RNA binding	Ribosome biogenesis; rRNA processing
AD/AR-DKC with RTEL1 deficiency	<i>RTEL1</i> (AD or AR)	DNA, ATP, DNA polymerase and metal ion binding; DNA helicase activity	DNA damage; DNA repair
AD-DKC with TERC deficiency	<i>TERC</i> (AD)	Telomerase RNA component	DNA replication
AD/AR-DKC with TERT deficiency	<i>TERT</i> (AD or AR)	DNA, chaperone, protein and metal ion -binding	Transcription and replication
AD-DKC with TINF2 deficiency	<i>TINF2</i> (AD)	Telomeric DNA binding	Transcription of telomeres
AD/AR-DKC with TPP1 deficiency	<i>TPP1</i> (AD or AR)	Peptidase activity; metal and ion binding	Development and cell differentiation; lipid and protein metabolic process
AR-DKC with DCLRE1B deficiency	<i>DCLRE1B/SNMI1/APOLLO</i> (AR)	5'-3' exonuclease activity	DNA damage; DNA repair
AR-DKC with PARN deficiency	<i>PARN</i> (AR (AD?))	3'-5' Exoribonuclease activity; cation binding; metal ion binding	Nonsense-mediated mRNA decay
AR-DKC with WRAP53 deficiency	<i>WRAP53</i> (AR)	RNA chaperone histone protein binding	DNA damage; DNA repair; Host-virus interaction
Coats plus syndrome	<i>STN1</i> (AR)	DNA binding	DNA repair; DNA replication;
Coats plus syndrome	<i>CTC1</i> (AR)	DNA binding	Cell cycle control; multicellular organism growth
SAMD9	<i>SAMD9</i> AD	Inflammatory response to tissue injury	Endosomal vesicle fusion

Table I. Continued.

Disease	Gene (MOI)	Molecular function	Biological process
Defects of vitamin B12 and folate metabolism			
Transcobalamin 2 deficiency	<i>TCN2</i> (AR)	Cobalamin binding; metal ion binding	Cobalt transport; ion transport;
SLC46A1/PCFT deficiency	<i>SLC46A1</i> (AR)	Folic acid binding; folic acid, heme, methotrexate and transporter activity	Transport of different cellular components
MTHFD1 deficiency	<i>MTHFD1</i> (AR)	ATP binding; enzymatic activity	Protein biosynthesis
Anhidrotic ectodermodyplasia with immunodeficiency (EDA-ID)			
EDA-ID with NEMO/IKBKG deficiency	<i>IKBKG</i> (<i>NEMO</i>) (XL)	Protein and metal ion binding	DNA damage; host-virus interaction; transcription
EDA-ID with IKBA GOF mutation	<i>NFKBIA</i> (<i>IKBA</i>) (XL)	Protein and enzyme binding	Host-virus interaction
EDA-ID with IKBKB GOF mutation	<i>IKBKB</i> (AD GOF)	ATP and protein kinase binding, protein kinase activity	Host-virus interaction
Calcium channel defects			
ORAI1 deficiency	<i>ORAI1</i> (AR)	Calmodulin-binding; store-operated calcium channel activity	Adaptive immunity; calcium transport;
STIM1 deficiency	<i>STIM1</i> (AR)	Calcium channel regulator activity; calcium ion binding	Calcium transport
Other defects			
Purine nucleoside phosphorylase deficiency	<i>PNP</i> (AR)	Drug protein nucleoside and phosphate binding	Immune response; interleukin-2 secretion; neutrophil degranulation; nucleotide biosynthetic process; regulation of T cell proliferation; response to drug; urate biosynthetic process
Immunodeficiency with multiple intestinal atresias	<i>TTC7A</i> (AR)	Component of a complex required to localize phosphatidylinositol 4-kinase (PI4K) to the plasma membrane	Cellular iron ion homeostasis; hemopoiesis; phosphatidylinositol phosphorylation
Tricho-Hepato-Enteric Syndrome (THES)	<i>TTC37</i> (AR)	Exosome-mediated RNA decay	Exonucleolytic catabolism of deadenylated mRNA
Tricho-Hepato-Enteric Syndrome (THES)	<i>SKIV2L</i> (AR)	ATP and RNA binding; RNA helicase activity	RNA catabolic process
Hepatic veno-occlusive disease with immunodeficiency	<i>SP110</i> (AR)	DNA, protein and metal ion binding; RNA polymerase II-specific	Host-virus interaction; transcription
BCL11B deficiency	<i>BCL11B</i> (AD)	DNA, metal binding; RNA polymerase	Transcription
Vici syndrome due to EPG5 deficiency	<i>EPG5</i> (AR)	Clearance of autophagosomal cargo innate and adaptive immune response	Autophagy; cellular response to dsDNA; nucleotide transport; toll-like receptor 9 signaling pathway

Table I. Continued.

Disease	Gene (MOI)	Molecular function	Biological process
Other defects			
HOIL1 deficiency	<i>HOIL1 (RBCK1)</i> (AR)	Protein, enzyme and metal ion binding	Host-virus interaction
HOIP deficiency	<i>RNF31</i> (AR)	Protein, metal ion and ubiquitin binding	Ubiquitination pathway
Hennekam-lymphangiectasia-lymphedema syndrome	<i>CCBE1</i> (AR)	Calcium ion collagen and protease binding	Angiogenesis and lymphangiogenesis
Hennekam-lymphangiectasia-lymphedema syndrome	<i>FAT4</i> (AR)	Calcium ion binding	Cell adhesion
<i>De novo</i> mutations in nuclear factor, erythroid 2-like (NFE2L2)	<i>NFE2L2</i> (AD)	DNA and protein binding; RNA polymerase II-specific	Host-virus interaction, transcription,
STAT5b deficiency	<i>STAT5B</i> (AR)	Chromatin, protein and hormone binding; RNA polymerase II	Transcription
STAT5b deficiency	<i>STAT5B</i> (AD)	DNA histone and metal ion binding; histone methyltransferase activity	Transcription
Kabuki syndrome 1 with KMT2D deficiency	<i>KMT2D (MLL2)</i> (AD)	DNA histone and metal ion binding; histone methyltransferase activity	Chromatin remodeling and morphogenesis
Kabuki syndrome 2 with KDM6A deficiency	<i>KDM6A</i> (XL)	DNA and zinc ion binding; RNA polymerase II-specific; histone methyltransferase activity	Apoptosis; transcription;
Wiedemann-Steiner syndrome	<i>KMT2A</i> (AD)		

MOI, mode of inheritance; XL, X-linked inheritance; AR, autosomal recessive inheritance; AD, autosomal dominant inheritance. WAS, WASP actin nucleation promoting factor; *WIPF1*, WAS/WASL interacting protein family member 1; *ARPC1B*, actin related protein 2/3 complex subunit 1B; *ATM*, ATM serine/threonine kinase; *NBN*, nibrin; *BLM (RECQL3)*, BLM RecQ like helicase; *DNMT3B*, DNA methyltransferase 3 β; *ZBTB24*, zinc finger and BTB domain containing 24; *CDCA7*, cell division cycle associated 7; *HELLS*, helicase, lymphoid specific; *PMS2*, PMS1 homolog 2, mismatch repair system component; *RNF168*, ring finger protein 168; *MCM4*, minichromosome maintenance complex component 4; *POLE*, DNA polymerase ε, catalytic subunit; *POLE2*, DNA polymerase ε 2, accessory subunit; *LIG1*, DNA ligase 1; *NSMCE3*, NSE3 homolog, SMC5-SMC6 complex component; *ERCC6L2*, ERCC excision repair 6 like 2; *GIN51*, GINS complex subunit 1; *TBX1*, T-box transcription factor 1; *CHD7*, chromodomain helicase DNA binding protein 7; *SEMA3E*, semaphorin 3E; *FOXN1*, forkhead box N1; *RMRP*, RNA component of mitochondrial RNA processing endoribonuclease; *SMARCAL1*, SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a like 1; *MYSM1*, Myb like, SWIRM and MPN domains 1; *RNU4ATAC*, RNA, U4atac small nuclear (U12-dependent splicing); *EXTL3*, exostosin like glycosyltransferase 3; *STAT3*, signal transducer and activator of transcription 3; *IL6R*, interleukin 6 receptor; *IL6ST*, interleukin 6 signal transducer; *ZNF341*, zinc finger protein 341; *ERBIN*, erbB2 interacting protein; *TGFBRI*, transforming growth factor β receptor 1; *TGFBRI2*, transforming growth factor β receptor 2; *SPINK5*, serine peptidase inhibitor Kazal type 5; *PGM3*, phosphoglucomutase 3; *CARD11*, caspase recruitment domain family member 11; *DKC1*, dyskerin pseudouridine synthase 1; *NHP2*, NHP2 ribonucleoprotein; *NOP10*, NOP10 ribonucleoprotein; *RTEL1*, regulator of telomere elongation helicase 1; *TERC*, telomerase RNA component; *TINF2*, TERC interacting nuclear factor 2; *TPPI*, tripeptidyl peptidase 1; *DCLRE1B/SNM1/APOLLO*, DNA cross-link repair 1B; *PARN*, poly(A)-specific ribonuclease; *WRAP53*, WD repeat containing antisense to TP53; *STN1*, STN1 subunit of CST complex; *CTCF*, CST telomere replication complex component 1; *SAMD9*, sterile alpha motif domain containing 9 like; *TCN2*, transcobalamin 2; *SLC46A1*, solute carrier family 46 member 1; *MTHFD1*, methyltetrahydrofolate dehydrogenase, cyclohydrolase and formyltetrahydrofolate synthetase 1; *KBKG (NEMO)*, inhibitor of nuclear factor κB kinase regulatory subunit γ; *NFKBIA* (IKBA), NFκB inhibitor α; *IKKB*, inhibitor of nuclear factor κB kinase subunit β; *ORAI1*, ORAI calcium release-activated calcium modulator 1; *STIM1*, stromal interaction molecule 1; *PNP*, purine nucleoside phosphorylase; *TTC7A*, tetrahydropeptide repeat domain 7A; *SP110*, SP110 nuclear body protein) *BCL11B*, BAF chromatin remodeling complex subunit BCL11B; *TTC37*, tetrahydropeptide repeat domain 37; *SKIV2L*, Ski2 like RNA helicase; *EPG5*, ectopic P-granules autophagy protein 5 homolog; *RBCK1/HOIL1*, RANBP2-type and C3HC4-type zinc finger containing 1; *RNF31*, ring finger protein 31; *CCBE1*, collagen and calcium binding EGF domains 1; *FAT4*, FAT atypical cadherin 4; *NFE2L2*, nuclear factor, erythroid 2 like 2; *STAT5B*, signal transducer and activator of transcription 5B; *KMT2D* (MLL2), lysine methyltransferase 2D; *KDM6A*, lysine demethylase 6A; *KMT2A*, lysine methyltransferase 2A.

thymus epithelium morphogenesis, lymphoid lineage cell migration into the thymus, regulation of positive thymic T cell selection, T cell homeostasis and T cell lineage commitment (Table I) (19,22,24-26).

The pathogenic complexity of combined immunodeficiencies associated with syndromic features could be explained by the multiple interactions between the mentioned genes and important cell processes, such as the cell cycle, DNA damage, DNA repair process, DNA replication, apoptosis, transcription, cell division, multicellular organism development, ribosome biogenesis and processing, immune response, autophagy and cell adhesion. The pathophysiological mechanisms mainly involved are: Missing enzymes, absent or non-functional proteins, abnormal DNA repair, altered signal transduction, developmental arrest in immune differentiation, impairment of cell-to-cell and intracellular communications (Table I) (19,22,24-26).

3. Mutational heterogeneity

The majority of combined immunodeficiencies with syndromic features are monogenic diseases caused by mutations in a pair of nuclear genes and only few diseases are caused by chromosomal microdeletions.

Most mutations are loss-of-function (LOF) mutations with a recessive pattern of transmission. Other mutations produce a gain of function (GOF). GOF mutations are almost always dominant (27). In some situations, for the same gene, distinct missense mutations may cause either LOF or GOF. An example of this is the *STAT3* gene (28). *STAT3* LOF mutation causes Job syndrome while *STAT3* GOF mutation causes a form of immunodeficiency characterized by an immune deregulation. Thus, in such situations it is absolutely necessary to perform genetic testing to detect the mutation and its effect on the protein (29). All of these can influence also the treatment strategy. In *STAT3* GOF the efficient treatment includes monoclonal antibody (mAb) against IL-6R and HSCRT, while in *STAT3* LOF the most efficient treatment is the long term use of antibiotics and humanized recombinant monoclonal against IgE (30-32).

4. Clinical heterogeneity and mode of inheritance

Clinical heterogeneity is even greater as in the case of combined immunodeficiencies with syndromic features when it presents an interindividual and interfamilial variable expressivity, in correlation with the type of mutation. In such cases, identification of a specific association of abnormalities allows an early diagnosis, sometimes even before the onset of immune manifestations (33). In the majority of cases, immunodeficiency clinical signs are not specific such as infections, skin inflammation, hematologic autoimmune/autoinflammatory disorders, and different types of malignancy. Thus discovery of a particular non-immune feature becomes very helpful for a precocious diagnosis (33-35).

Usually, the onset of disease occurs in childhood, but retarded manifestations could be found in the case of a hypomorphic mutations or a random X-chromosome inactivation in women heterozygote for a X-linked recessive mutation (33,36,37).

Infections observed in various primary immunodeficiency diseases can be bacterial, viral or fungal. Each infection has certain particularities. For example non-tuberculosis mycobacteria infections are found in *IKBK*, *IKBB*, *GOF NFKBIA/IKBA* deficiency; pyogenic pneumonia with pneumatocele formation and empyema/abscess and visceral abscess with *S. aureus* in childhood are specific for *STAT3* deficiency; recurrent pyogenic sepsis is found in *NEMO* deficiency (33).

Viral infections with EBV (Epstein-Barr virus) and HHV8 (human herpes virus 8) - Kaposi sarcoma in young subjects are associated with *STIM1* deficiency, AT (*ATM*), WAS (*WASP*), CHH (*RMRP*). Infection with HPV (human papilloma virus) with severe/recalcitrant warts, flat or verruca (often on trunk, face, neck, extremities, genital regions) are found in Netherton syndrome (*SPINK5*), WAS (*WASP*), *NEMO* deficiency (*IKBK*), AT (*ATM*). Widespread molluscum contagiosum is associated with WAS, *NEMO* deficiency (*IKBK*). Pneumonia with *Pneumocystis jirovecii* is present in WAS (*WASP*), *NEMO* deficiency (*IKBK*), VODI (*SP110*), *CARD11*. Chronic mucocutaneous infection with *Candida spp.* is found in *IKBK*, *IKBA*, *IKBB*, *NEMO* deficiency, VODI (*SP110*) and infection with *Aspergillus spp.* is specific for *STAT3* deficiency (33).

In combined immunodeficiencies, various inflammatory skin conditions are found: Generalized exfoliative erythroderma of infancy in Comèl-Netherton syndrome (*SPINK5*); diffuse early-onset eczema and erythroderma and muscle amylopectinosis in HOIL-1 deficiency; severe early-onset atopic eczema in WAS, Comèl-Netherton syndrome, PGM3, *STAT5b* deficiencies, *STAT3* deficiency; congenital livedo in FILS syndrome (*POLE*) (33).

Autoimmune/autoinflammatory disorders associated with primary immunodeficiencies include organ-specific autoimmunity (in 22q deletion syndrome, *WASP*, *ATM*, *STAT5B* mutations). Global hematologic autoimmunity changes have been observed in 22q deletion syndrome, *PNP*, *STIM1*, *ORAI1*, *WASP*, *ATM* and *STAT5B* mutations while hematologic autoimmunity with non-virally induced lymphoproliferation have been associated with *STIM1* deficiency, 22q11 deletion, 10p deletion. Other changes have been associated with sterile arthritis (*WASP* or *STAT5B* mutations); early-onset inflammatory bowel disease (*WASP* and *IKBK* mutations); trichohepatoenteric syndrome-*SKIV2L* and *TTC37* mutations, Veno-occlusive disease with immunodeficiency (VODI) *SP110* mutations; early-onset diarrhea and malabsorption from ICF-Immunodeficiency-centromeric instability-facial anomalies syndrome determined by mutations in *DNMTB3*, *ZBTB24*, *CDCA7* and *HELLS* genes) (33,38).

An increased risk of certain malignancies has been found in certain immunodeficiency syndromes. Various DNA repair deficiencies (*ATM*, *NBN*, *LIG1*) are associated with mainly lymphomas. MCM4 deficiency predisposes to EBV-associated lymphomas; Wiskott-Aldrich syndrome with myelodysplasia, leukemias and lymphomas. HHV8 is associated with primary Kaposi sarcoma (*TNFRSF4*, *IFNGR1*, *WAS* and *STIM1*); CHH (*RMRP*) with an increased risk of basal cell carcinoma and of EBV-associated lymphoproliferation (25,33,39-45).

In combined immunodeficiencies with syndromic features all type of monogenic transmission have been identified. Pedigree analysis is an easy-to-use tool available to any

practitioner to establish this fact. However, some genetic phenomena, such as low frequency of the disease (some of the immunodeficiencies are extremely rare diseases), incomplete penetrance of the disease, variable expressivity and *de novo* mutations, can complicate the process of identification of the type of transmission. A special situation is the allelic heterogeneity encountered for example in the case of Kabuki syndrome (KS): *KMT2D*-related KS is inherited in an autosomal dominant manner while *KDM6A*-related KS is inherited in an X-linked manner (45). There is also the variant in which mutations in a gene determine a condition that can be transmitted differently; *STAT5b* deficiency can be transmitted in an autosomal recessive or in an autosomal dominant model (33).

5. Conclusion

In conclusion, recognizing heterogeneity and its sources is extremely important for current medical practice, but also for the theoretical value of improving biological and biomedical applications.

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Authors' contributions

All three authors contributed equally to preparing the review and the data search and collection. LC carried out the writing of the original draft preparation and CG carried out the writing, review and editing of the manuscript. EVG conducted the validation and supervision of the literature review and writing. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

References

1. Abraham RS and Aubert G: Flow cytometry, a versatile tool for diagnosis and monitoring of primary immunodeficiencies. *Clin Vaccine Immunol* 23: 254-271, 2016.
2. Bonilla FA, Khan DA, Ballas ZK, Chinen J, Frank MM, Hsu JT, Keller M, Kobrynski LJ, Komarow HD, Mazer B, *et al*: Practice parameter for the diagnosis and management of primary immunodeficiency. *J Allergy Clin Immunol* 136: 1186-205.e1-78, 2015.
3. Fischer A, Provot J, Jais JP, Alcais A and Mahlaoui N; members of the CEREDIH French PID study group: Autoimmune and inflammatory manifestations occur frequently in patients with primary immunodeficiencies. *J Allergy Clin Immunol* 140: 1388-1393.e8, 2017.
4. Picard C, Bobby Gaspar H, Al-Herz W, Bousfiha A, Casanova JL, Chatila T, Crow YJ, Cunningham-Rundles C, Etzioni A, Franco JL, *et al*: International union of immunological societies: 2017 primary immunodeficiency diseases committee report on inborn errors of immunity. *J Clin Immunol* 38: 96-128, 2018.
5. Bousfiha A, Jeddane L, Picard C, Al-Herz W, Ailal F, Chatila T, Cunningham-Rundles C, Etzioni A, Franco JL, Holland SM, *et al*: Human inborn errors of immunity: 2019 update of the IUIS phenotypical classification. *J Clin Immunol* 40: 66-81, 2020.
6. Tangye SG, Al-Herz W, Bousfiha A, Chatila T, Cunningham-Rundles C, Etzioni A, Franco JL, Holland SM, Klein C, Morio T, *et al*: Human inborn errors of immunity: 2019 update on the classification from the international union of immunological societies expert committee. *J Clin Immunol* 40: 24-64, 2020.
7. Condino-Neto A and Espinosa-Rosales FJ: Changing the lives of people with primary immunodeficiencies (PI) with early testing and diagnosis. *Front Immunol* 9: 1439, 2018.
8. Stray-Pedersen A, Sorte HS, Samarakoon P, Gambin T, Chinn IK, Coban Akdemir ZH, Erichsen HC, Forbes LR, Gu S, Yuan B, *et al*: Primary immunodeficiency diseases: Genomic approaches delineate heterogeneous Mendelian disorders. *J Allergy Clin Immunol* 139: 232-245, 2017.
9. Primary Immunodeficiencies (PID) Driving Diagnosis for Optimal Care in Europe. European Reference Paper http://worldpiweek.org/sites/default/files/basic_page_documents/PI_European_Reference_Paper.pdf (accessed on May 1, 2020).
10. Immune Deficiency Foundation: Primary Immune Deficiency Diseases in America: 2007. The Third National Survey of Patients. Prepared by: Abt SRBI, Inc. May 1, 2009. <https://primaryimmune.org/wp-content/uploads/2011/04/Primary-Immunodeficiency-Diseases-in-America-2007The-Third-National-Survey-of-Patients.pdf> (accessed on 26 April 2020).
11. Chapel H, Prevot J, Gaspar HB, Español T, Bonilla FA, Solis L and Drabwell J; Editorial Board for Working Party on Principles of Care at IPOPI: Primary immune deficiencies-principles of care. *Front Immunol* 5: 627, 2014.
12. Suarez F, Mahlaoui N, Canioni D, Andriamanga C, Dubois d'Enghien C, Brousse N, Jais JP, Fischer A, Hermine O and Stoppa-Lyonnet D: Incidence, presentation, and prognosis of malignancies in ataxia-telangiectasia: A report from the French national registry of primary immune deficiencies. *J Clin Oncol* 33: 202-208, 2015.
13. Shapiro RS: Malignancies in the setting of primary immunodeficiency: Implications for hematologists/oncologists. *Am J Hematol* 86: 48-55, 2011.
14. Grimbacher B, Warnatz K, Yong PFK, Korganow AS and Peter HH: The crossroads of autoimmunity and immunodeficiency: Lessons from polygenic traits and monogenic defects. *J Allergy Clin Immunol* 137: 3-17, 2016.
15. de Jesus AA, Canna SW, Liu Y and Goldbach-Mansky R: Molecular mechanisms in genetically defined autoinflammatory diseases: Disorders of amplified danger signaling. *Annu Rev Immunol* 33: 823-874, 2015.
16. Jonkman-Berk BM, van den Berg JM, Ten Berge IJ, Bredius RG, Driessen GJ, Dalm VA, van Dissel JT, van Deuren M, Ellerbroek PM, van der Flier M, *et al*: Primary immunodeficiencies in the Netherlands: National patient data demonstrate the increased risk of malignancy. *Clin Immunol* 156: 154-162, 2015.
17. Comrie WA and Lenardo MJ: Molecular classification of primary immunodeficiencies of T lymphocytes. *Adv Immunol* 138: 99-193, 2018.
18. Gug C, Gorduza EV, Lăcătușu A, Vaida MA, Bîrsășteanu F, Puîu M and Stoicănescu D: CHARGE syndrome associated with de novo (11460Rfs*15) frameshift mutation of CHD7 gene in a patient with arteria lusoria and horseshoe kidney. *Exp Ther Med* 20: 479-485, 2020.

19. Mäkitie O and Vakkilainen S: Cartilage-hair hypoplasia-anaxenic dysplasia spectrum disorders. In: GeneReviews® [Internet]. Adam MP, Ardinger HH, Pagon RA, *et al* (eds). University of Washington, Seattle, WA, 1993-2020. 2012 Mar 15 [Updated 2020 Aug 6]. <https://www.ncbi.nlm.nih.gov/books/NBK84550/> (accessed on 17 April 2020).
20. Nagy R, Wang H, Albrecht B, Wiczorek D, Gillissen-Kaesbach G, Haan E, Meinecke P, de la Chapelle A and Westman JA: Microcephalic osteodysplastic primordial dwarfism type I with biallelic mutations in the RNU4ATAC gene. *Clin Genet* 82: 140-146, 2012.
21. HGNC Database: HUGO Gene Nomenclature Committee (HGNC), European Molecular Biology Laboratory, European Bioinformatics Institute (EMBL-EBI), Wellcome Genome Campus, Hinxton, Cambridge CB10 1SD, United Kingdom. Available online: <https://www.genenames.org/> (accessed on April 2020).
22. Savage SA: Dyskeratosis Congenita. In: GeneReviews® [Internet]. Adam MP, Ardinger HH, Pagon RA, *et al* (eds). University of Washington, Seattle, WA, 1993-2020. 2009 Nov 12 [Updated 2019 Nov 21]. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK22301/> Accessed April 17, 2020.
23. The UniProt Consortium: UniProt: A worldwide hub of protein knowledge. *Nucleic Acids Res* 47: D506-D515, 2019.
24. Al-Herz W, Bousfiha A, Casanova JL, Chatila T, Conley ME, Cunningham-Rundles C, Etzioni A, Franco JL, Gaspar HB, Holland SM, *et al*: Primary immunodeficiency diseases: An update on the classification from the international union of immunological societies expert committee for primary immunodeficiency. *Front Immunol* 5: 162, 2014.
25. Mäkitie O, Pukkala E, Teppo L and Kaitila I: Increased incidence of cancer in patients with cartilage-hair hypoplasia. *J Pediatr* 134: 315-318, 1999.
26. Abdel-Salam GM, Abdel-Hamid MS, Issa M, Magdy A, El-Kotoury A and Amr K: Expanding the phenotypic and mutational spectrum in microcephalic osteodysplastic primordial dwarfism type I. *Am J Med Genet A* 158A: 1455-1461, 2012.
27. Jung S, Lee S, Kim S and Nam H: Identification of genomic features in the classification of loss- and gain-of-function mutation. *BMC Med Inform Decis Mak* 15 (Suppl 1): S6, 2015.
28. Notarangelo LD and Fleisher TA: Targeted strategies directed at the molecular defect: Toward precision medicine for select primary immunodeficiency disorders. *J Allergy Clin Immunol* 139: 715-723, 2017.
29. Weinreich MA, Vogel TP, Rao VK and Milner JD: Up, down, and all around: Diagnosis and treatment of novel STAT3 variant. *Front Pediatr* 5: 49, 2017.
30. Alonso-Bello CD, Jiménez-Martínez MD, Vargas-Camaño ME, Hierro-Orozco S, Ynga-Durand MA, Berrón-Ruiz L, Alcántara-Montiel JC, Santos-Argumedo L, Herrera-Sánchez DA, Lozano-Patiño F and Castrejón-Vázquez MI: Partial and transient clinical response to omalizumab in IL-21-induced low STAT3-phosphorylation on Hyper-IgE syndrome. *Case Reports Immunol* 2019: 6357256, 2019.
31. Hafsi W and Yarrarapu SNS: Job Syndrome (Hyperimmunoglobulin E). [Updated 2020 Jul 17] In: StatPearls. [Internet] StatPearls Publishing, Treasure Island, FL, 2020 Jan. Available from <https://www.ncbi.nlm.nih.gov/books/NBK525947/> Accessed April 25, 2020.
32. Jhamnani RD and Rosenzweig SD: An update on gain-of-function mutations in primary immunodeficiency diseases. *Curr Opin Allergy Clin Immunol* 17: 391-397, 2017.
33. Rezaei N, Bonilla FA, Sullivan KF, De Vries E, Bousfiha AA, Puck J and Orange J: An introduction to primary immunodeficiency diseases. In: Rezaei N, Aghamohammadi A, Luigi ND. (eds.). *Primary Immunodeficiency Diseases*. Springer, Berlin, Heidelberg, pp1-81, 2017.
34. Arkwright PD and Gennery AR: Ten warning signs of primary immunodeficiency: A new paradigm is needed for the 21st century. *Ann N Y Acad Sci* 1238: 7-14, 2011.
35. Subbarayan A, Colarusso G, Hughes SM, Gennery AR, Slatter M, Cant AJ and Arkwright PD: Clinical features that identify children with primary immunodeficiency diseases. *Pediatrics* 127: 810-816, 2011.
36. Collin M, Bigley V, Haniffa M and Hambleton S: Human dendritic cell deficiency: The missing ID? *Nat Rev Immunol* 11: 575-583, 2011.
37. Nelson KS and Lewis DB: Adult-onset presentations of genetic immunodeficiencies: Genes can throw slow curves. *Curr Opin Infect Dis* 23: 359-364, 2010.
38. Gug C, Huțanu D, Vaida M, Doros G, Popa C, Stroescu R, Furău G, Furău C, Grigoriță L and Moșos I: De novo unbalanced translocation t(15;22)(q26.2;q12) with velo-cardio-facial syndrome: A case report and review of the literature. *Exp Ther Med* 16: 3589-3595, 2018.
39. de Miranda NF, Björkman A and Pan-Hammarström Q: DNA repair: The link between primary immunodeficiency and cancer. *Ann N Y Acad Sci* 1246: 50-63, 2011.
40. Leechawengwongs E and Shearer WT: Lymphoma complicating primary immunodeficiency syndromes. *Curr Opin Hematol* 19: 305-312, 2012.
41. Casey JP, Nobbs M, McGettigan P, Lynch S and Ennis S: Recessive mutations in MCM4/PRKDC cause a novel syndrome involving a primary immunodeficiency and a disorder of DNA repair. *J Med Genet* 49: 242-245, 2012.
42. Karalis A, Tischkowitz M and Millington GW: Dermatological manifestations of inherited cancer syndromes in children. *Br J Dermatol* 164: 245-256, 2011.
43. Byun M, Ma CS, Akçay A, Pedergrana V, Palendira U, Myoung J, Avery DT, Liu Y, Abhyankar A, Lorenzo L, *et al*: Inherited human OX40 deficiency underlying classic Kaposi sarcoma of childhood. *J Exp Med* 210: 1743-1759, 2013.
44. Leroy S, Moshous D, Cassar O, Reguerre Y, Byun M, Pedergrana V, Canioni D, Gessain A, Oksenhendler E, Fieschi C, *et al*: Multicentric Castleman disease in an HHV8-infected child born to consanguineous parents with systematic review. *Pediatrics* 129: e199-e203, 2012.
45. Adam MP, Hudgins L and Hannibal M: Kabuki Syndrome. In: GeneReviews®. [Internet]. Adam MP, Ardinger HH, Pagon RA, *et al* (eds). GeneReviews, University of Washington, Seattle, Seattle, WA, pp1993-2020. 2011 Sep 1. [Updated 2019 Oct 21]. Available from <https://www.ncbi.nlm.nih.gov/sites/books/NBK62111/>. Accessed April 26, 2020.



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