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

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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. 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 defects in a specific antibody response with normal serum Igs. These patients may present various clinical manifestations, including recurrent respiratory infections, autoimmunity, enteropathy, interstitial lung disease, lymphoproliferation, and allergic diseases. Lifelong Ig replacement therapy is the indicated treatment for the majority of these patients.

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. 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 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.

Although several mutated genes involved in B-cell proliferation, differentiation, and activation have been recognized in the pathogenesis of PADs in humans, 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) genes involved in the process of B-cell development are shown in Figure 1. Once a light chain is combined with the 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. B cells are activated by direct contact with a soluble antigen or attached to the surface of another cell, particularly macrophages and dendritic cells. Generally, antigens can be classified as either T cell–dependent (TD) or T cell–independent (TI). 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.

Activated B cells can either differentiate into plasmablasts or get recruited into a specialized region, called germinal centers (GCs). 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.

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.
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), p85α 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 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, Iγ, BLNK, p85α, 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 LRRCB. 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. AR forms of TCF3 deficiency are more severe than the AD forms and manifest recurrent bacterial infections and failure to thrive. 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. 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. LRRCB 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.

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. 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).

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 FANCI-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. 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. 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.

The transcription factors Pax5, E2a, and Ebf have been shown to play important roles in the early stages of B-cell differentiation in mice. Defect in Pax5 leads to arrest in B-cell development during the early stages of CD19+ to CD19-; 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. 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. Also, Ebf and E2a heterozygosity in mice demonstrates an approximately two-fold decrease in the number of pro-B-cell compartment, indicating that normal B-cell development depends on the presence of two wild-type alleles.

The surrogate light chain composed of the VpreB and J5 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. 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. 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 nucleotidyltransferase (DNTT), CD22, CD72, CD320, aprataxin- and PNPK-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), poly nucleotide kinase 3′-phosphatase (PNKP), SH3 domain-containing kinase
binding protein 1 (SH3KP1), 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. CSR is intra-chromosomal deletion recombination occurring between G-rich switch (S) regions, which are located upstream of all the C_H genes, except C_B. 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 apurinic/apyrimidinic (AP) site. Afterward, basic AP sites are nicked by AP endonuclelease (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. 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. 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. 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. Ku70/Ku80 can function as an anchor for binding DNA-PKcs and XRCC4. 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), and XRCC4 stimulate 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.
alternative end-joining, which use microhomology sequences of the repetitive elements shared between the $S_\mu$ and acceptor $S$ regions ($S_\gamma$, $S_\alpha$, and $S_\epsilon$).^{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 $\kappa$ light polypeptide gene enhancer in B cells, kinase gamma (IKBK), 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 $\kappa$B (NF-$\kappa$B) 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. UNG deficiency has been described as a cause of HlgM syndrome in a small number of patients (<1% of CSR-Ds). 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. 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.

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. 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, 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. MSH6 deficiency leads to CSR defect with abnormal SHM. 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. Of note, several severe ATM-deficient patients (ataxia-telangiectasia) are diagnosed as HlgM before a diagnosis of neurological manifestation. Therefore, ATM deficiency is much more frequent than other causes of HlgM, especially in countries with a high frequency of consanguinity, and the prognosis is not the same.

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.

Apart from genetic defects, recent studies have shown that epigenetic alterations might underlie many cases of PIDs. 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. It is unclear how the chromosomal changes lead to impaired 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 reorganizational 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. 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. 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 vivo and/or in vivo are listed in Table 2.

The important roles of proteins such as Ape1, H2ax, 53bp1, and Ku70/80 involved in the DSB pathway have been confirmed in CSR. In mammals, there are three types of AP endonuclease, Ape1 and Ape2, and PalI/AplI/Xip. 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. DSB response involves sensing DNA DSBs by the MRN (Mre11-Nbs1-Rad50) complex, which triggers Atm activation. Atm phosphorylates H2ax, converting it to γ-H2ax, 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. 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. 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. 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.

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. 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.

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. 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. 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. 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. 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. 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. 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. 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. 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.

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

Selective IgA deficiency (SlgAD) and common variable immunodeficiency (CVID) are the most prevalent PADs in humans. SlgAD 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 SlgAD is unknown (except for a minority of patients), the causative defect is
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 SlgAD 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 SlgAD 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 SlgAD is complicated by infections, they should be checked for IgG2 IgG4, even if total IgG level is normal). Moreover, SlgAD and CVID often coexist in members of the same family, and some affected subjects may initially present with SlgAD 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 SlgAD and CVID.25,27 CVID is identified by significant hypogammaglobulinemia, impaired specific antibody production. Clinical features of CVID include recurrent infections, benign and malignant 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-xB 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 PDAD 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 APRIL104 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-xB 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-xB 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/PIK3KR1), 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, monooletic 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 granulocytosis, 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-xB 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-xB 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. 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.

Mutations in TRNT1, NFKB1, NFKB2, IKZF1, ATP6AP1, PTEN, and IRF2BP2 have been associated with CVID-like patients 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. Other genetic defects including inducible T-cell costimulator (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. 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.

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. 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 region; however, the pathogenesis of IgG subclass deficiencies remains unclear similar to its counterpart-specific antibody deficiency associated with a low response to polyepptides 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 disorder 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. 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. 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). 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. 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. 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 Prdm1fl/lodCD19cre/ mice. The results showed that B-cell development was normal, but the serum level of Ig was significantly reduced, even in unimmunized mice. 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. 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 can be 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.

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

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. 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. 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 (PTPRC). 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 PID. 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). Vassiliou Lougaris: Writing-review & editing (equal). Asghar Aghamohammadi: Project administration (equal); Supervision (equal); Validation (equal); Investigation (equal); Project administration (equal); Validation (equal); Writing-original draft (equal); Writing-review & editing (equal).

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