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 10^5 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
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 involved 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).

Another 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, SP110 and KMT2D), DNA replication origin binding (MC4), single-stranded DNA binding (BLM, MCM4, STN1 and CTC1), or damaged DNA binding (NBN, DCLRE1B/SNMI/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, SP110, STAT5B, KMT2D (MLL2), TBX1, ZNF341 and NFE2L2, BCL11B) or transcription factor binding (NBN, TBX1, STAT3 and NFKBIA) (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 binding activity (WAS), small GTPase binding (WAS), phospholipase binding (WAS), protein kinase binding (WAS, ERCC6L2, STAT3, PARN and IKKβ), DNA-dependent protein kinase activity (ATM), helicase (BLM, HELLS, MCM4, ERCC6L2, CHD7, SMARCAL1, RTEL1, SKIV2L), hydrolase (HELLS, PMS2, MCM4, POLE, ERCC6L2, CHD7, SMARCAL1, MYSM1, RTEL1, TIP1, DCLRE1B/SNMI/APOLLO, PARN and MTHFD1), nuclease (PMS2, POLE, DCLRE1B/SNMI/APOLLO and PARN), metalloprotease (MYSM1), phosphoglucomutase activity (PGM3), DNA polymerase binding (RTEL1) (23).

Another process that is perturbed in immunodeficiencies is the ion binding and the main genes implied are TGFBR1, TGFBR2, ZNF341, DNMT3B, ZBTB24, RNF168, LIG1, MYSM1, EXT3L, RTEL1, TERT, PP1, PARN, TCN2, IKKβ (NEMO), SP110, 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 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, IKKβ, WRAP53, IKKβ (NEMO), NFKBIA, ORAI1, STIM1, PNP, HOIL1, KDM6A, KMT2A and IL6ST), Rac GTPase (WAS), SH3 domain binding (WAS, WIP1F1), profilin binding (WIPF1), ATP binding [IKKβ, TGFBR1, TGFBR2, ATM, BLM (RECQL3), HELLS, PMS2, MCM4, LIG1, ERCC6L2, SKIV2L, CHD7, SMARCAL1, RTEL1 and MTHFD1], chaperone binding (TERT and WRAP53), actin (actin filament) binding (WAS, WIPF1 and ARPC1B) (23).

Other genes, such as RMRP, RN4ATAC or TERC, encode noncoding RNA (part of RNAse MRP), small nuclear RNA and telomerase RNA component (Table 1). Mutations in these genes cause alterations in processing of ribosomal RNA. RMRP gene mutations disturb mitochondrial DNA replication and cell cycle control. RN4ATAC 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, CCB1 and 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 | WAS (XL) | GTPase regulator and binding activity; protein binding (actin, protein kinase); phospholipase binding | Fe-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 involved |
| Wiskott-Aldrich syndrome (WAS LOF) | WAS | Actin binding; profilin binding; SH3 domain binding | Fe-gamma receptor signaling pathway involved in phagocytosis; regulation of cell shape, immune response against microorganisms |
| WIP deficiency | WIPF1 (AR) | Actin binding; profilin binding; SH3 domain binding | Fe-gamma receptor signaling pathway involved in phagocytosis; regulation of cell shape, immune response against microorganisms |
| ARPC1B deficiency | ARPC1B | Actin filament and binding; structural constituent of cytoskeleton | Fe-gamma receptor signaling pathway involved in phagocytosis |
| DNA repair defects other than those listed in the 1st category | ATM (AR) | ATP, protein and DNA binding; DNA-dependent protein kinase activity | Cell cycle; DNA damage |
| Ataxia-telangiectasia | ATM (AR) | ATP, protein and DNA binding; DNA-dependent protein kinase activity | Cell cycle; DNA damage |
| Nijmegen breakage syndrome | NBN (AR) | Damaged DNA and protein binding; | Cell cycle; DNA damage; DNA repair; host-virus interaction; |
| Bloom syndrome | BLM (RECQL3) (AR) | DNA binding; DNA and ATP binding; DNA-methyltransferase activity; histone deacetylase binding | DNA damage; DNA repair; DNA replication; DNA methylation; regulation of histone methylation and transcription |
| ICF1 | DNMT3B (AR) | DNA binding; DNA and ATP binding; DNA-methyltransferase activity; histone deacetylase binding | DNA damage; DNA repair; DNA replication; DNA methylation; regulation of histone methylation and transcription |
| ICF2 | ZBTB24 (AR) | DNA-binding transcription factor activity | Transcription; transcription regulation |
| ICF3 | CDC47 (AR) | MYC-mediated cell transformation and apoptosis | Apoptosis; transcription |
| ICF4 | HELLS (AR) | Developmental protein; helicase activity; hydrolase; ATP binding | Cell cycle; transcription; multicellular organism development |
| PMS2 deficiency | PMS2 (AR) | DNA binding; ATPase activity | DNA damage; DNA repair |
| RNF168 deficiency (Riddle syndrome) | RNF168 (AR) | DNA binding; DNA and ATP binding | DNA damage; DNA repair; ubiquitin conjugation pathway |
| MCM4 deficiency | MCM4 (AR) | DNA binding; DNA helicase activity | Cell cycle; DNA replication |
| POLE1 (polymerase ε subunit 1) deficiency (FILS syndrome) | POLE (AR) | DNA and metal binding; DNA-directed DNA polymerase activity | DNA damage; DNA repair; DNA replication |
| POLE2 (polymerase ε subunit 2) deficiency | POLE2 (AR) | DNA binding; DNA-directed DNA polymerase activity | DNA replication |
| Ligase I deficiency | LIG1 (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                                                      | NSMCE3 (AR)      | Tumor antigen                                                                       | DNA damage, recombination and repair; growth regulation                              |
| ERCC6L2 (Hebo deficiency)                                              | ERCC6L2 (AR)     | DNA, ATP and protein kinase binding; helicase activity                               | DNA damage; DNA repair                                                                |
| GINS1 deficiency                                                       | GINS1 (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                                                        | TBX1 (AD)        | Developmental protein; DNA and transcription activator binding; RNA polymerase II  | Transcription; angiogenesis; thymus development; morphogenesis                      |
| CHARGE syndrome                                                        | CHD7 (AD)        | ATP and chromatin binding; DNA helicase activity; rRNA processing                   | RNA processing; transcription                                                         |
| CHARGE syndrome                                                        | SEMA3E (AD)      | Developmental protein; DNA-binding transcription activator                           | Angiogenesis; differentiation; neurogenesis                                           |
| Winged helix nude FOXN1 deficiency                                     | FOXN1 (AR)       | Developmental protein; DNA-binding transcription activator                           | Differentiation; transcription; thymus epithelium morphogenesis; lymphoid lineage    |
| Thymic defects with additional congenital anomalies                    |                  |                                                                                     | 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                                               | Del11q23 (AD)    |                                                                                     |                                                                                     |
| Immuno-osseous dysplasias                                              |                  |                                                                                     |                                                                                     |
| Cartilage hair hypoplasia (CHH)                                        | RMRP (AR)        | Noncoding RNA                                                                       | Processing of ribosomal RNA; cell cycle control                                       |
| Schimke immuno-osseous dysplasia                                       | SMARCAL1 (AR)    | Helicase activity; ATP binding                                                       | Cellular response to DNA damage stimulus                                              |
| MYSM1 deficiency                                                       | MYSM1 (AR)       | DNA histone and metal ion binding                                                   | Transcription                                                                        |
| MOPD1 deficiency                                                       | RNU4ATAC (AR)    | Small nuclear RNA (snRNA)                                                           | Part of spliceosome complex                                                           |
| EXT13 deficiency                                                       | EXT13 (AR)       | Metal ion binding; transferase activity                                             | Proteoglycan biosynthetic process; regulation of cell growth                          |
| Hyper-IgE syndromes (HIES)                                             |                  |                                                                                     |                                                                                     |
| STAT3 deficiency (Job syndrome)                                        | STAT3 (AD)       | DNA, enzyme and chromatin binding; RNA polymerase activity                          | Host-virus interaction; transcription                                                |
| IL6 receptor deficiency                                                | IL6R (AR)        | Cytokine and enzyme binding, cytokine receptor activity                             | Regulation of the immune response, acute-phase reactions and hematopoiesis            |
| Disease                                                                 | Gene (MOI)                        | Molecular function                                                                 | Biological process                                                                 |
|------------------------------------------------------------------------|-----------------------------------|------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|
| Hyper-IgE syndromes (HIES)                                             |                                   |                                                                                    |                                                                                    |
| IL6 signal transducer (IL6ST) deficiency                             | *IL6ST* (AR)                      | Cytokine and growth factor binding, cytokine receptor activity, binding            | Host-virus interaction                                                              |
| ZNF341 deficiency AR-HIES                                             | *ZNF341* (AR)                     | DNA and metal ion binding; DNA-binding transcription activator activity            | Transcription, transcription regulation                                              |
| ERBIN deficiency                                                       | *ERBIN* (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 (TGFBR deficiency)                               | *TGFBR1* (AD)                     | Activin, ATP and metal ion binding; protein kinase activity                        | Apoptosis, differentiation, growth regulation                                       |
| Loeys-Dietz syndrome (TGFBR deficiency)                               | *TGFBR2* (AD)                     | Activin-activated receptor activity; activin, ATP and metal ion binding           | Apoptosis, differentiation, growth regulation                                       |
| Comel-Netherton syndrome                                              | *SPINK5* (AR)                     | Serine-type endopeptidase inhibitor activity                                      | Cell differentiation; central nervous system development; regulation of T cell differentiation | Carbohydrate metabolism; hemopoiesis | Costimulatory signal for T-cell receptor-mediated T-cell activation; NF-kB activation in a T-cell receptor/CD3-dependent manner |
| PGM3 deficiency                                                       | *PGM3* (AR)                       | Magnesium binding; enzymatic activity                                             |                                                                                    |
| CARD11 deficiency (heterozygous)                                      | *CARD11* (AR AD LOF dominant negative) | CARD domain binding, guanylate kinase activity                                    |                                                                                    |
| Dyskeratosis congenita (DKC), myelodysplasia, short telomeres         |                                   |                                                                                    |                                                                                    |
| XL-DKC                                                                | *DKC1* (XL)                       | RNA-binding; telomerase RNA binding                                              | Ribosome biogenesis; rRNA processing                                                |
| AR-DKC with NHP2 deficiency                                           | *NHP2* (AR)                       | RNA-binding; telomerase RNA binding                                              | Ribosome biogenesis; rRNA processing                                                |
| AR-DKC with NHP3 or NOP10 deficiency                                  | *NOP10* (AR)                      | RNA-binding; telomerase RNA binding                                              | Ribosome biogenesis; rRNA processing                                                |
| AD/AR-DKC with RTEL1 deficiency                                       | *RTEL1* (AD or AR)                | DNA, ATP, DNA polymerase and metal ion binding; DNA helicase activity             | DNA damage; DNA repair                                                              |
| AD-DKC with TERC deficiency                                           | *TERC* (AD)                       | Telomerase RNA component                                                         | DNA replication                                                                    |
| AD/AR-DKC with TERT deficiency                                        | *TERT* (AD or AR)                 | DNA, chaperone, protein and metal ion -binding                                  | Transcription and replication                                                      |
| AD-DKC with TINF2 deficiency                                          | *TINF2* (AD)                      | Telomeric DNA binding                                                           | Transcription of telomeres                                                         |
| AD/AR-DKC with TPP1 deficiency                                        | *TPP1* (AD or AR)                 | Peptidase activity; metal and ion binding                                       | Development and cell differentiation; lipid and protein metabolic process           |
| AR-DKC with DCLRE1B deficiency                                        | *DCLRE1B/SMN1/ APOLLO* (AR)       | 5’-3’ exonuclelease activity                                                     | DNA damage; DNA repair                                                             |
| AR-DKC with PARN deficiency                                           | *PARN* (AR (AD?))                 | 3’-5’-Exoribonuclease activity; cation binding; metalion binding                 | Nonsense-mediated mRNA decay                                                       |
| AR-DKC with WRAP53 deficiency                                         | *WRAP53* (AR)                     | RNA chaperone histone protein binding                                            | DNA damage; DNA repair; Host-virus interaction                                      |
| Coats plus syndrome                                                   | *STN1* (AR)                       | DNA binding                                                                      | DNA repair; DNA replication;                                                       |
| Coats plus syndrome                                                   | *CTC1* (AR)                       | DNA binding                                                                      | Cell cycle control; multicellular organism growth                                  |
| SAMD9                                                                | *SAMD9* AD                        | Inflammatory response to tissue injury                                           | Endosomal vesicle fusion                                                           |
| Disease | Gene (MOI) | Molecular function | Biological process |
|---------|------------|--------------------|--------------------|
| Defects of vitamin B12 and folate metabolism | | | |
| Transcobalamin 2 deficiency | TCN2 (AR) | Cobalamin binding; metal ion binding | Cobalt transport; ion transport; Transport of different cellular components |
| SLC46A1/PCFT deficiency | SLC46A1 (AR) | Folic acid binding; folic acid, heme, methotrexate and transporter activity | |
| MTHFD1 deficiency | MTHFD1 (AR) | ATP binding; enzymatic activity | Protein biosynthesis |
| Anhidrotic ectodermodyplasia with immunodeficiency (EDA-ID) | | | |
| EDA-ID with NEMO/IKBKG deficiency | IKBKG (NEMO) (XL) | Protein and metal ion binding | DNA damage; host-virus interaction; transcription |
| EDA-ID with IKBA GOF mutation | NFKBIA (IKBA) (XL) | Protein and enzyme binding | Host-virus interaction |
| EDA-ID with IKBKB GOF mutation | IKBKB (AD GOF) | ATP and protein kinase binding, protein kinase activity | Host-virus interaction |
| Calcium channel defects | | | |
| ORAI-1 deficiency | ORAI1 (AR) | Calmodulin-binding; store-operated calcium channel activity | Adaptive immunity; calcium transport; |
| STIM1 deficiency | STIM1 (AR) | Calcium channel regulator activity; calcium ion binding | Calcium transport |
| Other defects | | | |
| Purine nucleoside phosphorylase deficiency | PNP (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 | TTC7A (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) | TTC37 (AR) | Exosome-mediated RNA decay | Exonucleolytic catabolism of deadenylated mRNA |
| Tricho-Hepato-Enteric Syndrome (THES) | SKIV2L (AR) | ATP and RNA binding; RNA helicase activity | RNA catabolic process |
| Hepatic veno-occlusive disease with immunodeficiency | SPI10 (AR) | DNA, protein and metal ion binding; RNA polymerase II-specific | Host-virus interaction; transcription |
| BCL11B deficiency | BCL11B (AD) | DNA, metal binding; RNA polymerase | Transcription |
| Vici syndrome due to EPG5 deficiency | EPG5 (AR) | Clearance of autophagosomal cargo innate and adaptive immune response | Autophagy; cellular response to dsDNA; nucleotide transport; toll-like receptor 9 signaling pathway |
| Disease                   | Gene (MOI)                                                                 | Molecular function                                                                 | Biological process                                                      |
|--------------------------|---------------------------------------------------------------------------|-----------------------------------------------------------------------------------|------------------------------------------------------------------------|
| HOIL1 deficiency         | HOIL1 (RBCK1) (AR)                                                       | Protein, enzyme and metal ion binding                                              | Other defects                                                          |
| HOIP deficiency          | RNF31                                                                     | Calcium ion colligating and protein binding                                         | Host-virus interaction, transcription, Apoptosis; transcription         |
| Hennekam-lymphangiectasia-lymphedema syndrome | CCBE1 (AR)                                                             | Calcium ion and protease binding                                                   | Angiogenesis and lymphangiogenesis                                      |
| HOIP deficiency          | RNF31                                                                     | Calcium ion and protease binding                                                   | Angiogenesis and lymphangiogenesis                                      |
| Hennekam-lymphangiectasia-lymphedema syndrome | CCBE1 (AR)                                                             | Calcium ion and protease binding                                                   | Angiogenesis and lymphangiogenesis                                      |
| De novo mutations in nuclear factor, erythroid 2-like (NFE2L2) deficiency | NFE2L2 (AR)                                                            | DNA and protein binding; RNA polymerase II specific transcription                | Host-virus interaction, transcription, Apoptosis; transcription         |
| De novo mutations in nuclear factor, erythroid 2-like (NFE2L2) deficiency | NFE2L2 (AR)                                                            | DNA and protein binding; RNA polymerase II specific transcription                | Host-virus interaction, transcription, Apoptosis; transcription         |
| Stat5b deficiency        | STAT5B                                                                     | Chomatin, protein and hormone binding; RNA polymerase II Transcription            | Transcription                                                          |
| Stat5b deficiency        | STAT5B                                                                     | Chomatin, protein and hormone binding; RNA polymerase II Transcription            | Transcription                                                          |
| KMT2D deficiency         | KMT2D (MLL2)                                                              | DNA histone and metal ion binding; histone methyltransferase activity              | Transcription                                                          |
| KMT2A deficiency         | KMT2A                                                                     | DNA histone and metal ion binding; histone methyltransferase activity              | Transcription                                                          |
| Wiedemann-Steiner syndrome | KDM6A (XL)                                                              | DNA histone and metal ion binding; histone methyltransferase activity              | Transcription                                                          |
| MOL, mode of inheritance: X-linked inheritance | AR, autosomal recessive inheritance; AD, autosomal dominant inheritance; AOM, autosomal Mendelian inheritance | Transcription, transcription, Host-virus interaction, transcription, Apoptosis | Host-virus interaction, transcription, Apoptosis; transcription         |

MOI, mode of inheritance; XL, X-linked inheritance; AR, autosomal recessive inheritance; AD, autosomal dominant inheritance; AOM, autosomal Mendelian inheritance.
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 IKBKG, IKKB, GOF NFKB1A/IKB 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 (IKBKG), AT (ATM). Widespread molluscum contagiosum is associated with WAS, NEMO deficiency (IKBKG). Pneumonia with Pneumocystis jirovecii is present in WAS (WASP), NEMO deficiency (IKBKG), VODI (SPI10), CARD11. Chronic mucocutaneous infection with Candida spp. is found in IKBG, IKB, IKBB, NEMO deficiency, VODI (SPI10) 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 HOIL1 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 IKBKG mutations); trichohepatoenteric syndrome -skiv2l and Ttcc7 mutations, Veno-occlusive disease with immunodeficiency (VODI) SPI10 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, IFNGRI, 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.

Ethics approval and consent to participate

Not applicable.

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Competing interests

The authors declare that they have no competing interests.

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