Genetic Defects in B-Cell Development and Their Clinical Consequences

H Abolhassani,[1,2] N Parvaneh,[1] N Rezaei,[1] L Hammarström,[2] A Aghamohammadi[1]

[1]Research Center for Immunodeficiencies, Pediatrics Center of Excellence, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran
[2]Division of Clinical Immunology, Department of Laboratory Medicine, Karolinska Institutet at Karolinska University Hospital Huddinge, Stockholm, Sweden

Abstract

Expression of selected genes in hematopoietic stem cells has been identified as a regulator of differentiation of B cells in the liver and bone marrow. Moreover, naïve B cells expressing surface immunoglobulin need other types of genes for antigen-dependent development in secondary lymphoid organs. Many advanced molecular mechanisms underlying primary antibody deficiencies in humans have been described. We provide an overview of the mutations in genes known to be involved in B-cell development and their clinical consequences.

Key words: Genetic disorder. B-cell development. Primary antibody deficiencies. Clinical phenotypes.

Resumen

Se ha identificado la expresión de genes seleccionados en las células pluripotenciales de médula ósea como reguladores de la diferenciación de las células B en el hígado y en médula ósea. Sin embargo, las células B naïve que expresan inmunoglubulinas de superficie, necesitan otros tipos de genes para su desarrollo en los órganos linfoides secundarios dependienteS de antígeno. Se han descrito muchos mecanismos moleculares avanzados que subrayan las inmunodeficiencias en humanos y esta revisión constituye una visión general de la mutación en todos los genes conocidos involucrados en el desarrollo de las células B y sus consecuencias clínicas.

Palabras clave: Alteraciones genéticas. Desarrollo de las células B. Deficiencias de Ac primarias. Fenotipos clínicos.

Introduction

Primary antibody deficiencies are the most common type of primary immunodeficiencies, accounting for approximately half of all reported cases [1,2]. Primary antibody deficiencies comprise a heterogeneous group of disorders with low serum Ig titers and/or specific antibody deficiencies [3,4]. These deficiencies often arise as a result of defects in early B-cell development, class-switch recombination, or terminal B-cell differentiation [5,6].

B cells play a central role in the humoral immune response and are the precursors of plasma cells. B-cell development begins in bone marrow and continues in secondary lymphoid organs. Expression of different lineage-specific markers on B-cell precursors indicates different stages of B-cell development [7].

Several genes are responsible for early B-cell development in bone marrow. These include Bruton tyrosine kinase *(BTK), IGA, IGB, λ5*, μ heavy chain, B-cell linker protein (*BLNK*), the p85a subunit of phosphoinositide 3-kinase (*PIK3R1*), and the E47 transcription factor. Mutations in genes involved in early B-cell development result in severe primary antibody deficiencies, which are characterized by blockade of B-cell differentiation before the production of surface Ig, markedly reduced mature B-cell counts in the peripheral circulation, profound hypogammaglobulinemia, and early onset of recurrent bacterial infections in affected children [8,9].

In secondary lymphoid organs, class-switch recombination (CSR) and somatic hypermutation (SHM) are the mechanisms necessary for the generation of effector plasma cells secreting high-affinity IgG, IgA, and IgE antibodies. The genes that play a key role in CSR and SHM are CD40 ligand *(CD40L)*,

CD40, inhibitor of kappa light polypeptide gene enhancer in B cells, kinase gamma (*IKBKG*), activation-induced cytidine deaminase (*AID*), and uracil N glycosylase (*UNG*). Defects in CSR are characterized by low serum levels of IgG, IgA, and IgE leading to recurrent bacterial infections with normal or elevated serum IgM levels [10].

The terminal stages of B-cell development are controlled by different genetic signatures including TNF receptor superfamily members (*TACI, BAFF-R*, and, potentially, *TWEAK*), MutS protein homolog 5 (*MSH5*), CD19–B-cell receptor (BCR) complex (*CD19, CD21*, and *CD81*) and the B-cell differentiation antigen, CD20 [11].

Genes Involved in Early B-Cell Development

B cells develop from a lymphoid precursor in bone marrow. Further B-cell development follows several steps, from pro–B cells (TdT^+ cells expressing CD34 and CD19) to pre–B cells (TdT^-, $CD34^-$, $CD19^+$, and cytoplasmic μ^+) and movement of matured B cells from bone marrow to peripheral blood [12,13]. Maturation of B cells involves a series of events, including commitment of progenitor cells to the B-cell lineage, proliferation of progenitor cells, rearrangement of antigen receptor genes, expression of cell surface markers, responses to extracellular signaling and selection events, and differentiation of B cells into functionally and phenotypically distinct subpopulations [8,14,15].

Pro–B cells comprise the earliest progenitor group committed to the B-cell lineage. Rag proteins seem to be expressed at this stage, and these could promote Ig gene recombination at the heavy chain locus. Consequently, the cells are differentiated into pre–B cells, which express the Igμ heavy chain on the cell surface, but their light chain locus has yet to be rearranged [12]. Expression of pre-BCR, which involves complexes of the μ heavy chain, heterodimeric surrogate light chains (SLC) containing λ5 and VpreB, and the signal-transducing proteins Igα and Igβ, is considered the first checkpoint in B-cell maturation. Several signaling molecules are involved in expression of pre-BCR and BCR and play a key role in transition of pro–B cells to the pre–B-cell stage [12].

BTK (AGMX1, ATK, BPK, IMD1, and PSCTK1)

BTK, which is activated downstream of the pre-BCR, is located on chromosome Xq22.1 (Figure 1). BTK plays an important role in transducing signals from the BCR that can mediate proliferation and maturation at the pre–B-cell stage [8,12]. Mutations in the gene lead to maturational arrest of B-cell development at this stage; therefore, a decreased B-cell count and agammaglobulinemia are expected in affected individuals [16].

BTK deficiency (also known as X-linked agammaglobulinemia [XLA]), in which B-cell development is arrested at the pro–B-cell to pre–B-cell stage, was the first primary immunodeficiency disease described by Bruton in 1952 [17]. During the last 10 years, a number of genetic mutations responsible for autosomal recessive forms of agammaglobulinemia have been discovered.

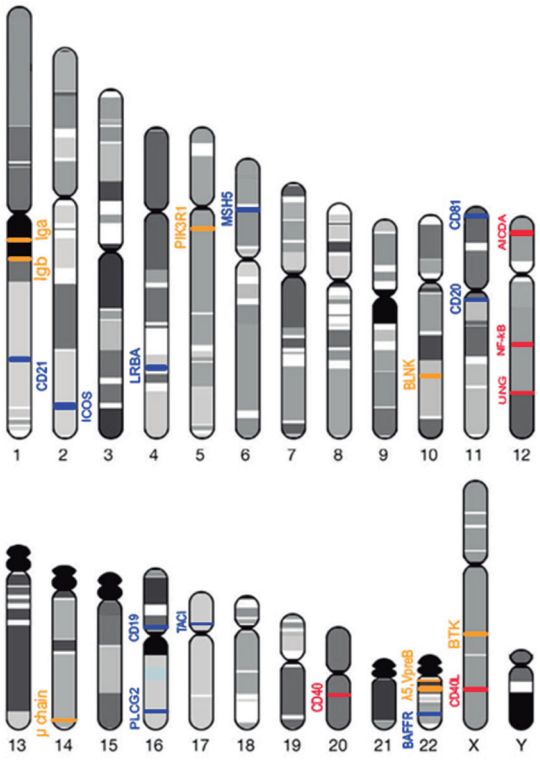

Figure 1. Chromosomal mapping of genes involved in early B-cell development (orange), class switching recombination (red), and terminal cell development (blue).

Although the disease was described more than 6 decades ago, mutations in the BTK gene were not identified until the early 1990s [18,19]. Mutations in BTK (a member of the Tec family of kinases) in mice (Xid mouse) generate a phenotype similar to that of humans. This finding increased our understanding of the pathogenic mechanisms of B-cell defects in XLA, although a less severe B-cell defect was observed in Xid, probably owing to expression of a second BTK-like kinase (Tec) in murine pre–B cells [12,20].

Autosomal Agammaglobulinemia Genes

Other genetic defects leading to agammaglobulinemia are inherited in an autosomal recessive manner. Nevertheless, the abovementioned genes remain intact in some patients with agammaglobulinemia, and the underlying gene defect should subsequently be identified [21-27]. In patients, with arrested early B-cell development, peripheral blood B cells usually account for less than 1%-2% of the total, and very low levels of all Ig classes are detected [8]. Subsequently, patients experience a variety of manifestations, mainly recurrent bacterial infections in the respiratory and gastrointestinal tracts (eg, recurrent otitis media, sinusitis, pneumonia, and diarrhea). In addition to bacterial and enteroviral infections, arthritis, and neutropenia can also be seen in up to 20% of patients [8,28,29]. Immunoglobulin replacement therapy is the treatment of choice in affected patients [30].

μ heavy chain (IGHM, neAGM1, MU, VH)

The IGHM gene is located on the long arm of chromosome 14 at position 14q32.33. The Ig heavy μ chain is a product of this gene (with 4 domains: CH1, CH2, CH3, and CH4). IgM could initially copresent with SLC in large pre–B cells. However, in small precursor pre–B cells and immature B cells, this molecule is associated with κ and λ light chains, which bind antigens [31] and subsequently lead to antigen uptake into clathrin-coated vesicles [32].

Signaling defects in IgM have been reported in females with consanguineous parents, who show a similar phenotype to that of patients with XLA because of the role of this molecule in the same pathway as the BCR [33,34]. Most patients have splice site defects leading to lack of expression of the μ heavy chain on the B-cell surface. Some authors indicate more severe clinical and laboratory manifestations, earlier onset of disease, and a lower B-cell count in the peripheral circulation of patients with μ heavy chain disease than in those with XLA [35-37]. Although IgM is not detected in most patients at the time of diagnosis, cases with measurable levels of IgM should not be excluded for a possible diagnosis of μ heavy chain defects. Normal percentages of pro–B cells, and no pre–B cells or B cells could suggest laboratory examination for signal-incapable mutants of μ heavy chain patients [38,39].

λ5 (IGLL1, AGM2, CD179b, IGL5, IGLJ14.1, IGO, VPREB2) and VpreB (IGI, IGVPB, VPREB1, CD179a)

The *IGLL1* and *IGI* genes are located on the long arm of chromosome 22 (22q11.23 and 11.22, respectively). *IGLL1* encodes the λ5 protein, which together with the product of a second gene (VpreB), forms the SLC [40]. The final product of this recombination is needed for transport of μ heavy chains to the pro–B-cell membrane [41]. The C-terminus of λ5 is similar to the J region and constant region sequences. Despite the presence of VpreB, λ5 is capable of folding and assembling the 2 proteins via its homology with the J region [42].

Humans have 3 genes for λ5 and only 1 gene for VpreB; however, 2 of the λ5 genes lack a promoter and the first exon and are thus considered pseudogenes. Since 1998, when λ5 deficiency was first described in humans, several cases of the same gene defect have been reported [25]. The main difference between patients with homozygous λ5 mutations and patients with XLA is the higher degree of maturity in the phenotype of B cells and decreased *VpreB* expression in intracytoplasmic staining of B cells in the bone marrow of patients with XLA. The pronounced severity in the clinical presentation of λ5-deficient patients may be due to the absence of or reduced light chain rearrangements [43,44]. Moreover, compound heterozygous variations in the *VpreB1* gene were reported in 2 unrelated patients and may have a role in disease etiology [45].

Igα (CD79A, CD79A, IGA) and Igβ (CD79B, AGM6, B29, IGB)

Both CD79A and CD79B (located on 19q13.2 and 17q23.3, respectively) products contribute to the transmembrane signal transduction module. The heterodimeric Igα/Igβ complex is covalently linked to pre-BCR and BCR components in order to enable progression of the downstream signaling cascade for enhancement of V-to-DJ rearrangement [46]. It is assumed that expression of this complex, as part of the complete pre-BCR, is necessary for B-cell differentiation in humans; however, Igα and Igβ have different roles in this regard [47,48]. Igα can be expressed on the cell surface in the absence of Igβ because of the single polarity of the transmembrane domain, thus enabling expression of Igα homodimers. Moreover, it has been suggested that the immunoreceptor tyrosine-based activation motif (ITAM) of Igα has unique binding partners that allow it to display functions that are not shared with Igβ [26]. Therefore, mutations in Igα, but not Igβ, affect V-to-DJ rearrangement. Furthermore, Igα has 2 separate functions, including chaperoning (escorting the transmembrane domain of the μ heavy chain to the cell surface) and signaling (ITAMs in the cytoplasmic domain). The former function is also observed with the cytoplasmic domains of Igβ [49].

Complete block in human B-cell development due to Igα deficiency was reported in 1999 in patients with autosomal recessive inheritance [50]. The patients had chronic diarrhea and malabsorption leading to failure to thrive. Normal or elevated numbers of $CD34^+$ and $CD19^+$ pro–B cells in bone marrow and neutropenia in peripheral blood are frequent in these cases. Pre–B cells (about 30% of normal) and splenic B cells (about 5% of normal) may be present in these patients [26]. Recently, a mutation in CD79b was reported to result in arrest of early B-cell development and autosomal recessive agammaglobulinemia [51].

BLNK (AGM4, BASH, LY57, SLP-65, SLP65, bca)

The gene responsible for production of the B-cell linker protein (BLNK) is located on 10q24.1. The adaptor protein BLNK is expressed in B-cell and myeloid lineages (with 30% homology in all regions up to SLP-76) [52]. After BCR cross-linking via *CMTM7, BLNK* is phosphorylated by Syk to assemble essential components of the signaling pathways needed for B-cell development [53,54]. However, *BLNK* is not necessary for the differentiation of pro–B cells to pre–B cells. This molecule is required for capping of BCR, activation of ERK connected with H-Ras, and phosphorylation of phospholipase C gamma 2 and calcium influx after stimulation of BCR [55,56]. *BLNK* has 2 splice variants; these differ in the midportion of the molecule, which contains a proline-rich region [57].

Mutations in *BLNK* were first reported in 1999. The patient had undetectable serum Ig levels and less than 0.01% B cells in the peripheral circulation. In addition, the clinical consequences of this finding were more severe than in XLA patients [24,58]. Transcripts for a rearranged μ heavy chain have been detected in the bone marrow of *BLNK*-deficient patients [59].

PIK3R1 (GRB1, p85, p85-ALPHA)

Phosphatidylinositol 3-kinase regulatory subunit alpha is an 85-kDa regulatory subunit enzyme. In humans, it is produced by the *PIK3R1* gene, which is located on 5q13.1

[60]. Although the extracellular signal for PI3K pathway activation is not clear in humans, defects in the chemokine CXCR4 in mice mimic manifestations of PIK3R1 deficiency in humans [61].

Mutations in *PIK3R1* have been implicated in patients with breast cancer [62], although in 2012, Conley et al [63] reported the case of a female with a homozygous premature stop codon in the catalytic subunit (p110d) who presented with an isolated defect in the development of pro–B cells and transient neutropenia without some of the features demonstrated in a CXCR5 knockout mouse model (eg, hypersensitivity to insulin, defective platelet function, and abnormal mast-cell development). Early onset of infections and multiple complications, including colitis, were also recorded.

Class-Switch Recombination Genes

Immunoglobulin CSR is central to the humoral immune response [64]. Hyper-IgM (HIGM) syndromes are a group of primary immunodeficiencies in which defective Ig-CSR leads to deficiency of IgG, IgA, and IgE with normal or elevated levels of IgM [65,66]. Several different gene products are involved in the Ig-CSR process, and defects in some these products have been described in patients with HIGM syndrome (Figure 2) [67].

Most, but not all, patients with Ig-CSR defects also have defects in the related process of SHM. These genetic disorders can be classified into defects restricted to B cells and defects that also affect the functions of other cells, including T cells and monocytes/macrophages, whose function requires integrity of the CD40 signaling pathway. The former group cause pure humoral immunodeficiency, while the latter are susceptible to opportunistic infections as a result of additional derangement of cell-mediated immunity [66,68,69].

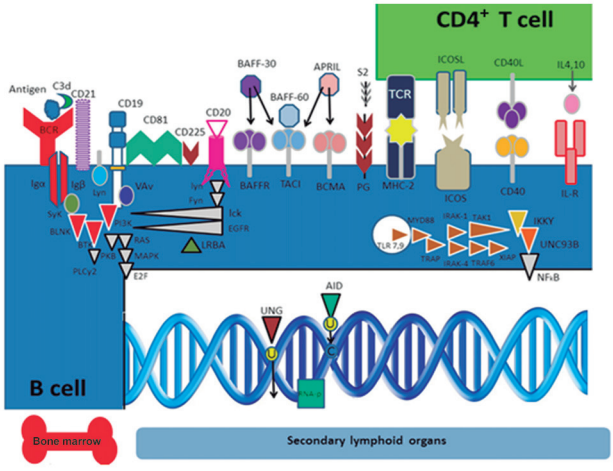

Figure 2. Cytoplasmic and membrane molecules encoded by genes involved in B-cell development

HIGM Syndrome as Part of Combined Immunodeficiency

CD40 is a 48-kD transmembrane glycoprotein surface receptor that is a member of the tumor necrosis factor receptor superfamily (TNFRSF) proteins [70]. Close cooperation between T cells and B cells involving CD40, which is constitutively expressed on B cells, and CD40 ligand (CD40L or CD154), which is transiently expressed on activated helper T cells, is required for B-cell proliferation, germinal center formation, CSR, and SHM [71-73].

Defects of signaling through the CD40 receptor affect not only B-cell function, but also macrophages/monocytes and dendritic cells. Lack of appropriate signaling in the latter results in impaired handling of opportunistic pathogens [68,70].

CD40L (CD154, HIGM1, IGM, IMD3, T-BAM, TNFSF5, TRAP, gp39, hCD40L)

The most common and best-recognized form of HIGM syndrome is caused by mutations in the gene encoding CD40L located on Xq26.3 [74-78]. CD40L, a member of the TNF family, is expressed in trimeric form on the cell surface and comprises a CD40 binding domain on the cell surface, a short transmembrane domain, and a cytoplasmic tail. Expression of the molecule is tightly regulated, occurring only transiently upon activation of T cells [79].

The CD40/CD40L axis is central to T-cell–dependent antibody responses. In response to cross-linking of CD40 by CD40L, B cells undergo clonal expansion, germinal center formation, CSR, SHM, and generation of long-lived plasma cells [80].

Signaling through the CD40 pathway involves the recruitment of adaptor proteins, TNF receptor–associated factors (TRAFs), and activity of cytoplasmic kinases such as IκB kinase (IKK) and mitogen-activated protein kinase (MAPK) [81,82].

About half of all patients have IgM levels within the normal range; the remainder have elevated levels at presentation [83]. There is no response to protein antigens, and memory B cells are either absent or present in much reduced numbers [84,85]. While primary follicles are present in the lymph nodes, germinal centers are characteristically absent or abortive [65]. Humoral immunodeficiency results in susceptibility to bacterial infections, particularly those affecting the respiratory tract. However, affected patients also succumb to opportunistic infections such as *Pneumocystis jiroveci* pneumonia and *Cryptosporidium parvum* diarrhea, suggesting compromised T-cell effector functions [86,87].

Interaction of activated CD4 cells expressing CD40L with CD40 expressing monocytes/macrophages normally potentiates the production of type 1 helper T cell (T_H1) cytokines, IL-12 and IFN-γ, which are important in the handling of opportunistic intracellular pathogens [83,86,88,89].

Severe liver/biliary tract disease, increased occurrence of gastrointestinal tumors, and neutropenia are also hallmarks of the disease [65,83].

Clinical management is based on regular administration of immunoglobulin and antibiotic prophylaxis; however, bone marrow transplantation from matched related or unrelated donors is the treatment of choice [90,91].

CD40 (Bp50, CDW40, TNFRSF5, p50)

Patients affected by CD40 deficiency are clinically and immunologically indistinguishable from those carrying genetic defects in the *CD40L* gene, except for their autosomal recessive mode of inheritance [92]. The mutations in the *CD40* gene located on 20q13.12 lead to a lack of surface expression of CD40 on B cells, macrophages, and dendritic cells. Patients usually have small tonsils and lymph nodes and present with a humoral defect and a propensity for opportunistic infections [93].

IKBKG (H2TF1, LYT-10, LYT10, NF-κB2, p105, p52)

Another X-linked form of HIGM is NF-κB essential modulator (NEMO) syndrome, which is characterized by the association of hypogammaglobulinemia with ectodermal dysplasia [94-96]. This condition is caused by hypomorphic mutations of the *IKBKG* gene encoding the inhibitor of NF-κB kinase subunit gamma (IKKγ), which is located on Xq28, a part of the kinase complex involved in releasing NF-κB from its association with the inhibitory complex IκB, thus allowing its translocation to the nucleus [94,96].

Null mutations in the same gene are lethal in males and cause incontinentia pigmenti in carrier females [97,98]. Ectodermic dysplasia is a consequence of downstream signaling impairment of the ectodysplasin receptor, whose signaling pathway is also dependent on NF-κB [65].

As noted earlier, signaling through CD40 on B cells involves NF-κB. Nonetheless, as NF-κB is involved in a number of T-cell, natural killer cell and Toll-receptor signaling pathways, immunodeficiency is broader than simply a humoral defect. Patients therefore experience not only bacterial infections, but also mycobacterial and opportunistic infections [99].

Defects of B-cell Intrinsic Ig-CSR

HIGM syndrome with pure humoral immunodeficiency and no susceptibility to opportunistic infections is caused by intrinsic B-cell defects in the mechanism of Ig-CSR. Historically, the expression of CD40L and activation of T cells have been reported to be normal in affected patients. However, B cells do not undergo CSR in vitro in the presence of CD40L or CD40 agonists [100-102].

AID (ACIDA, ARP2, CDA2, HIGM2)

Deficiency of activation-induced cytidine deaminase (AID) is the second most common genetic cause of HIGM syndrome [103].

AID is selectively expressed in germinal center B cells and is responsible for deaminating cytidine into uracil residues in the early phases of CSR and SHM. Mutations in *AID* (located on 12p13.31) cause an autosomal recessive syndrome of humoral deficiency characterized by markedly elevated serum levels of IgM, defective CSR and SHM, and massive lymph node hyperplasia. Memory B cells are present in normal numbers [104]. Patients usually present with recurrent respiratory infections due to pyogenic bacteria such as *Streptococcus pneumoniae, Haemophilus influenzae*, and *Staphylococcus aureus* during the first 2 years of life [105]. Autoimmune complications include immune cytopenia, hepatitis, and arthritis and affect about 20% of patients [104,106].

Development of ectopic lymphoid tissues in nonlymphoid organs probably predisposes to organ-specific autoimmunity [107]. Genotype/phenotype correlation has been detected in *AID* deficiency; patients who carry mutations located in the C-terminal domain of *AID* have preserved SHM and do not present lymphoid hyperplasia [108], thus suggesting a direct role for SHM in the control of B-cell proliferation inside the germinal centers [109].

An autosomal dominant form of *AID* deficiency has also been described and is caused by a mutation in the C-terminal domain of the molecule. This mutation results in defective CSR while leaving SHM unaffected [110,111].

UNG (DGU, HIGM4, HIGM5, UDG)

Uracil N glycosylase (UNG) deficiency has also been reported to cause HIGM syndrome [112]. This protein is encoded by the UNG gene and is located on 12q24.11. It is a DNA-repair enzyme that removes uracil from DNA after *AID* deaminates cytosine to uracil. Patients with mutations have a similar clinical picture to that of patients with AID deficiency. CSR is severely impaired, unlike SHM, which is only partially impaired [109].

Since UNG is also involved in the repair of spontaneously occurring base lesions, it has an antimutagenic function. UNG-deficient mice develop B-cell lymphomas over time [113]. There is thus a potential risk of development of lymphoma in UNG-deficient patients in adulthood [66].

PMS2 (HNPCC4, PMS2CL, PMSL2)

Postmeiotic segregation increased 2 (PMS2) is a protein involved in DNA mismatch repair [114] that is encoded by the *PMS2* gene, located on 7p22.1. Deficiency in PMS2 can lead to Ig-CSR defects [115]. A partial immunological phenotype of HIGM with low serum IgG is associated with low IgA, which can be corrected over time, probably because of the accumulation of long-lived plasma cells [69]. B cells are unable to undergo CSR following activation with CD40L and appropriate cytokines. SHM is normal, but the peripheral blood memory B-cell count is low. Humoral deficiency may remain the main symptom for several years. However, the major characteristic of PMS2 deficiency is the occurrence of gastrointestinal cancer (adenomas) during childhood.

Genes Involved in Terminal B-cell Development

Terminal B cells develop in the secondary lymphoid organs, where naïve B cells are converted to secretory plasma cells [116,117]. Defects in this process comprise a heterogeneous group of predominantly antibody deficiencies characterized by recurrent multiorgan infection and specific antibody deficiency [118-120]. Patients with common variable immunodeficiency (CVID) form the second largest cohort of primary immunodeficiency patients numerically and constitute an elusive group with a largely unknown genetic etiology [121]. CVID patients with early onset of hypogammaglobulinemia

and parental consanguinity sometimes have an affected relative (10-20%), whose disease is autosomal recessive [122]. Members with SIgAD and/or IgG subclass deficiency are also seen in this type of family [123]. Clinical and immunological classifications have been proposed in order to facilitate identification of a homogeneous subgroup of patients for evaluation of rare genetic disorders [124]. Although genes identified over the past 10 years (including *TACI, ICOS, BAFFR, CD81, CD20, CD19,* and *CD21*) are found in less than 10% of patients, they have nevertheless increased our awareness of novel mechanisms underlying defects in terminal B-cell development [125]. The clinical and immunological characteristics of patients with mutations in these genes are shown in the Table.

Genes Thought to Cause Monogenetic Mendelian Traits in CVID

ICOS (AILIM, CD278, CVID1)

The *ICOS* gene is located at 2q33.2 [126]. The product of this gene is the inducible T-cell costimulator, which belongs to the CD28 and CTLA-4 Ig-like costimulatory receptor family [127]. This molecule is expressed on activated T_H2 cells in homodimeric form and binds to ICOS ligand (ICOS-L), which is constitutively expressed on naive B cells and involved in signaling pathways related to T-dependent antibody responses [128].

Experimental studies have shown that ICOS protein is involved in the regulation of T-cell proliferation (secretion of IL-2, TNF-α, and IFN-γ) and humoral immune responses

Table. Clinical and Immunological Characteristics of Genes Involved in B-Cell Development[a]

Disease	Percentage of Patients	B Cells	Ig Levels	SAD	Memory B Cells	Inheritance	Other
Early B-cell defects							
BTK	85%	↓	↓	↓	↓	XL	
μ Heavy chain	5%	↓	↓	↓	↓	AR	
λ5	0.5%	↓	↓	↓	↓	AR	
Igα	<1%	↓	↓	↓	↓	AR	
Igβ	<0.5%	↓	↓	↓	↓	AR	
BLNK	<1%	↓	↓	↓	↓	AR	
PI3KR1	<0.5%	↓	↓	↓	↓	AR	
Class-switching defects							
CD40L	70%	NL	↑M, ↓G, A, E	↓TD	↓	XL	T-cell defect, SHM defect, liver disease,
CD40	<2%	NL	↑M, ↓G, A, E	↓TD	↓	AR	T-cell defect, SHM defect, liver disease,
NEMO	<2%	NL	↑M, ↓G, A, E	↓	↓	XL/AD	Lymphadenopathy, ectodermal dysplasia, SHM defect
AID	20%	NL	↑M, ↓G, A, E	↓	NL	AR	Lymphadenopathy, SHM defect
AID C terminal		NL	↑M, ↓G, A, E	↓	NL	AD	Lymphadenopathy, DNA cleavage
UNG	<2%	NL	↑M, ↓G, A, E	↓	NL	AR	Lymphadenopathy, lymphoma without autoimmunity
PMS2							
Terminal B-cell defects							
ICOS	<1%	NL	↓	↓	-	AR	Autoimmunity (ITP, AIHA)
CD19	<1%	NL	↓	↓	-	AR	Autoimmunity (ITP, AIHA)
CD81	<0.5%	NL	↓G	↓	↓	AR	
CD20	<0.5%	NL	↓G	↓TI	↓	AR	Impaired calcium response
CD21	<0.5%	NL	↓	↓	?	AR	
LRBA	<0.5%	NL	↓	↓	↓	AR	Autoimmunity, enteropathy
TACI	10%	NL	↓	↓TI	-	-	Autoimmunity (SLE) and allergic rhinitis
BAFFR	1%	↓	↓G,M	↓TI	↓	-	Elevated transitional B cells
MSH5	<0.5%	NL	↓	↓	?	-	

Abbreviations: AD, autosomal dominant; AIHA, autoimmune hemolytic anemia; AR, autosomal recessive; ITP, idiopathic thrombocytopenic purpura; NL, normal; SAD, specific antibody deficiency; SHM, somatic hypermutation; SLE, systemic lupus erythematosus; TD, T-cell–dependent antigens; TI, T-cell–independent antigens; XL, X-linked.

(secretion of IL-4, IL-5, IL-6) and is pivotal for superinduction of IL-10 [129]. The former mechanism may lead to dysregulation of terminal B-cell differentiation into memory and plasma cells. The number of circulating CXCR5-positive T cells, which are thought to be related to secretion of IL-12 and provide cognate help to B cells in germinal centers, was reduced in ICOS-deficient patients [130,131]. Selective impairment of IL-17 production was also observed in ICOS-deficient helper T cells stimulated by anti-CD3/anti-ICOS, which play a key role in the regulation of inflammatory processes in tissue [132].

Clinical *ICOS* deficiency was first reported in 2003 [133] in a patient with an autosomal recessive pattern. This case was followed by reports on 8 patients living along the River Danube who had a common ancestry owing to a founder mutation [134-138]. Major clinical features of *ICOS* deficiency include diminished Ig levels, autoimmunity, lymphocytic infiltration, malignancy, reduced class-switched and memory B-cell counts, and defective IgG1 and IgE antibody production in response to immunization, suggesting reduced germinal center formation [127,139,140]. Histopathology revealed severely aberrant and vestigial germinal centers in the patients' lymph nodes [141,142].

CD19 (B4, CVID3)

The *CD19* gene is located on the short arm of chromosome 16 at 16p11.2. The product of this gene belongs to the BCR coreceptor family [143]. This cell surface molecule, which remains expressive until the plasma cell stage, stabilizes and assembles with the antigen receptor of B cells in order to decrease the threshold for antigen receptor–dependent stimulation [144-148]. CD19 has been shown to interact with CD81, CD82, VAV2, complement receptor 2 (CD21), and Leu-13 (CD225) to form the CD19 complex, which mediates regulation of B-cell development, activation, growth, and motility [149, 150]. Ligation and phosphorylation of the internal tail of CD19 by PI-3 kinase is followed by binding of Src-family kinases and antigen-dependent Ca_2^+ signaling [151]. Furthermore, stabilization of the MYC oncoprotein associated with the development of B-cell lymphoma depends on CD19 concentrations [146-148].

Human CD19 deficiency was first reported in 2006 and was shown to be involved an autosomal recessive inheritance pattern. Clinically, the disease resembled a CVID phenotype with early-onset hypogammaglobulinemia (low IgG and IgA and/or IgM), impaired memory B and $CD5^+$ B-cell function, and autoimmune glomerulonephritis [152]. All 6 reported cases had normal B-cell counts, and the discrepancy between CD19 and CD20 counts observed with flow cytometry in a patient with a CVID phenotype could have helped to diagnose these individuals. Vaccination responses both to polysaccharide and to peptide antigens are severely impaired in CD19 deficiency [153-155].

CD81 (S5.7, TAPA1, TSPAN28, CVID6)

The CD81 gene is located on the short arm of chromosome 11 at 11p15.5. The product of this gene belongs to the transmembrane 4 superfamily [156]. This cell surface protein is the target of the antiproliferative antibody 1 (TAPA-1) and tetraspanin-28 (Tspan-28) proteins and interacts directly with the Ig superfamily member 8 (IGSF8, CD316), TSPAN4, CD9, PTGFRN, CD117, CD29, and CD36 [157, 158].

Signal transduction through CD81 in complex with CD19 plays an important role in the fine-tuning and amplification of BCR signals after antigen binding in B cells [159]. CD81 also associates with T-cell surface markers (CD4 and CD8) to generate a costimulatory CD3 signal [156]. In endothelial cells, the CD81 protein combines with integrins to facilitate muscle cell fusion and support myotube maintenance [160]. CD81 plays a critical role in susceptibility to viral infections including hepatitis C (attachment to the E1/E2 glycoproteins heterodimer) and human immunodeficiency virus infection (virion assembly and release by the gag protein) [161-163].

In 2010, CD81 deficiency was first described as an autosomal recessive Mendelian trait with clinical manifestations similar to those observed in CD19-deficient patients [149]. However, the patient with CD81 deficiency had normal serum IgA levels and multiple autoimmune diseases, including acute glomerulonephritis, Henoch–Schonlein purpura, and autoimmune thrombocytopenia [121,164].

CD21 (CR2, C3DR, CR, SLEB9, CVID7)

The *CD21* gene is located on the long arm of chromosome 1 at position 1q32.2. The complement component receptor 2 binds to iC3b, C3dg, and C3d [165]. The presence of CR2 receptors as coreceptors in CD19 complex on the surface of B cells enables activation and maturation of these cells by derivatives of the complement system, especially via the C3d-antigen complex [166,167]. CR2 is a gateway molecule for binding and entry of Epstein-Barr virus (EBV) into B cells and follicular dendritic cells [158,168].

Compound heterozygous mutations in CD21 were reported in 2012 [169]. The patient had late onset-hypogammaglobulinemia, low numbers of class-switched memory B cells and a specific antibody deficiency, even after administration of the polysaccharide vaccine. A new subset of B cells ($IgM^+IgD^+CD21^{low}$ cells) has been reported to be prominent in a subgroup of CVID cases. This subset is large, overexpresses CD86, and is more susceptible to division in vivo with a high anergic status [170]. Because of a defective negative selection process in $IgM^+IgD^+CD21^{low}$ cells, the subset comprises autoreactive B cells associated with inadequate peripheral activation and limited activation through the calcium pathway [171].

CD20 (MS4A1, B1, Bp35, LEU-16, MS4A2, S7, CVID5)

The *CD20* gene is located on the long arm of chromosome 11 at position 11q12.2. The product of this gene is B-lymphocyte antigen CD20 [172]. This glycosylated phosphoprotein is a member of the membrane-spanning 4A family, which is expressed on the surface of all B cells and is first detected at the pro-B stage before progressively increasing in concentration until maturity [173]. Although this coreceptor has no clear natural ligand, it assumed that CD20 protein acts as a calcium-dependent channel. The function of CD20 protein is to enable optimal B-cell immune responses, specifically against T-independent antigens [174]. This marker is expressed

at all stages of B-cell development, except in pro–B cells, plasmablasts, and plasma cells [175].

The only patient with CD20 reported to date had a homozygous mutation at a splice site of the *CD20* gene, resulting in abolished expression of mRNA and protein. The authors also observed reduced B-cell differentiation into plasma cells due to diminished calcium responses upon BCR triggering [176]. Furthermore, the number of class-switched memory B cells was reduced, and SHM was impaired. Surprisingly, the patient's IgA and IgM serum levels rose during 5 years of follow-up; however, serum IgG levels and T-independent specific antibody responses remained consistently low. Altogether, *CD20* deficiency should be considered in cohorts of IgG subclass–deficient patients with early onset of disease and sinopulmonary infections.

LRBA (BGL, CDC4L, LAB300, LBA, CVID8)

The *LRBA* gene is located on the long arm of chromosome 4 at 4q31.3. In humans, it encodes the lipopolysaccharide-responsive and beige-like anchor protein, which is a member of the BEACH-WD40 protein family [177]. *LRBA* interacts with signaling enzymes (PKA and PKC) with an A-kinase anchoring protein (AKAP) motif to compartmentalize these signaling molecules in organelles and membranes [178]. It has been suggested that *LRBA* plays a role in apoptosis, and increased apoptosis has been observed in *LRBA*-deficient, EBV-immortalized B-cell lines [179]. Phosphorylation of BAD, a key apoptosis regulator, was diminished in *LRBA*-deficient cells (PKA reduced S112 phosphorylation) and was restored when the cells where reconstituted with wild-type *LRBA* [180].

To date, 11 autosomal recessive *LRBA*-deficient patients with childhood-onset humoral immune deficiency have been diagnosed using genetic linkage analysis in consanguineous families. Autoimmunity (especially idiopathic thrombocytopenic purpura), bronchiectasis due to lymphoid interstitial pneumonia, inflammatory bowel disease, growth retardation, and CNS granuloma formation are other associated complications in this disease, and all patients with *LRBA* deficiency showed reduced counts of switched memory B cells [178,181,182].

PLCG2 (FCAS3)

The *PLCG2* gene, which is located on the long arm of chromosome 16 at 16q23.3, encodes 1-phosphatidyl-inositol-4, 5-bisphosphate phosphodiesterase gamma-2 [183]. This enzyme interacts with PTPN11, LYN, BTK, SHC1, and GAB2 to mediate activation signaling, CSR, and receptor editing in B cells [184,185]. Autoinhibitory interaction with the cSH2 domain plays an important role in this process [186]. A mutant form of this enzyme shows enhanced activation at subphysiologic temperatures, especially in B cells and mast cells [187,188].

Thirteen cases from 27 patients with PLCG2-associated antibody deficiency and immune dysregulation had hypogammaglobulinemia accompanied by cold urticaria and pleiotropic immune dysregulation [189]. These patients also had recurrent infections because of antibody deficiency (except IgE serum levels) and impaired central tolerance [190]. Autoimmunity (50%) and granulomatous lesions (25%) are common features of patients with this disorder. Laboratory and immunologic investigation revealed diminished class-switched memory B cells, impaired B-cell calcium flux, and low numbers of natural killer cells [56,191-193].

Genes Associated With CVID in Patients With Polygenic Traits

TACI (TNFRSF13B, CD267, TNFRSF14B, CVID2)

TACI is a highly polymorphic gene located on the short arm of chromosome 17 at 17p11.2. It encodes the transmembrane activator and calcium-modulator and cyclophilin ligand interactor protein (the lymphocyte-specific member 13B of the tumor necrosis factor receptor superfamily) with high variability in amino acid substitutions [194]. TACI protein interacts with the calcium-modulator and cyclophilin ligand (CAML), the B-cell activating factor (BAFF), a proliferation-inducing ligand (APRIL), and TWEPRIL [195].

Signaling through this protein activates several transcription factors in B cells via binding to TRAFs including calcineurin, NFAT, AP-1, and NF-κB [196]. Together with BAFF-R and the B-cell maturation antigen (BCMA), TACI protein constitutes a complex signaling network that modulates CSR and plasma cell formation and negatively regulates B-cell homeostasis [197]. This network has partly overlapping expression patterns and functions that might compensate each other within this redundant system [198].

TACI protein is also found on a subset of T cells. TLR ligands were recently found to act as a signaling regulator between the TACI protein and Toll-like receptor pathways. Production and activation of TACI depend strongly on stimulation of adaptor protein MyD88, which acts synergistically with APRIL and BAFF. TACI binds poorly, and its affinity is sometimes higher for BAFF and APRIL [199]. TACI is also highly expressed on human marginal zone B cells and switched memory B cells, although it is rare or absent on mature naive and transitional B cells [200]. Additional molecular studies will be required to determine exactly how *TACI* mutations affect the clinical phenotype of patients with predominantly antibody deficiency [201].

Since 2005, TACI deficiency has been reported in roughly 10% of patients with CVID [202]. Complex patterns of inheritance (homozygous, heterozygous, and compound heterozygous), mostly in the hotspot extracellular portion of the molecule (C104R and A181E) and incomplete penetrance and phenotypic diversity in clinical manifestations of *TACI*-deficient patients, suggest that modifying factors may play a role [196,203]. Observations of heterozygous *TACI* null mutations may suggest that such defects could exert their effects via haploinsufficiency rather than by being dominant-negative proteins [204]. However, heterozygous C104R patients had a significant correlation with the CVID phenotype, with low numbers of $IgD^{-}CD27^{+}$ B cells, autoimmunity, and polylymphocytic infiltrations [205]. Therefore, *TACI* mutations (especially in carriers of single mutations) are not diagnostic of CVID or predictive of the development of this immune defect; *TACI* is only a disease susceptibility or

disease-associated gene. Indeed, individuals with monoallelic mutations are more likely to develop CVID and autoimmune phenomena, although no clear genotype–phenotype correlation has been established [206]. Screening for mutations in *TACI* to predict prognosis or help in genetic counseling is therefore unlikely to be useful [207]. No specific single gene has been identified in *TACI*-deficient relatives; however, genetic linkage studies demonstrate evidence for another causative gene on chromosome 4q22 or 16q23 [208]. Although the functional impairment of several TLR pathways in association with TACI has been studied, the effects have not been linked to specific genetic defects.

BAFF-R (TNFRSF13C)

The BAFF-R gene is located on the long arm of chromosome 22 at 22q13.2. The homotrimeric protein encoded by this gene is a receptor belonging to the tumor necrosis factor receptor family (type III transmembrane protein) [209,210]. Together with the BCR, this receptor forms a complex receptor network (TACI/BCMA/BAFF-R) that is required for BAFF-mediated proliferation and differentiation of transitional and mature B cells [143,211]. Activation of BAFF-R is followed by survival signals from BclXL and Mcl1 (via NF-κB, induced by NIK and TRAF 3) and mTOR (via AKT induced by PI3K) [212,213].

The report of 2 individuals with a homozygous deletion in the *BAFF-R* gene in 2009 showed that while this molecule is important for B-cell survival in humans, it is not absolutely necessary [134]. An immunology study of cases with this deletion revealed lymphopenia, late-onset antibody deficiency (except for serum IgA, unlike most CVID patients), involvement of long-term humoral memory (except for IgA+ memory), short-lived plasma cells (except for IgA secreting plasma cells from mucosal tissues), a relative increase in transitional B-cell counts, and reduced specific antibody responses, especially to polysaccharide antigens [214].

MSH5 (G7, MUTSH5, NG23)

The *MSH5* gene is located on the short arm of chromosome 6 at 21p21.33. MutS protein homolog 5, which is encoded by the *MSH5* gene, is a member of the mutS family, which is involved in DNA mismatch repair and meiotic recombination processes [215]. This protein forms hetero-oligomers with another member of this family, mutS homolog 4. Four transcriptional variants formed by alternative splicing lead to the 3 different isoforms needed for Ig class-switch regulation, thus facilitating CSR between Sμ and Sα [216]. Indeed, DNA Holliday junctions between homologous DNA strands are resolved by means of a sliding clamp on DNA (*MSH5* and *MSH4*) after meiotic chromosomal crossovers [217,218].

In 2007, Sekine et al [219] reported patients with nonsynonymous mutations in *MSH5* presenting with different Ig deficiencies (CVID and SIgAD). Furthermore, individuals who are heterozygous for *MSH5* nonsynonymous alleles are healthy with regard to changes in switch joint mutation rates. Therefore, *MSH5* variants do not seem to play a major role in patients with primary immunodeficiency disease.

Conclusion

Approximately 30 genes causing B-cell developmental defects in humans have been described since 1952. Advances in DNA technology—in particular, next-generation sequencing—are likely to result in the identification of many rare primary immunodeficiency diseases for which the causative genes remain unknown. Identification of a genetic basis for these diseases has a direct effect on the development of therapy, screening, detection of carriers, and family counseling.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Asghar Aghamohammadi

Children's Medical Center Hospital
62 Qarib St., Keshavarz Blvd.
Tehran 14194, Iran
E-mail: aghamohammadi@tums.ac.ir

