REVIEW

WILEY

Known and potential molecules associated with altered B cell development leading to predominantly antibody deficiencies

Parisa Amirifar[1,2] | Reza Yazdani[1,3] | Gholamreza Azizi[4] |
Mohammad Reza Ranjouri[1] | Anne Durandy[5] | Alessandro Plebani[6] |
Vassilios Lougaris[6] | Lennart Hammarstrom[7,8] | Asghar Aghamohammadi[1] |
Hassan Abolhassani[1,7,8]

[1]Research Center for Immunodeficiencies, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran

[2]Department of Medical Genetics, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

[3]Primary Immunodeficiency Diseases Network (PIDNet), Universal Scientific Education and Research Network (USERN), Tehran, Iran

[4]Non-Communicable Diseases Research Center, Alborz University of Medical Sciences, Karaj, Iran

[5]Human Lymphohematopoiesis Laboratory, Institut Imagine, Inserm U1163, Paris Descartes Sorbonne, Paris Cite University, Paris, France

[6]Pediatrics Clinic and "A. Nocivelli" Institute for Molecular Medicine, Department of Clinical and Experimental Sciences, University of Brescia, ASST Spedali Civili of Brescia, Brescia, Italy

[7]Division of Clinical Immunology, Department of Biosciences and Nutrition, Karolinska Institute, Stockholm, Sweden

[8]Division of Clinical Immunology, Department of Laboratory Medicine, Karolinska Institute at Karolinska University Hospital Huddinge, Stockholm, Sweden

Correspondence
Hassan Abolhassani, Division of Clinical Immunology, Department of Biosciences and Nutrition, NEO, Blickagangen 16, Karolinska Institute, Stockholm, SE-14157, Sweden.
Email: hassan.abolhassani@ki.se

Editor: Fabio Candotti

Abstract

Predominantly antibody deficiencies (PADs) encompass a heterogeneous group of disorders characterized by low immunoglobulin serum levels in the presence or absence of peripheral B cells. Clinical presentation of affected patients may include recurrent respiratory and gastrointestinal infections, invasive infections, autoimmune manifestations, allergic reactions, lymphoproliferation, and increased susceptibility to malignant transformation. In the last decades, several genetic alterations affecting B-cell development/maturation have been identified as causative of several forms of PADs, adding important information on the genetic background of PADs, which in turn should lead to a better understanding of these disorders and precise clinical management of affected patients. This review aimed to present a comprehensive overview of the known and potentially involved molecules in the etiology of PADs to elucidate the pathogenesis of these disorders and eventually offer a better prognosis for affected patients.

1 | INTRODUCTION

Predominantly antibody deficiencies (PADs) are the most common form of primary immunodeficiencies (PIDs) with different etiologies and varied clinical manifestations.[1] In recent years, numerous experimental approaches have been undertaken in order to better clarify the pathogenesis of PADs; nonetheless, the majority of affected patients remain without a genetic diagnosis. The spectrum of PADs is extensive, ranging from patients with a profound decrease in all serum immunoglobulins (Igs) and B-cell numbers to defect in a specific antibody response with normal serum Igs.[2,3] These patients may present various clinical manifestations, including recurrent respiratory infections, autoimmunity, enteropathy, interstitial lung disease, lymphoproliferation, and allergic diseases.[4] Lifelong Ig replacement therapy is the indicated treatment for the majority of these patients.[5]

Early B-cell development is a highly regulated process that takes place in the bone marrow (BM). The differentiation of peripheral B cells into memory B cells and plasma cells takes place in the secondary lymphoid organs leading to antibody production required for antigen recognition, neutralization, opsonization and phagocytosis, complement activation, antibody-mediated cytotoxicity, and controlling of inflammation and apoptosis. Defect in any step of B-cell maturation may lead to a reduction in serum Ig and/or impaired antibody physiological function.[6] Overall, defect in early B-cell development, class switch recombination (CSR), or terminal B-cell differentiation led to PADs. Impairment in early B-cell development gives rise to a block of B-cell differentiation, leading to the lack of circulating B cells and severe reduction in all serum Ig levels. Production of different isotype (IgG, IgA, and IgE) immunoglobulins in secondary lymphoid organs is achieved through CSR and somatic hypermutation [7] mechanisms, and defects in these processes result in decreased serum IgG, IgA, and IgE levels but normal or increased IgM serum levels. Finally, defects in genes involved in the terminal stages of B-cell development may be involved in the pathogenesis of common variable immunodeficiency or other isolated Ig subclass defect.[4]

Although several mutated genes involved in B-cell proliferation, differentiation, and activation have been recognized in the pathogenesis of PADs in humans,[8-10] multiple other molecules involved in B-cell development, based on animal studies or pathway/structural analysis, may have a potential role in the etiology of PADs. This review presents a comprehensive overview of known and potential molecules that could be involved in the pathogenesis of PADs.

2 | EARLY B-CELL DEVELOPMENT

Early B-cell development is characterized by the functional rearrangement process of the *heavy-chain (H-chain)* and *light-chain (L-chain)*

Key message

Over the last 3 decades, we have witnessed the ongoing rapid identification, and occasionally detailed molecular biochemical, and cellular characterization, of genetic variants that cause, or are at least associated with, human diseases impacting B cell function and humoral immunity. This report summarizes comprehensively the known genes and potential candidates which should be considered by treating physicians mainly clinical immunologist.

loci.[11] In the first stage, early pro-B cells rearrange the short D (diversity) and J (joining) segments of the H-chain and become late pro-B cell, followed by a second rearrangement combining an upstream selected V gene segment with the short DJ region. In humans, there are approximately 50 known/functional V_H genes, 27 known functional D_H gene segments, and 6 known J_H segments located on chromosome 14.[12-15] The pre–B-cell stage is characterized by the initiation of a functional rearrangement of the H-chain gene segments through the μ content region making a complex with a surrogate light chain. In the next stage of immature B cell, VDJ recombination of the H-chain and VJ recombination of the L-chain (κ and λ chains) arise to produce a B-cell receptor (BCR) with a complete form of surface IgM.[16] The genes involved in the process of B-cell development are shown in Figure 1. Once a light chain is combined with the μ-H-chain, the cell is differentiated to immature B cell and the BCR is formed as well with δ constant region making IgD (using alternative splicing). At this point, IgM and IgD molecules are produced and co-expressed on the cell surface, and the immature B cells that passed the process of central negative selection can now leave the BM and migrate through the blood to the periphery such as the spleen and lymph nodes. These cells can then differentiate into transitional (T1/T2), follicular (FO), or marginal zone (MZ) B cells.[17] B cells are activated by direct contact with a soluble antigen or attached to the surface of another cell, particularly macrophages and dendritic cells.[18] Generally, antigens can be classified as either T cell–dependent (TD) or T cell–independent (TI).[19] TD antigens activate B cells with coordination of T cells, whereas TI antigens activate B cells by recognition and binding of a microbial constituent to Toll-like receptors (TLRs) or by binding of BCRs to repeated epitopes on a bacterial pathogen.[20,21]

Activated B cells can either differentiate into plasmablasts or get recruited into a specialized region, called germinal centers (GCs).[22] In the GCs, B cells are targeted by clonal expansion, selection by affinity maturation through somatic hypermutation, and CSR. The outcome of the GC reaction is the production of both plasma cells and memory B cells, which will be discussed in the next sections.[21,23]
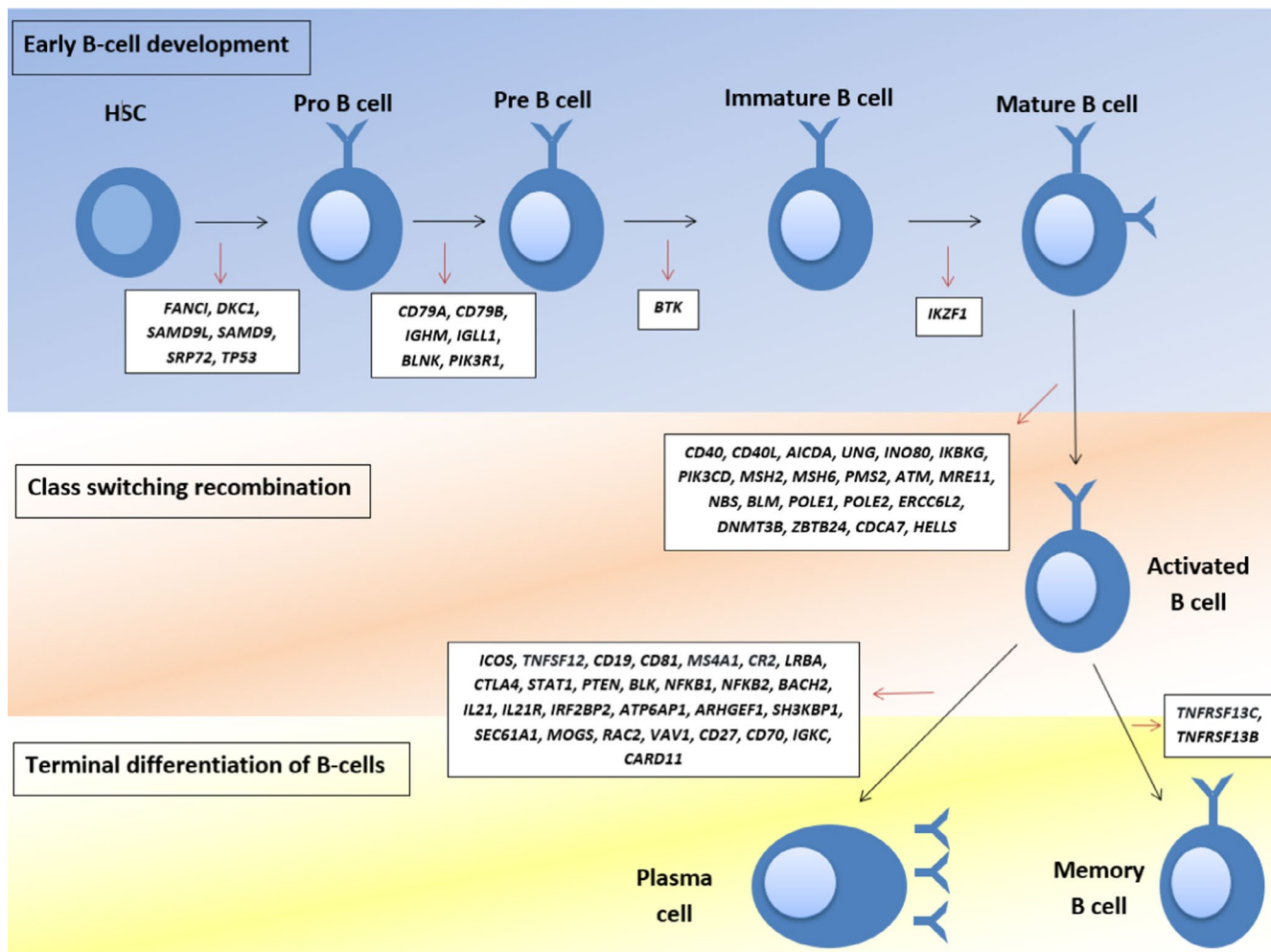
FIGURE 1 Known mutated genes involved in human B-cell deficiencies

2.1 | Known gene and protein defects in early B-cell development defects

The essential genes involved in human early B-cell development include Bruton's tyrosine kinase *(BTK)*, Igα *(CD79A)*, Igβ *(CD79B)*, Ig lambda–like polypeptide 1 *(IGLL1)*, Ig heavy constant Mu *(IGHM)*, B-cell linker protein *(BLNK)*, p85a subunit of phosphoinositide 3-kinase *(PIK3R1)*, p110δ subunit of phosphoinositide 3-kinase *(PIK3CD)*, folliculin-interacting protein 1 *(FNIP1)*, DNA topoisomerase II beta *(TOP2B)*, Leucine-rich repeat-containing protein 8A *(LRRC8A)*, transcription factor 3 *(TCF3)*, and solute carrier family 39 member 7 *(SLC39A7/ZIP7)* (Figure 1).[2,24] Loss-of-function mutations in these genes lead to arrest in B-cell differentiation, markedly reduced peripheral mature B-cell number, profound agammaglobulinemia, associated with early onset (within the first year of life) of recurrent respiratory and gastrointestinal infections.[25-27]

Agammaglobulinemia is the classical prototype of PADs due to early B-cell development defects, which can be inherited as X-linked, autosomal recessive (AR) or autosomal dominant (AD).[28] Mutations of the *BTK* gene in humans lead to severely reduced peripheral B-cell numbers and low Ig serum levels of all classes causing X-linked

agammaglobulinemia (XLA).[29] BTK plays a central role in signal transduction downstream of the pre-BCR and BCR complexes. Clinical manifestations in XLA patients are often observed between the ages of 6 and 12 months, when the fetus-transferred maternal IgG are catabolized. Typically, affected patients may present with recurrent bacterial otitis media, sinusitis, bronchitis, pneumonia, leading to the development of bronchiectasis, and chronic diarrhea due to encapsulated bacterial infection.[30] Moreover, they can develop severe chronic viral infections disseminated or encephalitis.[7,31-33]

In addition to the X-linked form, AR agammaglobulinemia (ARA) is also observed in almost 10% of agammaglobulinemia patients. Similar to XLA, ARA is characterized by a severe reduction in all of the Ig classes and the absence of peripheral B cells; however, the maturation arrest in BM is more severe at the pro–B-cell stage.[34] ARA is a genetically heterogeneous disorder caused by biallelic defects in genes including *IGHM*, Igα, Igβ, λ5, *BLNK*, p85a, p110δ, *TCF3*, *FNIP1* and *ZIP7* that their productions play essential roles in the signal transduction of the pre-BCR complex.[34,35] IGHM deficiency, however, is the most frequent form of ARA.[34]

In recent years, three types of autosomal dominant agammaglobulinemia have been also described. These forms are caused

by heterozygous loss-of-function mutations in *TCF3*, *TOP2B*, and *LRRC8*.[28] TCF3 is a transcriptional activator that plays a critical role in lymphocyte development. Generally, heterozygous dominant-negative mutations in *TCF3*, encoding the transcription factor E47, are associated with AD agammaglobulinemia, whereas nonsense loss-of-function mutations in *TCF3* are pathogenic only in an autosomal recessive state and cause ARA.[36] AR forms of TCF3 deficiency are more severe than the AD forms and manifest recurrent bacterial infections and failure to thrive.[36] *TOP2B* encodes a DNA topoisomerase II beta, an essential gene required to control and alter the topologic states of DNA during replication and transcription, with no previously known role in B-cell development.[37] Heterozygous mutations in *TOP2B* are related to B-cell immunodeficiency-limb anomaly-urogenital malformation syndrome, also known as Hoffman's syndrome that present with dysmorphic facial features and thus may be classified as syndromic combined immunodeficiency.[37,38] *LRRC8* encodes a protein belonging to the leucine-rich repeat family of proteins, which are involved in various biological processes, including cell adhesion, cellular trafficking, and hormone-receptor interactions. For the first time, this gene was isolated from the translocation site on chromosome 9 of a girl with agammaglobulinemia and minor facial anomalies.[39]

In addition to genes mentioned in early B-cell development, some genes involved in the process of VDJ recombination such as recombination-activating genes 1 and 2 (*RAG1* and *RAG2*), Artemis nuclease (*DCLRE1C*), DNA-dependent protein kinase or DNA-PK (*PRKDC*), DNA ligase IV (*LIG4*), and non-homologous end-joining factor 1 or Cernunnos (*NHEJ1*) have also been involved in early B-cell development in humans.[25] Although defects in these genes disrupt B-cell differentiation, they also severely affect T-cell maturation and cellular immunity and thus are considered as forms of severe combined immunodeficiency (SCID).[1]

It has been reported that genetic defects in other pathways can also disrupt early B-cell development in humans. For example, mutations in the genes, such as *FANC1-23* (family with 23 genes), *DKC1-13* (family with 13 genes), *SAMD9L*, *SAMD9*, *SRP72*, and *TP53*, have been observed in patients with bone marrow failure. All of these genes have been demonstrated to play major roles in the early stage of B-cell maturation; hence, a defect in these genes may lead to humoral immunodeficiency.[1] Moreover, some metabolic diseases are known to cause non-specific early B-cell defects. Mutations in *TCN2*, *SLC46A1*, and *MTHFD1* genes cause defects of vitamin B12 and folate metabolism and are characterized by megaloblastic anemia and decreased Ig levels.[40] Genes involved in nucleotide metabolism including adenosine deaminase (ADA), purine nucleoside phosphorylase (PNP), and adenylate kinase 2 (AK2) can be presented with severe B lymphopenia. A detailed list of known genetic and protein defects in early B-cell development of humans is provided in Table 1.

2.2 | Known gene and protein defects in animal models with early B-cell development defects

In mice, the different B-cell compartments have been described more in detail than in humans. Extensive research with various mutant models has provided fundamental insights into early B-cell development. Moreover, several genetic defects affecting components of the pre-BCR or downstream signaling molecules may be responsible for different alterations in B-cell biology between humans and mice, an aspect that has to be kept always in mind.[41]

The transcription factors Pax5, E2a, and Ebf have been shown to play important roles in the early stages of B-cell differentiation in mice.[42] Defect in *Pax5* leads to arrest in B-cell development during the early stages of CD19^{-} to CD19^{+} [43,44]; therefore, *Pax5*-deficient mice have a block in early B-cell development at the transition from DJ to VDJ rearrangement and frequently develop high-grade lymphomas.[45] *Ebf* and *E2a* are necessary for early B-cell differentiation. Targeted disruption of *Ebf* or *E2a* in mice causes a severe defect in early B-cell development before Ig gene rearrangement.[46] Also, *Ebf* and *E2a* heterozygosity in mice demonstrates an approximately twofold decrease in the number of pro–B-cell compartment, indicating that normal B-cell development depends on the presence of two wild-type alleles.[47]

The surrogate light chain composed of the VpreB and λ5 protein is a component of the early B-cell stage. In mice, in contrast to humans, there are two *VpreB* genes (*VpreB1* and *VpreB2*). In *VpreB1*^{-/-} *VpreB2*^{-/-} mice, the total numbers of IgM + immature and mature B cells were significantly decreased.[48] A detailed list of known genetic and protein defects in early B-cell development of animal models is provided in Table 1.

2.3 | Predictive gene and protein defects for early B-cell development defects

The Human Gene Connectome (HGC) was used to predict the set of all biologically plausible routes, distances, and degrees of separation between all pairs of human genes associated with early B-cell development. We used the HGC platform for gene-specific connectome that contains the set of all available human genes sorted on the basis of their predicted biological proximity to abovementioned specific genes of interest identified in agammaglobulinemia patients and animal models. The HGC is a powerful approach for human genotype-phenotype high-throughput studies, for which it can be used to rank any list of genes within a gene-specific connectome for an experimentally validated core gene.[49] According to these parameters, the predicted main genes that were identified to be associated with early B-cell development based on co-expression (47.3%), physical interaction (17.9%), and pathway similarly (14.2%) are X-ray repair cross-complementing 4 (*XRCC4*), *XRCC5*, *XRCC6*, pre-B lymphocyte 3 (*VPREB3*), polymerase DNA lambda (*POLL*), DNA nucleotidylexotransferase (*DNTT*), *CD22*, *CD72*, *CD320*, aprataxin- and PNKP-like factor (*APLF*), dipeptidyl-peptidase 4 (*DPP4*), polymerase DNA mu (*POLM*), MYB proto-oncogene, transcription factor (*MYB*), *CKLF*-like MARVEL transmembrane domain-containing 3 (*CMTM3*), Pescadillo Ribosomal Biogenesis Factor 1 (*PES1*), ES cell–expressed Ras (*ERAS*), phosphoinositide 3-kinase catalytic subunit alpha (*PIK3CA*), lymphoid enhancer-binding factor 1 (*LEF1*), aprataxin (*APTX*), polynucleotide kinase 3′-phosphatase (PNKP), SH3 domain-containing kinase

TABLE 1 List of known gene and protein defects in early B-cell development, class switch recombination, and terminal B-cell differentiation of human and animal models

Early B-cell development	
Known gene and protein defects in PAD disorders	B-cell–intrinsic genes: *CD79A, CD79B, BLNK, IGHM, PIK3R1* (biallelic LOF), *PIK3CD* (biallelic LOF), *BTK, IGLL1, IKZF1*(encoded for IKAROS), *TCF3* (monoallelic GOF, biallelic LOF), *TOP2B, LRRC8, FNIP1*
	VDJ rearrangement genes: *RAG1, RAG2, DCLRE1C* (encoded for ARTEMIS), *PRKDC, NHEJ1, LIG4* (these genes also affect T-cell development as combined deficiencies)
	Metabolic genes: *TCN2, SLC46A1, MTHFD1, ADA, PNP, AK2*
	Bone marrow failure genes: *FANCI–23, DKC1-13, SAMD9L, SAMD9, SRP72, TP53*
Known gene and protein defects in animal models	*Il7r, Vpreb, E2a, Ebf, Pax5, H2ax, Ku70, Ku80*
Class switch recombination	
Known gene and protein defects in PAD disorders	T-dependent genes: *CD40, CD40L, RELA, GINS1*
	B-cell–intrinsic genes: *AICDA, UNG, INO80, MSH2, MSH6, CTNNBL1*
	DNA repair genes: *PMS2, ATM, MRE11, NBS, BLM, POLE1, POLE2, ERCC6L2*
	Epigenetic genes: *DNMT3B, ZBTB24, CDCA7, HELLS*
	NF-κB pathway genes: *IKBKG, NFKBIA, IKBKB*
Known gene and protein defects in animal models	*Stat6, Traf2, SphK1, Itgam, Rad50*
Terminal differentiation of B cells	
Known gene and protein defects in PAD disorders	B-cell–intrinsic genes: *TNFRSF13C* (encoded for TACI), *TNFRSF13B* (encoded for BAFFR), *TNFSF12* (encoded for TWEAK), *TNFSF13* (encoded for APRIL), *CD19, CD81, MS4A1* (encoded for CD20), *CR2* (encoded for CD21), *LRBA, CTLA4, STAT1, PTEN, BLK, NFKB1, NFKB2, BACH2, IL21, IL21R, IRF2BP2, ATP6AP1, ARHGEF1, SH3KBP1, SEC61A1, MOGS, RAC2, VAV1, CD27, CD70, IGKC, CARD11*
	T-dependent and others with dominant B-cell deficiency: *ICOS, ICOSL, PIK3R1* (monoallelic LOF), *PIK3CD* (monoallelic GOF), *PIK3CG, NIK, REL, MSN, STK4, DOCK8, WAS, MYSM1, FOXN1, RNU4ATAC, EXTL3, TTC7A, TTC37, SKIV2L, SP110, EPG5, RBCK1, RNF31, CCBE1, FAT4, NFE2L2, STAT5B, KMT2D, KDM6A, KMT2A, CXCR4 GOF, TPP2, SH2D1A, XIAP, CTPS1, RASGRP1, CARMIL2, MAGT1, PRKCD, PLCG2*
Known gene and protein defects in animal models	*Irf4, Xbp1, Bcl6, Blimp1, Bcma*

Abbreviations: GOF, gain-of-function; LOF, loss-of-function.

binding protein 1 (*SH3KBP1*), and SH3 domain-binding protein 5 (*SH3BP5*). Figure 2 summarizes the proximity and connectivity of each of these predicted candidate genes to other known early B-cell development genes. Moreover, we provided a list of predicted gene and protein defects in the early B-cell development stage in Table 2.

3 | CLASS SWITCH RECOMBINATION

Class switch recombination process occurs rapidly after activation of mature B cells via their membrane-bound antibody molecule in secondary lymphoid organs, resulting in a switch from IgM/IgD to IgG-, IgE-, or IgA-expressing cells. This biological mechanism improves the ability of antibodies to eliminate the infection based on the specificity of the pathogen.[50] CSR is intra-chromosomal deletional recombination occurring between G-rich switch (S) regions, which are located upstream of all the C_H genes, except Cδ.[51] The recombination is initiated by the B cell–specific activation-induced cytidine deaminase (AICDA or AID), which deaminates cytosine (dC) in S regions to uracil (dU). Subsequently, the base excision repair (BER) enzyme uracil DNA glycosylase (UNG) excises dU and leaves a basic apyrimidinic/apurinic (AP) site. Afterward, basic AP sites are nicked

by AP endonuclease (APE) and single-strand DNA breaks (SSBs) take place. If SSBs are sufficiently near each other on both DNA strands, which is the case in selected S regions for CSR, required DSBs are created.[50,52] The free ends of the DSBs are subsequently rejoined by an end-joining type of DNA recombination, predominantly non-homologous end-joining (NHEJ).

Generally, KU70, KU80, XRCC4, and LIG4 are essential for NHEJ recombination during CSR.[53] Heterodimer KU70–KU80 binds to the broken DNA end and recruits other proteins to facilitate the binding of XRCC4-ligase IV complex to DNA ends.[54] XRCC4 stimulates the joining and ligation activities of ligase IV. Binding the XRCC4-ligase IV complex to DNA ends relies on the assembly of the DNA-dependent protein kinase complex (DNA-PK) to the broken DNA ends.[54] Ku70/Ku80 can function as an anchor for binding DNA-PKcs and XRCC4.[55] On the other hand, MRN (MRE11-NBS1-RAD50) complex, BLM, DNA polymerase epsilon subunit 1 and 2 (POLE1 and POLE2), ERCC excision repair 6–like 2 (*ERCC6L2*), cohesin complex (NIPBL and SMC1A), and kinase ataxia-telangiectasia mutant (ATM), which activate and coordinate the cellular response to DSBs, contribute to CSR.[56,57] These proteins are important for appropriate S-S recombination by preventing aberrant recombination and translocations and may conduct another DNA repair mechanism known as
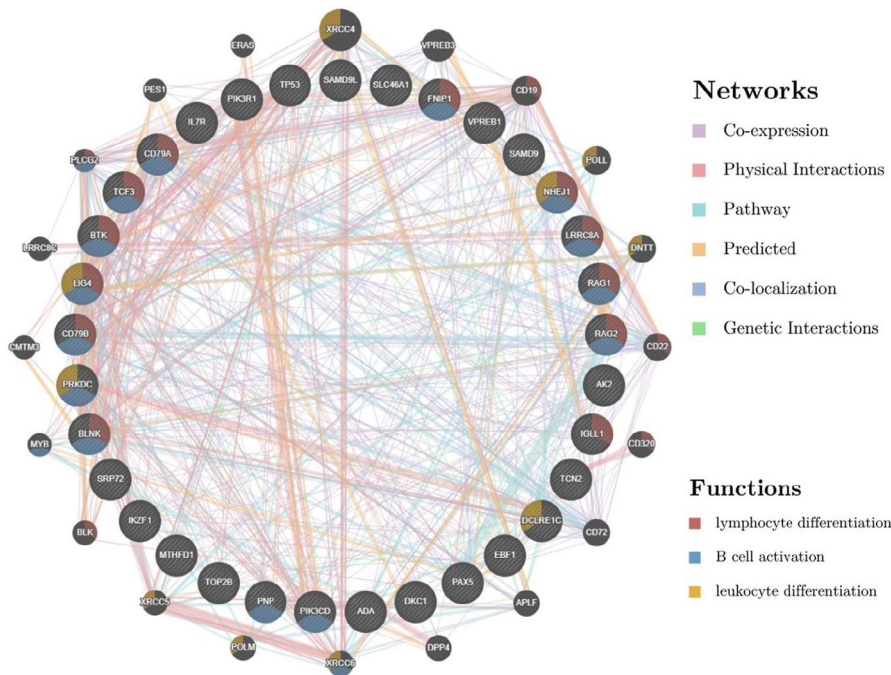
FIGURE 2 Predicted genes and protein involved (non-hachured circles) in human early B-cell development, which should be searched in patients with unknown cause of agammaglobulinemia

TABLE 2 List of predicted gene and protein defects in early B-cell development, class switch recombination, and terminal B-cell differentiation

Early B-cell development	
Genes, if mutated, predicted to cause PAD	XRCC4, XRCC5, XRCC6, VPREB3, POLL, DNTT, CD22, CD72, CD320, APLF, DPP4, POLM, MYB, CMTM3, PES1, ERAS, PIK3CA, LEF1, APTX, PNKP, SH3KBP1, SH3BP5
Class switch recombination	
Genes, if mutated, predicted to cause PAD	CHUK, MLH1, RBBP8, TOP3A, DNMT3A, DNMT3L, DNMT1, TERF2, TERF2IP, GINS2, MSH3, RAD51B, RAD51, BRIP1, BRCA1, BRCA2, BECN1, MDC1, EXO1, MLH3, NFKBIB, ZBTB17, POLE4, PCNA, AP1B1, SPTY2D1, BIRC2, SPO11
Terminal differentiation of B cells	
Genes, if mutated, predicted to cause PAD	IFITM1, MAFK, DGKA, TCL1A, NFKBIE, SLAMF1, TLE2, TNFRSF12A, ADAMTS3, RASSF5, MAP4K1, CD37, PRKCQ, RPLP0, KEAP1, SLAMF7, ERAS, TNIP2, PTPRCAP

alternative end-joining, which use microhomology sequences of the repetitive elements shared between the Sμ and acceptor S regions (Sγ, Sα, and Sε).[50]

3.1 | Known gene and protein defects in CSR deficiencies

Class switch recombination deficiencies (CSR-Ds), previously termed hyper-IgM (HIgM) syndromes, are characterized by low serum levels of IgG, IgA, and IgE but elevated or normal serum levels of IgM. Affected patients with hypogammaglobulinemia with hyper-IgM present typically recurrent bacterial infections.[58] CSR-Ds selectively results from various defects of CSR machinery caused by mutations in some intrinsic B-cell genes including AID, UNG, INO80 complex subunit (INO80), post-meiotic segregation 2 (PMS2), and MutS E.coli homolog 6 (MSH6).[25,27] Moreover, other known genes such as

CD40 ligand (CD40L), CD40, and inhibitor of κ light polypeptide gene enhancer in B cells, kinase gamma (IKBKG), are important for CSR and impact the FO helper T-cell (TFH) CSR induction in the germinal center of secondary lymphoid organs.[59,60] Recently, two predicted genes with close ontology to CSR pathways (RELA and GINS1 genes) have been described with impaired nuclear factor κB (NF-κB) activation and DNA repair, respectively.[61,62]

AID and UNG deficiencies have an autosomal recessive inheritance with some shared clinical manifestations such as infectious susceptibility, although the former is characterized uniquely by lymphoid and tonsillar hyperplasia, elevated risk of autoimmunity, and lymphomas. AID deficiency is caused by mutations scattered throughout the gene, with no hot spot. Biallelic mutations of AID is characterized by abrogation of both CSR and somatic hypermutation (SHM) processes.[63] However, heterozygous nonsense mutations located in the C-terminal part of AID lead to defective CSR and hyper-IgM mild clinical phenotype but normal SHM, which cause an

autosomal dominant form of AID deficiency.[64] UNG deficiency has been described as a cause of HIgM syndrome in a small number of patients (<1% of CSR-Ds).[65] Of note, CSR but not SHM is impaired in this disorder. It has been reported that CSR is decreased by about 95% in B lymphocytes from patients with deleterious mutations in *UNG* and UNG-deficient mice.[66] Recently, an autosomal form of PAD has been described due to *CTNNBL1* mutation, which reduces its binding to AID, resulting in less nuclear translocation of AID.[67]

As mentioned above, the DNA mismatch repair (MMR) pathway plays a role in CSR, and defects in MMR components may cause abnormal switched isotype levels and switch junctions.[68] There are two main MMR components that are associated with CSR-Ds in humans: PMS2 and MSH6. PMS2 deficiency is associated with variable CSR defect but normal SHM. Although the immunodeficiency can be the first symptom during several years,[69,70] the main symptom of individuals with germline PMS2 deficiency is the early onset of malignancy, similar to what observed with somatic defects in the MMR pathway.[71] MSH6 deficiency leads to CSR defect with abnormal SHM.[70] This PAD is typically characterized by a family or personal history of cancer, decreased serum levels of IgG2, decreased counts of CD27+ cells, and increased IgM in some patients, but without significant clinical immunological features.[72] Of note, several severe ATM-deficient patients (ataxia-telangiectasia) are diagnosed as HIgM before a diagnosis of neurological manifestation. Therefore, ATM deficiency is much more frequent than other causes of HIgM, especially in countries with a high frequency of consanguinity, and the prognosis is not the same.[73-75]

INO80 deficiency appears as a very rare autosomal recessive CSR-D. This gene encodes a subunit of the chromatin remodeling complex, which is involved in transcriptional regulation, DNA replication, and DNA repair. INO80 is involved in the conformational modification of the Ig locus essential in the S region recombination mechanism in CSR. This form of CSR deficiency is characterized by severe and recurrent bacterial infections, especially upper respiratory infections, and decreased serum levels of IgG and IgA with increased IgM.[76]

Apart from genetic defects, recent studies have shown that epigenetic alterations might underlie many cases of PIDs.[77] For instance, immunodeficiency, centromeric instability, and facial dysmorphism (ICF) syndrome occurs due to hypomethylation of DNA regions. Until now, four genes are responsible for ICF: *DNMT3B*, *ZBTB24*, *CDCA7*, and *HELLS*.[78-80] It is unclear how the chromosomal changes lead to impair B-cell differentiation (especially in the class switch process) and activation, but it seems that correct epigenetic modifications are required for normal Ig genes remodeling and regional accessibility. A list of a known gene and protein defects in class switch recombination stage of human is provided in Table 1.

3.2 | Known gene and protein defects in animal models with CSR deficiencies

Up to now, approximately 10% of patients with CSR-Ds do not have a genetic diagnosis.[50] In many of these patients, the clinical and biological features are nearly similar to autosomal dominant AID deficiency with severe CSR defect and normal SHM.[50] Animal model studies may be of help in identifying the molecular cause of these CSR-Ds. The genes that have been implicated in the CSR process in ex vivo and/or in vivo are listed in Table 2.

The important roles of proteins such as Ape1, H2ax, 53bp1, and Ku70/Ku80 involved in the DSB pathway have been confirmed in CSR.[57] In mammals, there are three types of AP endonuclease, Ape1 and Ape2, and Palf/Aplf/Xip-1.[68] Ape1 is a main AP endonuclease in the BER pathway. Ape1-deficient mouse B cells have a reduction in Ig switching in the periphery, indicating an important role of Ape1 in CSR.[81] DSB response involves sensing DNA DSBs by the MRN (Mre11-Nbs1-Rad50) complex, which triggers Atm activation.[57] Atm phosphorylates H2ax, converting it to γH2ax, which in turn interacts with 53bp1. Research data have shown that CSR was reduced threefold in B cells from MRN-deficient mice. Cell viability and proliferation were also reduced in these mutant cells. Therefore, besides *MRE11*, *NBS*, and *ATM* mutant humans that have been discovered, *Rad50* could be a potential candidate gene.[82] In H2ax-deficient mice, Ig switching, particularly to IgG3 and IgG1, is reduced about 30% of wild type, and this is not due to defective cell proliferation.[83] 53bp1 is another important component of the DSB repair mechanism. CSR is markedly reduced (approximately by 90%) in *53bp1⁻/⁻* splenic mouse B cells, but the role of 53bp1 in CSR is not clear yet. It has been demonstrated that serum levels of IgG, IgA, and IgE isotypes are strongly decreased, although IgM levels are normal.[84] Moreover, Ku heterodimer is a main component of the NHEJ pathway that binds the broken DNA end and recruits other proteins such as Aid to facilitate the processing and ligation of the DNA ends. Ku70/Ku80-deficient B cells do not have switched isotypes in their serum, demonstrating Ku70/Ku80 are necessary for keeping B cells alive. It is suggested that Ku heterodimer is essential for CSR, given the evidence that CSR can occur by an alternative end-joining pathway.[85,86]

Sphingosine kinase 1 (Sphk1) plays an important role in tumor necrosis factor (TNF) signaling and the NF-κB activation pathway. The lack of this protein in *SphK1⁻/⁻* mice resulted in reduced CD40-mediated Ig switching (especially IgE switching) and impaired plasma cell differentiation.[87] Also, TNF receptor–associated factor 2 (Traf2) is a main intracellular signaling mediator that acts downstream of various members of the TNF superfamily. It has been reported that Traf2-deficient mice develop an inflammatory disorder characterized by autoantibody accumulation and reduced isotype switching. These results suggest that Traf2 is essential for CD40-mediated isotype switching and activation in B cells.[88]

Integrin subunit alpha M (Itgam) and signal transducer and activator of transcription 6 (Stat6) are additional factors, which can play major roles in CSR mechanism.[89] *Itgam* encodes integrin CD11b, which is expressed on the surface of innate immune cells and is implicated in biological functions of macrophages, monocytes, and granulocytes. A recent study demonstrated that class switching and affinity maturation of antibodies were severely impaired in CD11b-deficient mice.[90] Stat6 is activated in response to IL-4 and contributes to different cellular functions including mitogenesis and lymphocyte

differentiation. Evaluation of Stat6^{-/-} mice showed normal development of naive lymphoid cells, but impaired Ig class switching to IgE.[89] A list of known genes and protein defects in the class switch recombination stage of animal models is provided in Table 1.

3.3 | Predictive gene and protein involved in CSR defects

Similar to Section 2.3, HGC analysis was conducted on the known human CSR-Ds and experimental genes based on animal models in order to predict the set of all biologically relevant candidates for patients with hyper-IgM syndrome without a genetic diagnosis.[49] According to these prediction analyses, the main genes that were identified to be associated with CSR based on co-expression (12.6%), physical interaction (11.9%), and pathway similarly (9.0%) are as follows: conserved helix-loop-helix ubiquitous kinase (*CHUK*), mutL homolog 1 (*MLH1*), *MLH3*, RB binding protein 8 endonuclease (*RBBP8*), DNA topoisomerase 3-alpha (*TOP3A*), *DNMT3A*, *DNMT3L*, *DNMT1*, telomeric repeat binding factor 2 (*TERF2*), TERF2-interacting protein (*TERF2IP*), GINS complex subunit 2 (*GINS2*), *MSH3*, *RAD51B*, *RAD51*, breast cancer 1 (*BRCA1*), breast cancer 2 (*BRCA2*) and BRCA1-interacting protein C-terminal helicase 1 (*BRIP1*), Beclin 1 (*BECN1*), mediator of DNA damage checkpoint 1 (*MDC1*), exonuclease 1 (*EXO1*), *NFKBIB*, *ZBTB17*, *POLE4*, proliferating cell nuclear antigen (*PCNA*), adaptor-related protein complex 1 beta 1 subunit (*AP1B1*), SPT2 chromatin protein domain-containing 1 (*SPTY2D1*), baculoviral IAP repeat-containing 2 (*BIRC2*), and initiator of meiotic double-stranded breaks (*SPO11*). Figure 3 summarizes the proximity and connectivity of each of these predicted candidate genes to other known CSR-associated genes. In addition, a list of predicted gene and protein involved in the CSR stage is shown in Table 2.
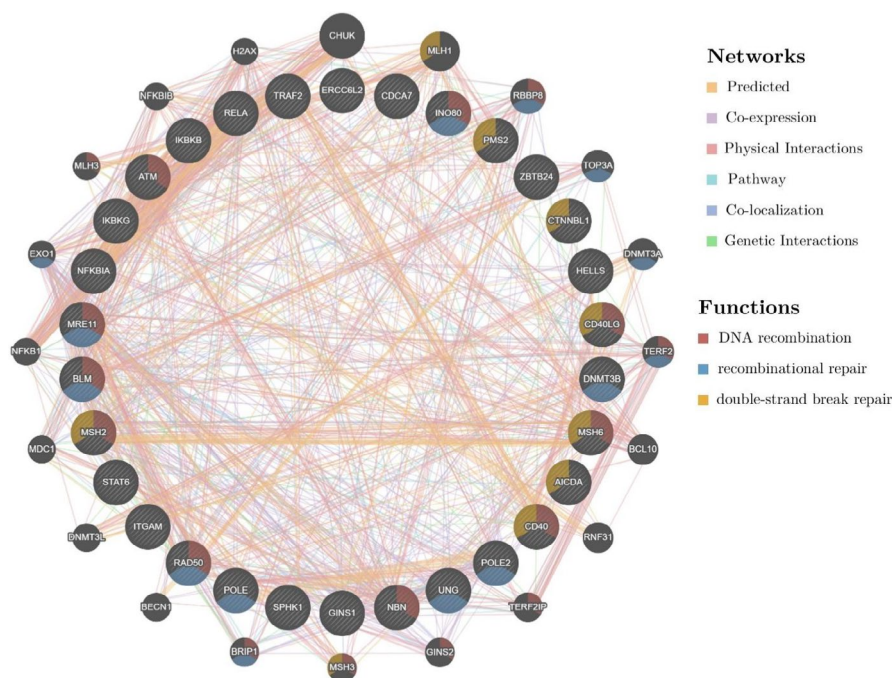
4 | TERMINAL DIFFERENTIATION OF B CELLS

Naive B cells are divided into three subsets of B cells: FO B cells that are the majority of mature B cells located in the follicles of lymphoid organs; MZ B cells that localize at the outer limit of the splenic white pulp; and B1 cells that are mainly found within the peritoneal and pleural cavities.[6,21]

MZ B cells generate IgM-producing plasmablasts in the initial response to a pathogen, even upon encounter with low amounts of bacterial antigens. Moreover, they are involved in TI and TD responses.[91] FO B cells have mature B-cell features that are distinct from B1 B cells and MZ B cells. FO B cells recirculate throughout the blood and need cognate help from T cells to differentiate between antibody-producing memory B cells.[6] Mature B cells that undergo stimulation upon exposure to antigen experience CSR and are differentiated into either plasma or memory B cells based on the intensity of B-cell receptor signal.[92] Memory B cells appear during TD reactions in the GC. Plasma cells represent the terminal differentiation step of mature B cells and secrete large quantities of antibodies in response to antigens.[42]

4.1 | Known gene and protein defects in terminal B-cell disorders

Selective IgA deficiency (SIgAD) and common variable immunodeficiency (CVID) are the most prevalent PADs in humans.[25] SIgAD is defined by a decreased or absent level of serum IgA (less than 0.07 g/l) with normal levels of IgG and IgM in patients older than 4 years. Although the nature of the genetic defect in SIgAD is unknown (except for a minority of patients [93]), the causative defect is

FIGURE 3 Predicted genes and protein involved (non-hachured circles) in human CSR, which should be searched in patients with unknown cause of hyper-IgM syndrome

hypothesized to either impair the class switching to IgA or to depend on a maturational failure of IgA-producing lymphocytes. Generally, the pedigrees of individuals with SIgAD occasionally demonstrate familial clustering with no distinct Mendelian inheritance pattern. Autosomal recessive, autosomal dominant, and sporadic transmission patterns have been reported in these patients.[94] Almost 60% of SIgAD patients are asymptomatic, whereas other patients manifest some clinical manifestation such as recurrent infections, diarrhea, allergies, or autoimmune disorders (more often when associated with IgG2/IgG4 subclasses deficiency—important because when a SIgAD is complicated by infections, they should be checked for IgG2 IgG4, even if total IgG level is normal). Moreover, SIgAD and CVID often coexist in members of the same family, and some affected subjects may initially present with SIgAD and eventually develop CVID. Therefore, it seems that the involvement of hereditary factors and genetic association is the same, at least in some cases, in the pathogenesis of SIgAD and CVID.[25,27] CVID is identified by significant hypogammaglobulinemia, impaired specific antibody production. Clinical features of CVID include recurrent infections, benign and malign lymphoproliferative disorders, autoimmunity, gastrointestinal infections, and cancers. Although several investigations into the pathogenesis of CVID have been conducted over the years, the exact cause of this disease has been elucidated only in a limited number of cases.

Mutations in several genes, such as the CD19-B-cell receptor complex (CD19, CD21, and CD81), CD20, CCA-adding transfer RNA nucleotidyltransferase 1 (TRNT1), NF-κB subunit 1 and 2 (NFKB1 and NFKB2), IKAROS family zinc finger 1 (IKZF1), mannosyl-oligosaccharide glucosidase (MOGS), ATPase H$^+$ transporting accessory protein 1 (ATP6AP1), phosphatase and tensin homolog (PTEN), rho guanine nucleotide exchange factor 1 (ARHGEF1), SH3 domain-containing kinase binding protein 1 (SH3KBP1), SEC61 translocon subunit alpha 1 (SEC61A1), Rac family small GTPase 2 (RAC2), TNF receptor superfamily member 13b (TNFRSF13B or TACI), TNF receptor superfamily member 13c (TNFRSF13C or BAFFR), TNF superfamily member 12 (TNFSF12 or TWEAK), TNF superfamily member 13 (TNFSF13, APRIL), and interferon regulatory factor 2 binding protein 2 (IRF2BP2), have been observed in PAD patients with CVID phenotype.[3,95] Moreover, a heterozygous gain-of-function mutation in PIK3CD and heterozygous loss-of-function mutation in PIK3R1 are associated with activated PI3K-delta syndrome (APDS-1 and APDS-2, respectively) and should be considered as a differential diagnosis.[96] Recently, autosomal recessive defects in PIK3CG have been identified with APDS-like phenotype and antibody deficiency.[97,98] All of these genes have been demonstrated to play important roles in human and mouse B-cell development, differentiation, and activation. Some of these genes encode important surface molecules involved in this pathway.

The B-cell co-receptor complex consists of CD19, CD21, CD81, and CD225 molecules that are involved in BCR-mediated signaling. Patients lacking CD19, CD21, or CD81 demonstrate normal B-cell count in the periphery; however, affinity maturation and antibody responses are impaired, leading to hypogammaglobulinemia

and increased susceptibility to various infections.[99,100] BAFFR,[101] TACI,[102] TWEAK,[103] and APRIL[104] are part of a complex system of TNF superfamily, which are involved in B-cell homeostasis, activation, and Ig isotype switching. BAFF binds to three different receptors, namely TACI, B-cell maturation antigen (BCMA), and BAFFR. BAFF/BAFFR interaction leads to CD40-like pathway activation that is important for B-cell survival by upregulation of NF-κB and BCL2. On the other hand, TACI is expressed mainly on B cells and is upregulated upon B-cell activation. Interaction between APRIL with its ligands (TACI and BMCA) is a significant event for B-cell survival and differentiation.[25] TWEAK besides contributing to proliferation and migration of endothelial cells, and polarization of the immune system to TH1 adaptive response, is also involved in B-cell differentiation. Defect in TWEAK causes inhibition of B-cell survival and proliferation, and inhibition of Ig class switching by downregulation of the noncanonical BAFF-induced NF-κB pathway.[103] CD20 is a human B-cell surface molecule that is widely expressed from early pre–B-cell stages until terminal differentiation into plasma cells, and defect in CD20 leads to severe reduction in switched memory B cells and decreased IgG levels with relatively increased IgM and IgA.[105] Moreover, patients with CD27 and CD70 deficiencies can mimic the diagnosis of CVID with higher susceptibility to EBV infection and lymphoma. These patients present with hypogammaglobulinemia since CD27/CD70 interaction is required for the fine-tuning of TFH and B-cell interaction in GC of secondary lymphoid organs.[106-108]

PI3K subunits (PIK3CD/PI3KR1), RAC2, CARD11, MOGS, ARHGEF1, and SH3KBP1 are part of the cytoplasmic pathway that is related to a small subset of patients with CVID-like phenotype.[109] PI3K signaling plays a critical role at several stages of B-cell development. Patients with monoallelic activating mutations in either PIK3CD or loss-of-function mutations of PI3KR1 present with recurrent sinopulmonary infections, increased frequency of transitional B cells, decreased numbers of naive CD4 and CD8 T cells, reduced class-switched memory B cells (increased IgM and decreased IgG2), B-cell lymphopenia, and CD4$^+$ lymphopenia.[110] RAC2 is a member of the Rho family of GTPases that are crucial regulators of cell signaling and the actin cytoskeleton. Defects in RAC2, monoallelic or biallelic, result in recurrent sinopulmonary infections, defects in B- and T-cell development, reduced chemotaxis activity, and reduced numbers of neutrophil granules.[111,112] Recently, an autosomal dominant gain-of-function mutation in the RAC2 gene was identified in SCID patients whose clinical presentation overlaps with the reticular dysgenesis (such as congenital agranulocytosis, lymphopenia, and lymphoid and thymic hypoplasia with absent cellular and humoral immunity functions) but without AK2 mutations and deafness.[113] CARD11 is an important adapter protein downstream of protein kinase C and has an important role in the activation of T and B cells through NF-κB activation. According to their location within the CARD11 gene, loss-of-function mutations lead to variable phenotype from combined immunodeficiency to severe atopic dermatitis. In contrast, gain-of-function mutations in CARD11 give rise to B-cell expansion with NF-κB and T-cell anergy (BENTA). The main symptoms of BENTA disease include splenomegaly, recurrent sinopulmonary infections, impaired

B-cell differentiation and T-cell proliferation, and increased number of transitional B cells with decreased number of T regulatory cells.[114] The *SH3KBP1* gene encodes an adapter protein involved in the regulation of diverse signal transduction pathways and is required in the control of cell shape and migration. This protein has an important role in B-cell activation. Patients with *SH3KBP1* mutations suffer from severe bacterial infections due to defective antibody production. The *ARHGEF1* gene encodes a member of the Rho GTPases, which plays a fundamental role in numerous cellular processes via modulation of the function of the RAS superfamily. Defects in SH3KBP1 cause bronchiectasis and recurrent infections in humans.[115]

Mutations in *TRNT1*, *NFKB1*, *NFKB2*, *IKZF1*, *ATP6AP1*, *PTEN*, and *IRF2BP2* have been associated with CVID-like patients [109] with reduced numbers of total peripheral B cells and switched B cells. These genes encode molecules involved in various biological processes such as inflammation, immunity, differentiation, and cell growth.[109] Other genetic defects including inducible T-cell costimulatory (*ICOS*) and its ligand (*ICOSL*), lipopolysaccharide-responsive beige-like anchor protein (*LRBA*), cytotoxic T-lymphocyte associated protein 4 (*CTLA4*), signal transducer and activator of transcription 1 (*STAT1*), BLK proto-oncogene, Src family tyrosine kinase (*BLK*), BTB domain and CNC homolog 2 (*BACH2*), *IL21*, *IL21R*, and Vav Guanine nucleotide exchange factor 1 (*VAV1*) have been identified in patients with a tentative diagnosis of CVID.[95,116] It has been demonstrated that these genes are associated with multiple components of the immune system, including both humoral and cell-mediated immunity. In individuals with a defect in the abovementioned genes, defects in both B-cell and T-cell development and function are observed and are associated with increased susceptibility to autoimmune phenomena and viral infections.[116]

IgG subclass deficiency is one of the most common PADs in both pediatric age groups and adults presenting with recurrent bacterial infections. This disorder is defined by persistently low levels of one or two IgG subclass, with a normal level of total IgG and IgM. IgG2 or IgG3 deficiencies are the most common entities in this group of diseases.[117] Individuals with IgG subclass deficiency may suffer from infections or may be completely asymptomatic. In some cases, defects in the IgG subclasses are due to dysregulation of the expression of the gamma regions[118]; however, the pathogenesis of IgG subclass deficiencies remains unclear similar to its counterpart-specific antibody deficiency associated with a low response to polypeptides or polysaccharides antigens/vaccines.

Regarding specific chain deficiencies, Ig heavy-chain deletion and kappa light-chain deficiency are categorized in PADs. Ig heavy-chain deletion is an autosomal recessive PAD caused by chromosomal deletions of the IgG heavy-chain locus located on 14q32.32. Homologous recombination is known as the main cause of this chromosomal deletion process. In some cases, IgG and/or IgA subclasses, as well as IgE, may be lost, but the deletion of IgM is not involved.[119] Kappa light-chain deficiency is an autosomal recessive disease characterized by the complete absence of Ig κ chains. An important gene associated with this PAD is the immunoglobulin kappa constant region gene (*IGKC*) located on chromosome 2p11.2

and was the first genetic defect to be described as responsible for humoral immunodeficiency in 1985. Although this disease can be associated with complex conditions, it can also be asymptomatic. The pathogenesis of the disease is associated with the failure of B cells to express kappa chains; however, the reason for this remains not clear.[120] Known gene and protein defects in the terminal B-cell differentiation stage of humans are provided in Table 1.

4.2 | Known gene and protein defects in animal models with terminal B-cell defects

Several transcription factors control B-cell differentiation into memory B cells or plasma cells. These transcription factors play major roles to regulate mutually antagonistic programs and can be separated into factors that promote and maintain B-cell identities, such as paired box 5 (*Pax5*), B-cell lymphoma 6 (*Bcl6*) and BTB Domain And CNC Homolog 2 (*Bach2*), and factors that control differentiation into memory B cells or plasma cells, such as interferon regulatory factor 4 (*Irf4*), B lymphocyte-induced maturation protein 1 (*Blimp1)* and X-box binding protein 1 (*Xbp1*).[121] Bcl6 and Pax5 suppress plasma cell development and propel to memory B-cell development; thus, suppression of both is critical for the plasma cell development.[43,122] In B cells, the downregulation of *Pax5* expression during plasma cell differentiation contributes to the suppression of *Xbp1* expression. Loss of Pax5 is mediated by high-level expression of *Xbp1* and *Blimp1*, which are essential for plasma cell differentiation. Recent studies have demonstrated that Xbp1 predominantly functions to boost Ig secretion and remodeling of the endoplasmic reticulum that is characteristic of plasma cells.[123] *Blimp1*, encoded by Prdm1, is a transcriptional factor that promotes terminal differentiation of B cells and T cells. Mice with *Prdm1* deficiency cannot survive *in utero*; therefore, Shapiro-Shelef et al. generated mice in which *Prdm1* was specifically eliminated in mature B cells of *Prdm1*flox/floxCD19cre/+ mice. The results showed that B-cell development was normal, but the serum level of Ig was significantly reduced, even in unimmunized mice.[124] Regarding the transcriptional factors involved in B-cell development, Bcl6 and Irf4 are vital as well. Bcl6 is highly expressed on GC B cells and is required for their formation. It has been reported that Bcl6-deficient mice do not generate GC cells, but differentiation to memory or plasma cells is not affected. Also, Bcl6-deficient B cells can differentiate into memory cells or plasma cells independently of GC reactions.[125] In addition to Bcl6, Irf4 is also critical for all stages of development of T and B cells. In B cells, Irf4 is important for light-chain rearrangement and transcription and is critical for B-cell development at the pre-B stage. Moreover, Irf4 is needed for CSR and memory or plasma cell differentiation. It seems that Irf4-deficient B cells are unable to differentiate into memory or plasma cells. On the other hand, the induction of Irf4 promotes the formation of memory and plasma cells, which is also described by Irf4 gain-of-function model.[126]

As above mentioned, interaction of Bcma with Baff and April is a significant event for B-cell survival and differentiation. April is a TNF

FIGURE 4 Predicted genes and protein involved (non-hachured circles) in human terminal B-cell development, which should be searched in patients with unknown cause of dysgammaglobulinemia
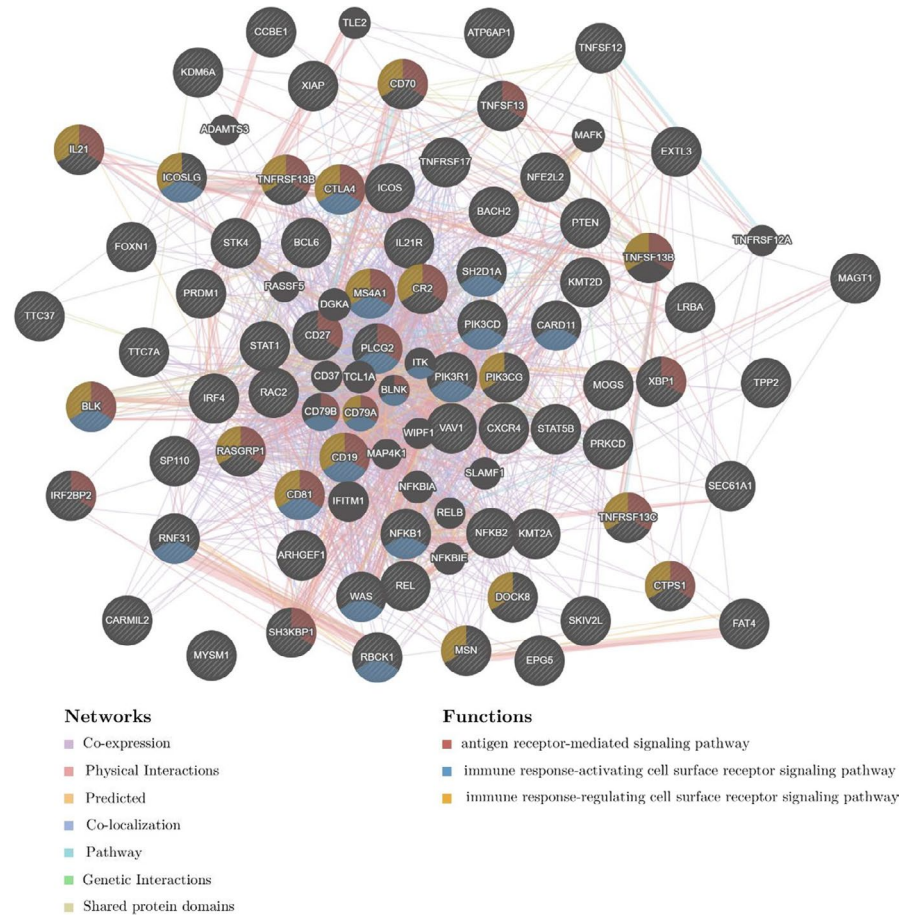
family member that binds to the Bcma on B cells and Taci on B and T cells. To investigate the role of Bmca, April-deficient mice were generated. An investigation showed that mice with April deficiency had normal in vitro T- and B-cell development and proliferation. However, serum levels of IgA were mainly decreased, and serum IgA antibody responses to mucosal immunization with TD antigens and to TI antigens were defected in an April$^{-/-}$ mice. It seems that April downregulates TD antibody responses and promotes switching to IgA.[127] On the other hand, previous results showed that Bcma-deficient mice had a normal B-cell compartment, but the survival of long-lived plasma cells was impaired.[128] Known gene and protein defects in the terminal B-cell differentiation stage of animal models are provided in Table 1.

4.3 | Predictive gene and protein defects

We finally conducted the abovementioned HGC analysis for the identification of some genes potentially associated with other known genes involved in terminal B-cell defects.[49] The predictor algorithms revealed adjacent proteins with co-expression (51.9%), physical interaction (17.9%), and co-localization (6.9%) including interferon-induced transmembrane protein 1 (*IFITM1*), MAF BZIP transcription factor K (*MAFK*), diacylglycerol kinase alpha (*DGKA*), TCL1 family AKT coactivator A (*TCL1A*), *NFKBIE*,

signaling lymphocytic activation molecule family member 1 (*SLAMF1*), *SLAMF7*, transducin-like enhancer protein 2 (*TLE2*), *TNFRSF12A*, ADAM metallopeptidase with thrombospondin type 1 motif 3 (ADAMTS3), Ras association domain family member 5 (RASSF5), mitogen-activated protein kinase kinase kinase kinase 1 (*MAP4K1*), *CD37*, protein kinase C theta (*PRKCQ*), ribosomal protein lateral stalk subunit P0 (*RPLP0*), kelch-like ECH-associated protein 1 (*KEAP1*), ES cell–expressed Ras (*ERAS*), TNFAIP3-interacting protein 2 (*TNIP2*), and protein tyrosine phosphatase receptor type C–associated protein (*PTPRCAP*). Figure 4 summarizes the proximity and connectivity of each of these predicted candidate genes to other known genes involved in terminal B-cell development. A list of predicted gene and protein defects in terminal B-cell differentiation stage is provided in Table 2.

5 | CONCLUSION

Predominantly antibody deficiencies are the most frequent forms of PIDs. Clinical manifestations of affected patients may include recurrent infections, enteropathy, lymphoproliferation, allergy, autoimmunity, and malignancy. Recent advances in the understanding of the molecular basis of B lymphocyte differentiation and identification of the genes involved in many PADs cause a significant improvement in our understanding of the pathogenesis of these disorders, which in turn sets the basis for better and in some cases targeted treatment for affected patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Parisa Amirifar: Conceptualization (equal); Investigation (equal); Writing-original draft (lead). **Reza Yazdani:** Investigation (equal); Validation (equal); Writing-review & editing (equal). **Gholamreza Azizi:** Investigation (equal); Writing-original draft (supporting). **Mohammad Reza Ranjouri:** Investigation (equal); Writing-original draft (equal). **Anne Durandy:** Writing-review & editing (equal). **Alessandro PLEBANI:** Writing-review & editing (equal). **Vassilios Lougaris:** Writing-review & editing (equal). **Lennart Hammarström:** Writing-review & editing (equal). **Asghar Aghamohammadi:** Project administration (equal); Supervision (equal); Validation (equal). **Hassan Abolhassani:** Investigation (equal); Project administration (equal); Validation (equal); Writing-original draft (equal); Writing-review & editing (equal).

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/pai.13589.

ORCID

Parisa Amirifar https://orcid.org/0000-0002-7782-824X
Reza Yazdani https://orcid.org/0000-0002-5578-6595
Gholamreza Azizi https://orcid.org/0000-0001-5658-2511
Asghar Aghamohammadi https://orcid.org/0000-0002-9454-1603
Hassan Abolhassani https://orcid.org/0000-0002-4838-0407

REFERENCES

1. Tangye SG, Al-Herz W, Bousfiha A, et al. Human inborn errors of immunity: 2019 update on the classification from the international union of immunological societies expert committee. *J Clin Immunol*. 2020;40(1):24-64.
2. Smith T, Cunningham-Rundles C. Primary B-cell immunodeficiencies. *Hum Immunol*. 2019;80(6):351-362.
3. Abolhassani H, Parvaneh N, Rezaei N, Hammarstrom L, Aghamohammadi A. Genetic defects in B-cell development and their clinical consequences. *J Investig Allergol Clin Immunol*. 2014;24(1):6-22.
4. Azizi G, Yazdani R. Predominantly antibody deficiencies. *Immunol Genet J*. 2018;1:52-80.
5. Azizi G, Abolhassani H, Asgardoon MH, et al. The use of immunoglobulin therapy in primary immunodeficiency diseases. *Endocr Metab Immune Disord Drug Targets*. 2016;16(2):80-88.
6. Pieper K, Grimbacher B, Eibel H. B-cell biology and development. *J Allergy Clin Immunol*. 2013;131(4):959-971.
7. Quan PL, Wagner TA, Briese T, et al. Astrovirus encephalitis in boy with X-linked agammaglobulinemia. *Emerg Infect Dis*. 2010;16(6):918-925.
8. Yazdani R, Abolhassani H, Kiaee F, et al. Comparison of common monogenic defects in a large predominantly antibody deficiency cohort. *J Allergy Clin Immuno Pract*. 2019;7(3):864-878.e9.
9. Abolhassani H, Aghamohammadi A, Fang M, et al. Clinical implications of systematic phenotyping and exome sequencing in patients with primary antibody deficiency. *Genet Med*. 2019;21(1):243-251.
10. Tangye SG, Al-Herz W, Bousfiha A, et al. The ever-increasing array of novel inborn errors of immunity: an interim update by the IUIS committee. *J Clin Immunol*. 2021;41(3):666-679.
11. Tonegawa S. Molecular biology of immunologic recognition. *Tanpakushitsu Kakusan Koso*. 1987;32(3):239.
12. Corbett SJ, Tomlinson IM, Sonnhammer EL, Buck D, Winter G. Sequence of the human immunoglobulin diversity (D) segment locus: a systematic analysis provides no evidence for the use of DIR segments, inverted D segments, "minor" D segments or DD recombination. *J Mol Biol*. 1997;270(4):587-597.
13. Ravetch JV, Siebenlist U, Korsmeyer S, Waldmann T, Leder P. Structure of the human immunoglobulin μ locus: characterization of embryonic and rearranged J and D genes. *Cell*. 1981;27(3):583-591.
14. Wood C, Tonegawa S. Diversity and joining segments of mouse immunoglobulin heavy chain genes are closely linked and in the same orientation: implications for the joining mechanism. *Proc Natl Acad Sci USA*. 1983;80(10):3030-3034.
15. Kofler R, Geley S, Kofler H, Helmberg A. Mouse variable-region gene families: complexity, polymorphism and use in non-autoimmune responses. *Immunol Rev*. 1992;128(1):5-21.
16. Mårtensson I, Ceredig R. Role of the surrogate light chain and the pre-B-cell receptor in mouse B-cell development. *Immunology*. 2000;101(4):435.
17. Bonilla FA, Oettgen HC. Adaptive immunity. *J Allergy Clin Immunol*. 2010;125(2):S33-S40.
18. Heath WR, Kato Y, Steiner TM, Caminschi I. Antigen presentation by dendritic cells for B cell activation. *Curr Opin Immunol*. 2019;58:44-52.
19. Hardy RR, Hayakawa K. B cell development pathways. *Annu Rev Immunol*. 2001;19(1):595-621.
20. Atisha-Fregoso Y, Zou Y-R, Diamond B. *B Cells and Generation of Antibodies. Dubois' Lupus Erythematosus and Related Syndromes*: Elsevier. 2019;101-115.
21. Klein U, Dalla-Favera R. Germinal centres: role in B-cell physiology and malignancy. *Nat Rev Immunol*. 2008;8(1):22-33.
22. O'Leary JG, Goodarzi M, Drayton DL, von Andrian UH. T cell–and B cell–independent adaptive immunity mediated by natural killer cells. *Nat Immunol*. 2006;7(5):507-516.
23. Basso K, Dalla-Favera R. Germinal centres and B cell lymphomagenesis. *Nat Rev Immunol*. 2015;15(3):172-184.
24. Vale AM, Schroeder HW Jr. Clinical consequences of defects in B-cell development. *J Allergy Clin Immunol*. 2010;125(4):778-787.
25. Rezaei N, Notarangelo LD, Aghamohammadi A. *Primary Immunodeficiency Diseases*. Springer; 2008.
26. Notarangelo L, Casanova J-L, Fischer A, et al. Primary immunodeficiency diseases: an update. *J Allergy Clin Immunol*. 2004;114(3):677-687.
27. Aghamohmmadi A, Lougaris V, Plebani A, Miyawaki T, Durandy A, Hammarström L. *Predominantly Antibody Deficiencies. Primary Immunodeficiency Diseases*: Springer; 2008:97-130.
28. Pashangzadeh S, Yazdani R, Nazari F, Azizi G, Abolhassani H, Aghamohammadi A. Agammaglobulinemia: epidemiology, pathogenesis, clinical phenotype, diagnosis, prognosis and management. *Endocr Metab Immune Disord Drug Targets*. 2020;20(9):1434-1447.
29. Ochs HD, Smith C. X-linked agammaglobulinemia. A clinical and molecular analysis. *Medicine*. 1996;75(6):287-299.
30. Hardy RR. B-cell commitment: deciding on the players. *Curr Opin Immunol*. 2003;15(2):158-165.
31. Bucciol G, Moens L, Payne K, et al. Chronic Aichi virus infection in a patient with X-linked agammaglobulinemia. *J Clin Immunol*. 2018;38(7):748-752.
32. Frémond ML, Pérot P, Muth E, et al. Next-generation sequencing for diagnosis and tailored therapy: a case report of astrovirus-associated progressive encephalitis. *J Pediatric Infect Dis Soc*. 2015;4(3):e53-e57.
33. Gofshteyn J, Cárdenas AM, Bearden D. Treatment of chronic enterovirus encephalitis with fluoxetine in a patient with X-linked agammaglobulinemia. *Pediatr Neurol*. 2016;64:94-98.

34. Conley ME, Broides A, Hernandez-Trujillo V, et al. Genetic analysis of patients with defects in early B-cell development. *Immunol Rev.* 2005;203(1):216-234.

35. Al-Herz W, Bousfiha A, Chapel H, et al. Primary immunodeficiency diseases: an update on the classification from the international union of immunological societies expert committee for primary immunodeficiency. *Front Immunol.* 2011;2:54.

36. Boisson B, Wang Y-D, Bosompem A, et al. A recurrent dominant negative E47 mutation causes agammaglobulinemia and BCR–B cells. *J Clin Investig.* 2013;123(11):4781-4785.

37. Papapietro O, Chandra A, Eletto D, et al. Topoisomerase 2β mutation impairs early B-cell development. *Blood.* 2020;135(17):1497-1501.

38. Broderick L, Yost S, Li D, et al. Mutations in topoisomerase IIβ result in a B cell immunodeficiency. *Nat Commun.* 2019;10(1):1-15.

39. Sawada A, Takihara Y, Kim JY, et al. A congenital mutation of the novel gene LRRC8 causes agammaglobulinemia in humans. *J Clin Invest.* 2003;112(11):1707-1713.

40. Watkins D, Rosenblatt DS. Immunodeficiency and inborn disorders of vitamin B12 and folate metabolism. *Curr Opin Clin Nutr Metab Care.* 2020;23(4):241-246.

41. Shi W, Liao Y, Willis SN, et al. Transcriptional profiling of mouse B cell terminal differentiation defines a signature for antibody-secreting plasma cells. *Nat Immunol.* 2015;16(6):663-673.

42. Singh H, Pongubala JM, Medina KL. *Gene Regulatory Networks that Orchestrate the Development of B Lymphocyte Precursors. Mechanisms of Lymphocyte Activation and Immune Regulation XI*: Springer; 2007:57-62.

43. Nera K-P, Kohonen P, Narvi E, et al. Loss of Pax5 promotes plasma cell differentiation. *Immunity.* 2006;24(3):283-293.

44. Nutt SL, Urbanek P, Rolink A, Busslinger M. Essential functions of Pax5 (BSAP) in pro-B cell development: difference between fetal and adult B lymphopoiesis and reduced V-to-DJ recombination at the IgH locus. *Genes Dev.* 1997;11(4):476-491.

45. Melchers F. *B-Cell Development: How to Become One of the Chosen Ones. The Autoimmune Diseases*: Elsevier; 2020:155-170.

46. O'Riordan M, Grosschedl R. Coordinate regulation of B cell differentiation by the transcription factors EBF and E2A. *Immunity.* 1999;11(1):21-31.

47. Herblot S, Aplan PD, Hoang T. Gradient of E2A activity in B-cell development. *Mol Cell Biol.* 2002;22(3):886-900.

48. Mundt C, Licence S, Shimizu T, Melchers F, Mårtensson IL. Loss of precursor B cell expansion but not allelic exclusion in VpreB1/VpreB2 double-deficient mice. *J Exp Med.* 2001;193(4):435-445.

49. Itan Y, Zhang SY, Vogt G, et al. The human gene connectome as a map of short cuts for morbid allele discovery. *Proc Natl Acad Sci USA.* 2013;110(14):5558-5563.

50. Stavnezer J, Guikema JE, Schrader CE. Mechanism and regulation of class switch recombination. *Annu Rev Immunol.* 2008;26:261-292.

51. Dunnick W, Hertz GZ, Scappino L, Gritzmacher C. DNA sequences at immunoglobulin switch region recombination sites. *Nucleic Acids Res.* 1993;21(3):365-372.

52. Muramatsu M, Kinoshita K, Fagarasan S, Yamada S, Shinkai Y, Honjo T. Pillars article: class switch recombination and hypermutation require activation-induced cytidine deaminase (AID), a potential rna editing enzyme. Cell. 2000. 102: 553-563. *J Immunol.* 2018;201(9):2530-2540.

53. Stavnezer J, Schrader CE. IgH chain class switch recombination: mechanism and regulation. *J Immunol.* 2014;193(11):5370-5378.

54. Kotnis A, Du L, Liu C, Popov SW, Pan-Hammarström Q. Non-homologous end joining in class switch recombination: the beginning of the end. *Philos Trans R Soc Lond B Biol Sci.* 2009;364(1517):653-665.

55. Soulas-Sprauel P, Le Guyader G, Rivera-Munoz P, et al. Role for DNA repair factor XRCC4 in immunoglobulin class switch recombination. *J Exp Med.* 2007;204(7):1717-1727.

56. Liu X, Liu T, Shang Y, et al. ERCC6L2 promotes DNA orientation-specific recombination in mammalian cells. *Cell Res.* 2020;30(9):732-744.

57. Chaudhuri J, Alt FW. Class-switch recombination: interplay of transcription, DNA deamination and DNA repair. *Nat Rev Immunol.* 2004;4(7):541-552.

58. Etzioni A, Ochs HD. The hyper IgM syndrome—an evolving story. *Pediatr Res.* 2004;56(4):519-525.

59. Foy TM, Aruffo A, Bajorath J, Buhlmann JE, Noelle RJ. Immune regulation by CD40 and its ligand GP39. *Annu Rev Immunol.* 1996;14(1):591-617.

60. Johnson J, Filipovich AH, Zhang K. *X-Linked Hyper IgM Syndrome. GeneReviews® [Internet].* Seattle, WA: University of Washington; 2013.

61. Badran YR, Dedeoglu F, Leyva Castillo JM, et al. Human RELA haploinsufficiency results in autosomal-dominant chronic mucocutaneous ulceration. *J Exp Med.* 2017;214(7):1937-1947.

62. Cottineau J, Kottemann MC, Lach FP, et al. Inherited GINS1 deficiency underlies growth retardation along with neutropenia and NK cell deficiency. *J Clin Invest.* 2017;127(5):1991-2006.

63. Revy P, Muto T, Levy Y, et al. Activation-induced cytidine deaminase (AID) deficiency causes the autosomal recessive form of the Hyper-IgM syndrome (HIGM2). *Cell.* 2000;102(5):565-575.

64. Durandy A, Peron S, Taubenheim N, Fischer A. Activation-induced cytidine deaminase: structure–function relationship as based on the study of mutants. *Hum Mutat.* 2006;27(12):1185-1191.

65. Imai K, Slupphaug G, Lee W-I, et al. Human uracil–DNA glycosylase deficiency associated with profoundly impaired immunoglobulin class-switch recombination. *Nat Immunol.* 2003;4(10):1023-1028.

66. Rada C, Williams GT, Nilsen H, Barnes DE, Lindahl T, Neuberger MS. Immunoglobulin isotype switching is inhibited and somatic hypermutation perturbed in UNG-deficient mice. *Curr Biol.* 2002;12(20):1748-1755.

67. Kuhny M, Forbes LR, Cakan E, et al. Disease-associated CTNNBL1 mutation impairs somatic hypermutation by decreasing nuclear AID. *J Clin Invest.* 2020;130(8):4411-4422.

68. Stavnezer J, Guikema JE, Schrader CE. Mechanism and regulation of class switch recombination. *Annu Rev Immunol.* 2008;26(1):261-292.

69. Peron S, Metin A, Gardes P, et al. Human PMS2 deficiency is associated with impaired immunoglobulin class switch recombination. *J Exp Med.* 2008;205(11):2465-2472.

70. Gardes P, Forveille M, Alyanakian MA, et al. Human MSH6 deficiency is associated with impaired antibody maturation. *J Immunol.* 2012;188(4):2023-2029.

71. Van Oers JM, Roa S, Werling U, et al. PMS2 endonuclease activity has distinct biological functions and is essential for genome maintenance. *Proc Natl Acad Sci USA.* 2010;107(30):13384-13389.

72. Gardès P, Forveille M, Alyanakian M-A, et al. Human MSH6 deficiency is associated with impaired antibody maturation. *J Immunol.* 2012;188(4):2023-2029.

73. Amirifar P, Mozdarani H, Yazdani R, et al. Effect of class switch recombination defect on the phenotype of ataxia-telangiectasia patients. *Immunol Invest.* 2020;50:201-215.

74. Mohammadinejad P, Abolhassani H, Aghamohammadi A, et al. Class switch recombination process in ataxia telangiectasia patients with elevated serum levels of IgM. *J Immunoassay Immunochem.* 2015;36(1):16-26.

75. Moeini Shad T, Yousefi B, Amirifar P, et al. Variable abnormalities in T and B cell subsets in ataxia telangiectasia. *J Clin Immunol.* 2021;41(1):76-88.

76. Kracker S, Di Virgilio M, Schwartzentruber J, et al. An inherited immunoglobulin class-switch recombination deficiency associated with a defect in the INO80 chromatin remodeling complex. *J Allergy Clin Immunol.* 2015;135(4):998-1007.e6.

77. Campos-Sanchez E, Martínez-Cano J, del Pino ML, López-Granados E, Cobaleda C. Epigenetic deregulation in human primary immunodeficiencies. *Trends Immunol.* 2019;40(1):49-65.

78. Hansen RS, Wijmenga C, Luo P, et al. The DNMT3B DNA methyltransferase gene is mutated in the ICF immunodeficiency syndrome. *Proc Natl Acad Sci USA.* 1999;96(25):14412-14417.

79. De Greef JC, Wang J, Balog J, et al. Mutations in ZBTB24 are associated with immunodeficiency, centromeric instability, and facial anomalies syndrome type 2. *Am J Human Genet.* 2011;88(6):796-804.

80. Thijssen PE, Ito Y, Grillo G, et al. Mutations in CDCA7 and HELLS cause immunodeficiency–centromeric instability–facial anomalies syndrome. *Nat Commun.* 2015;6(1):1-8.

81. Masani S, Han L, Yu K. Apurinic/apyrimidinic endonuclease 1 is the essential nuclease during immunoglobulin class switch recombination. *Mol Cell Biol.* 2013;33(7):1468-1473.

82. Du L, Dunn-Walters DK, Chrzanowska KH, et al. A regulatory role for NBS1 in strand-specific mutagenesis during somatic hypermutation. *PLoS One.* 2008;3(6):e2482.

83. Fernandez-Capetillo O, Lee A, Nussenzweig M, Nussenzweig A. H2AX: the histone guardian of the genome. *DNA Repair.* 2004;3(8–9):959-967.

84. Reina-San-Martin B, Chen J, Nussenzweig A, Nussenzweig MC. Enhanced intra-switch region recombination during immunoglobulin class switch recombination in 53BP1−/−B cells. *Eur J Immunol.* 2007;37(1):235-239.

85. Manis JP, Gu Y, Lansford R, et al. Ku70 is required for late B cell development and immunoglobulin heavy chain class switching. *J Exp Med.* 1998;187(12):2081-2089.

86. Casellas R, Nussenzweig A, Wuerffel R, et al. Ku80 is required for immunoglobulin isotype switching. *EMBO J.* 1998;17(8):2404-2411.

87. Kim EY, Sturgill JL, Hait NC, et al. Role of sphingosine kinase 1 and sphingosine-1-phosphate in CD40 signaling and IgE class switching. *FASEB J.* 2014;28(10):4347-4358.

88. Jabara HH, Laouini D, Tsitsikov E, et al. The binding site for TRAF2 and TRAF3 but not for TRAF6 is essential for CD40-mediated immunoglobulin class switching. *Immunity.* 2002;17(3):265-276.

89. Shimoda K, van Deursent J, Sangster MY, et al. Lack of IL-4-induced Th2 response and IgE class switching in mice with disrupted State6 gene. *Nature.* 1996;380(6575):630-633.

90. Park S, Sim H, Kim H-I, et al. CD11b regulates antibody class switching via induction of AID. *Mol Immunol.* 2017;87:47-59.

91. Xu W, Banchereau J. The antigen presenting cells instruct plasma cell differentiation. *Front Immunol.* 2014;4:504.

92. Abolhassani H. *Immunologic Memory. Reference Module in Biomedical Sciences*: Elsevier; 2020.

93. Abolhassani H, Aghamohammadi A, Hammarstrom L. Monogenic mutations associated with IgA deficiency. *Expert Rev Clin Immunol.* 2016;12(12):1321-1335.

94. Yel L. Selective IgA deficiency. *J Clin Immunol.* 2010;30(1):10-16.

95. Bousfiha A, Jeddane L, Picard C, et al. Human inborn errors of immunity: 2019 update of the IUIS phenotypical classification. *J Clin Immunol.* 2020;40(1):66-81.

96. Jamee M, Moniri S, Zaki-Dizaji M, et al. Clinical, immunological, and genetic features in patients with activated PI3Kdelta syndrome (APDS): a systematic review. *Clin Rev Allergy Immunol.* 2020;59(3):323-333.

97. Takeda AJ, Maher TJ, Zhang Y, et al. Human PI3Kgamma deficiency and its microbiota-dependent mouse model reveal immunodeficiency and tissue immunopathology. *Nat Commun.* 2019;10(1):4364.

98. Thian M, Hoeger B, Kamnev A, et al. Germline biallelic PIK3CG mutations in a multifaceted immunodeficiency with immune dysregulation. *Haematologica.* 2020;105(10):e488.

99. Sander CA, Medeiros LJ, Weiss LM, Yano T, Sneller MC, Jaffe ES. Lymphoproliferative lesions in patients with common variable immunodeficiency syndrome. *Am J Surg Pathol.* 1992;16(12):1170-1182.

100. Salzer U, Warnatz K, Peter HH. Common variable immunodeficiency-an update. *Arthritis Res Ther.* 2012;14(5):223.

101. Schneider P. The role of APRIL and BAFF in lymphocyte activation. *Curr Opin Immunol.* 2005;17(3):282-289.

102. von Bülow G-U, van Deursen JM, Bram RJ. Regulation of the T-independent humoral response by TACI. *Immunity.* 2001;14(5):573-582.

103. Wang H-Y, Ma CA, Zhao Y, et al. Antibody deficiency associated with an inherited autosomal dominant mutation in TWEAK. *Proc Natl Acad Sci USA.* 2013;110(13):5127-5132.

104. Yeh TW, Okano T, Naruto T, et al. APRIL-dependent lifelong plasmacyte maintenance and immunoglobulin production in humans. *J Allergy Clin Immunol.* 2020;146(5):1109-1120.e4.

105. Kuijpers TW, Bende RJ, Baars PA, et al. CD20 deficiency in humans results in impaired T cell–independent antibody responses. *J Clin Investig.* 2010;120(1):214-222.

106. Ghosh S, Kostel Bal S, Edwards ESJ, et al. Extended clinical and immunological phenotype and transplant outcome in CD27 and CD70 deficiency. *Blood.* 2020;136(23):2638-2655.

107. Abolhassani H, Edwards ES, Ikinciogullari A, et al. Combined immunodeficiency and Epstein-Barr virus-induced B cell malignancy in humans with inherited CD70 deficiency. *J Exp Med.* 2017;214(1):91-106.

108. Alkhairy OK, Perez-Becker R, Driessen GJ, et al. Novel mutations in TNFRSF7/CD27: Clinical, immunologic, and genetic characterization of human CD27 deficiency. *J Allergy Clin Immunol.* 2015;136(3):703-712.e10.

109. Yazdani R, Habibi S, Sharifi L, et al. Common variable immunodeficiency: epidemiology, pathogenesis, clinical manifestations, diagnosis, classification and management. *J Investig Allergol Clin Immunol.* 2020;30(1):14-34.

110. Elgizouli M, Lowe D, Speckmann C, et al. Activating PI3Kδ mutations in a cohort of 669 patients with primary immunodeficiency. *Clin Exp Immunol.* 2016;183(2):221-229.

111. Kurkchubasche AG, Panepinto JA, Tracy TF Jr, Thurman GW, Ambruso DR. Clinical features of a human Rac2 mutation: a complex neutrophil dysfunction disease. *J Pediatr.* 2001;139(1):141-147.

112. Alkhairy OK, Rezaei N, Graham RR, et al. RAC2 loss-of-function mutation in 2 siblings with characteristics of common variable immunodeficiency. *J Allergy Clin Immunol.* 2015;135(5):1380-1384.e5.

113. Lagresle-Peyrou C, Olichon A, Sadek H, et al. A gain-of-function RAC2 mutation is associated with bone-marrow hypoplasia and an autosomal dominant form of severe combined immunodeficiency. *Haematologica.* 2021;106(2):404-411.

114. Stepensky P, Keller B, Buchta M, et al. Deficiency of caspase recruitment domain family, member 11 (CARD11), causes profound combined immunodeficiency in human subjects. *J Allergy Clin Immunol.* 2013;131(2):477–485.e1.

115. Bouafia A, Lofek S, Bruneau J, et al. Loss of ARHGEF1 causes a human primary antibody deficiency. *J Clin Investig.* 2019;129(3):1047-1060.

116. Richardson CT, Slack MA, Dhillon G, et al. Failure of B cell tolerance in CVID. *Front Immunol.* 2019;10:2881.

117. Carvalho WNF, Ferreira FDCJ, Damaceno N, Vidal FP, Gonzales CL, Mastroti R. Evolution of IgA deficiency to IgG subclass deficiency and common variable immunodeficiency. *Allergol Immunopathol.* 2000;28(1):18-20.

118. Pan Q, Hammarström L. Molecular basis of IgG subclass deficiency. *Immunol Rev.* 2000;178:99-110.

119. Brusco A, Saviozzi S, Cinque F, Bottaro A, DeMarchi M. A recurrent breakpoint in the most common deletion of the Ig heavy chain locus (del A1-GP-G2-G4-E). *J Immunol.* 1999;163(8):4392-4398.

120. van der Loo W, Mougel F, Bouton C, Sanchez MS, Monnerot M. The allotypic patchwork pattern of the rabbit IGKC1 allele b5wf: genic exchange or common ancestry? *Immunogenetics*. 1999;49(1):7-14.

121. Nutt SL, Taubenheim N, Hasbold J, Corcoran LM, Hodgkin PD, editors. The genetic network controlling plasma cell differentiation. *Semin Immunol*. 2011;23(5):341-349. Elsevier.

122. Alinikula J, Nera KP, Junttila S, Lassila O. Alternate pathways for Bcl6-mediated regulation of B cell to plasma cell differentiation. *Eur J Immunol*. 2011;41(8):2404-2413.

123. Shaffer A, Shapiro-Shelef M, Iwakoshi NN, et al. XBP1, downstream of Blimp-1, expands the secretory apparatus and other organelles, and increases protein synthesis in plasma cell differentiation. *Immunity*. 2004;21(1):81-93.

124. Shapiro-Shelef M, Lin K-I, McHeyzer-Williams LJ, Liao J, McHeyzer-Williams MG, Calame K. Blimp-1 is required for the formation of immunoglobulin secreting plasma cells and pre-plasma memory B cells. *Immunity*. 2003;19(4):607-620.

125. Toyama H, Okada S, Hatano M, et al. Memory B cells without somatic hypermutation are generated from Bcl6-deficient B cells. *Immunity*. 2002;17(3):329-339.

126. Klein U, Casola S, Cattoretti G, et al. Transcription factor IRF4 controls plasma cell differentiation and class-switch recombination. *Nat Immunol*. 2006;7(7):773-782.

127. Castigli E, Scott S, Dedeoglu F, et al. Impaired IgA class switching in APRIL-deficient mice. *Proc Natl Acad Sci USA*. 2004;101(11):3903-3908.

128. Hardenberg G, Van Bostelen L, Hahne M, Medema JP. Thymus-independent class switch recombination is affected by APRIL. *Immunol Cell Biol*. 2008;86(6):530-534.