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Primary B-cell immunodeficiencies

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ABSTRACT

Primary B-cell immunodeficiencies refer to diseases resulting from impaired antibody production due to either molecular defects intrinsic to B-cells or a failure of interaction between B-cells and T-cells. Patients typically have recurrent infections and can vary with presentation and complications depending upon where the defect has occurred in B-cell development or the degree of functional impairment. In this review, we describe B-cell specific immune defects categorized by presence or absence of peripheral B-cells, immunoglobulins isotypes and evidence of antibody impairment.

1. Introduction

About 20% of serum proteins are immunoglobulins, containing all the antibody species that a human needs for protection against most infections [1]. Functional antibodies are the end product of multiple steps that include continuous reconfiguration of genes for the B-cell antigen receptors (BCR) along with the elimination of perhaps 90% of poly-reactive and autoreactive B-cells during this process [2]. One of the most illuminating lessons about B-cell biology has arisen from studies of the primary immune defects that prevent normal B-cell development. While more than 300 primary immune defects are now known [3], clinically, the most common defects found in patient populations are those that impair B-cell development or function (Fig. 1).

B-cell immunodeficiencies are often distinguished from other immune defects, by age of onset, clinical parameters, severity and mode of inheritance. The types of infections that hallmark an underlying B-cell defect include recurrent infections that are typically encapsulated bacteria, distinct from patients with T-cell or combined immunodeficiencies, who are more likely to have opportunistic or severe viral or infections. B-cell defects are quite heterogeneous, and include loss of immune globulins, and/or impaired antibody production. These result from molecular defects intrinsic to B-cells, failure of required interactions between B- and T-cells, loss of appropriate bone marrow or germinal center responses, and defects of immune regulation. These defects result in a variable loss of B-cells, reduction or absence of serum immunoglobulins and/or loss of antibody function. B-cell immunodeficiencies are categorized into the following: 1) a severe reduction in all serum immunoglobulin isotypes with profoundly decreased or absent B cells, recognized as agammaglobulinemia; 2) severe reduction in at least 2 serum immunoglobulin isotypes (typically IgG and IgA) with normal or low number of B cells (CVID phenotype); 3) severe reduction in serum IgG and IgA with normal/elevated IgM with normal numbers of B cells (Hyper IgM syndrome); 4) Isotype or light chain deficiencies with generally normal numbers of B cells (these are outlined in Table 1).

2. Agammaglobulinemia: severe reduction in All serum immunoglobulin isotypes with profoundly decreased or absent B-cells

2.1. X-linked agammaglobulinemia (XLA)

Agammaglobulinemia is characterized by absence of circulating B-cells with severe reduction in all serum immunoglobulin levels.

Abbreviations: AID, activation-induced cytidine deaminase; ALPS, autoimmune lymphoproliferative syndrome; APDS, activated phosphoinositide 3-kinase delta syndrome; BAFF, B-cell activating factor of the tumor necrosis family; BCR, B-cell receptor; BLNK, B-cell linker; BTK, Bruton's tyrosine kinase; CD40L, CD40 ligand; CSR, class-switch recombination; CTLA4, cytotoxic T-lymphocyte associated protein 4; CVID, common variable immunodeficiency; HIGM, hyper-IgM; ICOS, inducible T cell costimulator; Ig, immunoglobulin; LRBA, lipopolysaccharide (LPS)-responsive and beige-like anchor protein; mTOR, mechanistic target of rapamycin; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PI3K, phosphatidylinositol 3-kinase; PID, primary immunodeficiency; SAD, specific antibody deficiency; SHM, somatic hypermutation; SIGAD, selective IgA deficiency; SIgMD, selective IgM deficiency; TACI, transmembrane activator and calcium-modulator and cyclophilin ligand interactor; THI, transient hypogammaglobulinemia of infancy; TNF, tumor necrosis factor; TWEAK, TNF-like weak inducer of apoptosis; UNG, uracil-DNA glycosylase; XLA, X-linked agammaglobulinemia

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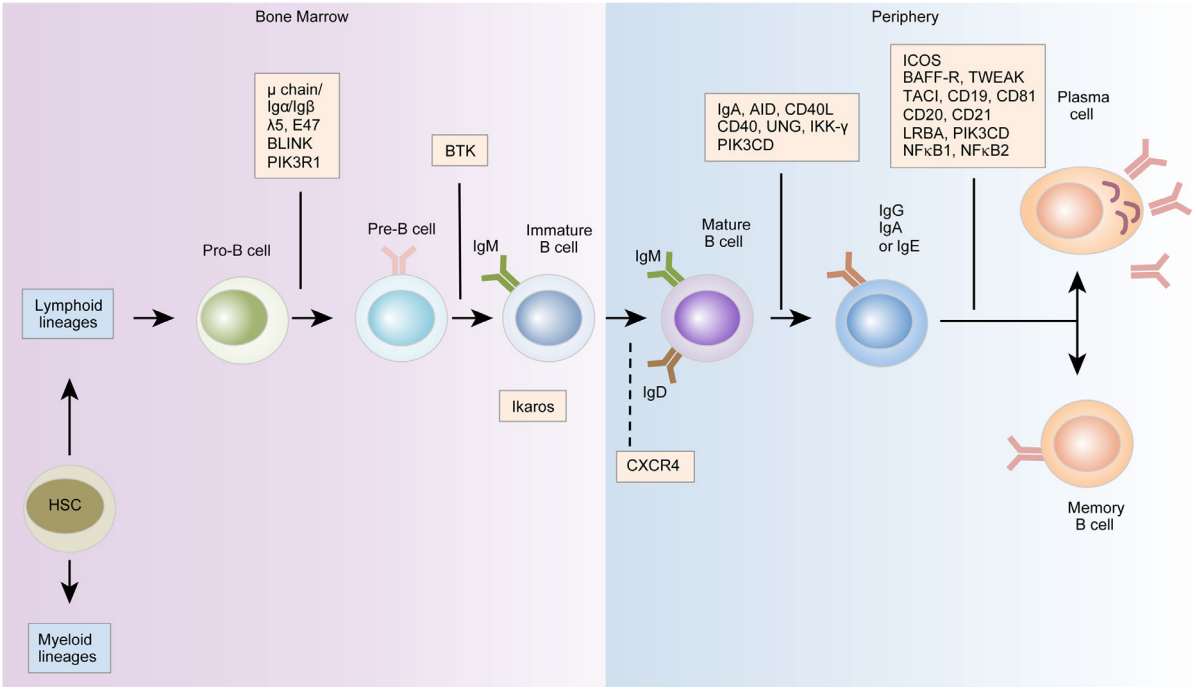

Fig. 1. Gene and protein defects in B-cell development and function. Hematopoietic stem cells (HSCs) give rise to progenitor (pro)-B cells, which then rearrange their immunoglobulin heavy-chain gene segments to generate precursor (pre)-B cells. Pre-B cells subsequently rearrange their immunoglobulin light-chain gene segments to produce a functional cell-surface receptor (IgM), composed of heavy and light chains. After the receptor engages with antigen, downstream events lead to the induction of proliferation and differentiation of the B-cell. In the periphery, after stimulation with antigen, mature B-cells further develop following class-switch recombination and somatic hypermutation and, ultimately, memory B-cell or plasma cell differentiation. Developmental blocks throughout B-cell maturation and differentiation occur as a result of defects in genes encoding the molecules indicated in boxes. Blocks in the function of mature B cells can also occur. Primary immunodeficiency syndromes that cause these blocks are also listed. AID, activation-induced cytidine deaminase; BAFFR, B-cell-activating-factor receptor; BLNK, B-cell linker; BTK, Bruton's tyrosine kinase; CD40L, CD40 ligand; ICOS, inducible T-cell co-stimulator; E47, E47 Transcription Factor/TCF3 gene; IgA, selective IgA deficiency; LRBA, lipopolysaccharide (LPS)-responsive and beige-like anchor protein; factor kappa-light-chain-enhancer of activated B cells; NFKB, nuclear factor kappa-light-chain-enhancer of activated B cells; PIK3, phosphatidylinositol 3-kinase; μ chain, μ immunoglobulin heavy chain; IKK-γ, inhibitor-of-nuclear-factor-κB kinase-γ; TACI, transmembrane activator and calcium-modulating cyclophilin-ligand interactor; TWEAK, TNF-like weak inducer of apoptosis; UNG, uracil-DNA glycosylase.

Clinically, this is a rare defect (1:100,000 to 1:200,000 depending on ethnicity and the specific genetic defect) [4]. Both X-linked and autosomal recessive forms of the disease have been described. The classic disorder of B-cell development is X-linked agammaglobulinemia (XLA), first described in 1952 by Ogden Bruton, who reported an eight-year-old boy with recurrent bacterial sepsis and absence of the globulin fraction on serum protein electrophoresis [5]. With additional patients being recognized, an X-linked inheritance pattern was observed [6,7]. The hallmark of XLA is the lack of circulating B-cells. While pro-B-cell and pre-B-cells are present in the bone marrow, suggesting that hematopoietic stem cells enter the B-cell lineage, these cells are not able to efficiently progress to maturation [8]. Linkage studies mapped the gene for XLA to the mid-portion of the long arm of the X-chromosome; it was subsequently identified concurrently by European and American groups [9,10], who called the gene Bruton's tyrosine kinase (BTK; OMIM: 300300) in honor of Bruton's discovery. BTK is a member of a family of cytoplasmic tyrosine kinases and is expressed at all stages of B-cell differentiation except for plasma cells [11]. The BTK gene is encoded in 19 exons spread over 37 kb on chromosome Xq22. Mutations in BTK account for approximately 85% of patients presenting with congenital agammaglobulinemia [12,13].

2.2. Autosomal agammaglobulinemias

As early as the 1970s, a few females were also identified with phenotypical features identical to XLA [14]. Other reports observed cases of congenital agammaglobulinemia ascribed to an autosomal recessive inheritance pattern; these are mainly due to defects in components of the pre-BCR complex or downstream signaling pathways. The pro-B-cell to pre-B-cell transition, along with sequential immunoglobulin gene rearrangements and normal B-cell development, require surface expression of a functional pre-BCR complex. As a consequence, defects of the BCR structure itself, including the μ heavy chain, surrogate light chains, (VpreB and λ5), the Igα (CD79) and Igβ genes (CD79B) which form the heterodimeric transmembrane signal transduction elements, lead to autosomal forms of agammaglobulinemia. After *BTK*, the gene encoding for the μ heavy chain, *IGHM* (located on chromosome 14q32.33) is the second most frequently mutated gene in patients with agammaglobulinemia, but still account for only about 5% of agammaglobulinemic patients [15]. All the reported mutations of the μ heavy chain are associated with the complete absence of B-cells in the peripheral circulation [16,17]. Up to 60% of mutations are large deletions encompassing the *IGHM* gene (OMIM: 147020) but a smaller number of point mutations have been reported. Clinically, although there is considerable overlap, the patients with μ heavy chain defects tend to have a more severe phenotype and are diagnosed earlier than patients with mutations in *BTK* [16,17]. While recurrent sinopulmonary infections are common to both, patients with μ heavy chain defects may have a higher incidence of enteroviral infections and *Pseudomonal* sepsis. Neutropenia has also been reported in almost one-third of patients with this disorder [15].

Another component of the BCR is the surrogate light chain which facilitates transportation of the μ heavy chain to the cell surface; this protein ensures that the μ heavy chain can bind to conventional light chains before the rearrangement of the light chain genes [18]. The *IGLL1* and *IGI* genes are located on the long arm of chromosome 22

Table 1
Primary B-cell Immunodeficiencies.

Disease[a]	Genetic defect	Inheritance[b]	Immunoglobulin level and antibody response	Associated features
Severe Reduction in All Serum Immunoglobulin Isotypes with Profoundly Decreased or Absent B Cells (Agammaglobulinemia)				
BTK deficiency, X-linked agammaglobulinemia (XLA)	*BTK*	XL	All isotypes decreased in most, some have detectable immunoglobulins	Severe bacterial infections, normal numbers of pro-B cells
μ heavy chain deficiency	*IGHM*	AR	All isotypes decreased	Severe bacterial infections, normal numbers of pro-B cells
λ 5 deficiency	*IGLL1*	AR	All isotypes decreased	Severe bacterial infections, normal numbers of pro-B cells
Igα deficiency	*CD79a*	AR	All isotypes decreased	Severe bacterial infections, normal numbers of pro-B cells
Igβ deficiency	*CD79b*	AR	All isotypes decreased	Severe bacterial infections, normal numbers of pro-B cells
BLNK deficiency	*BLNK*	AR	All isotypes decreased	Severe bacterial infections, normal numbers of pro-B cells
PIK3R1 deficiency	*PIK3R1*	AR/AD	All isotypes decreased	Severe bacterial infections, decreased or absent pro-B cells
E47 transcription factor deficiency	*TCF3*	AD	All isotypes decreased	Recurrent bacterial infections
Severe Reduction in at Least 2 Serum Immunoglobulin Isotypes with Normal or Low Number of B Cells (CVID phenotype)				
CVID of unknown gene defect	Unknown	AD or AR	Low IgG and IgA with low/normal IgM; poor antibody response	Variable clinical expression, most have recurrent sinopulmonary infections, enteropathy, autoimmune, granulomatous and/or lymphoproliferative complications
TACI deficiency	*TNFRSF13B (TACI)*	AD or AR	Low IgG and IgA and/or IgM	Variable clinical expression
BAFF receptor deficiency	*TNFRSF13C (BAFF-R)*	AR	Low IgG and IgM	Variable clinical expression
TWEAK deficiency	*TWEAK (TNFSF12)*	AD	Low IgM and A, lack of anti-pneumococcal antibody	Pneumonia, bacterial infections, warts, thrombocytopenia, neutropenia
CD19 deficiency	*CD19*	AR	Low IgG and IgA and/or IgM	Recurrent infections, may have glomerulonephritis
CD81 deficiency	*CD81*	AR	Low IgG, low or normal IgA and IgM	Recurrent infections, may have glomerulonephritis
CD20 deficiency	*CD20*	AR	Low IgG, normal or elevated IgM and IgA	Recurrent infections
CD21 deficiency	*CD21*	AR	Low IgG, impaired anti-pneumococcal response	Recurrent infections
LRBA deficiency	*LRBA*	AR	All isotypes decreased	Recurrent infections, enteropathy, autoimmune cytopenias, lymphoproliferative complications, endocrinopathy
CTLA4 deficiency	*CTLA4*	AD	All isotypes decreased	Recurrent sinopulmonary infections, enteropathy, autoimmune, and/or lymphoproliferative complications
PIK3CD mutation (GOF)	*PIK3CD GOF*	AD	All isotypes decreased	Severe bacterial infections; decreased or absent pro-B cells, EBV
NFκB1 deficiency	*NFKB1*	AD	Normal or low IgG, IgA, IgM, low or normal B cells, low memory B cells	Recurrent sinopulmonary infections, COPD, EBV proliferation, autoimmune cytopenias, alopecia and autoimmune thyroiditis
NFκB2 deficiency	*NFKB2*	AD	Low serum IgG, A and M; low B cell numbers	Recurrent sinopulmonary infections, alopecia and endocrinopathies
Severe Reduction in Serum IgG and IgA with Normal/Elevated IgM and Normal Numbers of B cells (Hyper IgM syndrome)				
CD40L deficiency	*CD40LG*	XL	IgG and IgA decreased, IgM increased	Bacterial and opportunistic infections
CD40 deficiency	*CD40*	AR	IgG and IgA decreased, IgM increased	Bacterial and opportunistic infections
AID deficiency	*AICDA*	AR	IgG and IgA decreased, IgM increased	Bacterial infections, enlarged lymph nodes and germinal centers
UNG deficiency	*UNG*	AR	IgG and IgA decreased, IgM increased	Enlarged lymph nodes and germinal centers
Isotype, Light Chain, or Functional Deficiencies with Generally Normal Numbers of B Cells				
Ig heavy chain mutations and deletions	Mutation or chromosomal deletion at *14q32*	AR	One or more IgG and/or IgA subclasses as well as IgE may be absent	May be asymptomatic
Kappa chain deficiency	*IGKC*	AR	All immunoglobulins have lambda light chain	Asymptomatic
Isolated IgG subclass deficiency	Unknown	?	Reduction in one or more IgG subclass	Usually asymptomatic, a minority may have poor antibody response to specific antigens and recurrent viral/bacterial infections
IgG subclass deficiency with IgA deficiency	Unknown	?	Reduced IgA with decrease in one or more IgG subclass	Recurrent bacterial infections
Selective IgA deficiency	Unknown	?	Very low to absent IgA with other isotypes normal, normal subclasses and specific antibodies	Bacterial infections, autoimmunity mildly increased
Specific antibody deficiency with normal Ig levels and normal B cells	Unknown	?	Normal	Reduced ability to produce antibodies to specific antigens
Transient hypogammaglobulinemia of infancy	Unknown	?	IgG and IgA decreased	Normal ability to produce antibodies to vaccine antigens, usually not associated with significant infections
Selective IgM deficiency	Unknown	?	Absent serum IgM	Pneumococcal/bacterial infections

[a] Ig, Immunoglobulin.
[b] AD, autosomal dominant; AR, autosomal recessive; XL, X-linked.

(22q11.23 and 11.22) and encode for λ5 and VpreB proteins, respectively. Surrogate light chain λ5 deficiency (OMIM: 146770) was first described in a male with agammaglobulinemia and markedly reduced numbers of B-cells [19], but other cases have been reported [17].

Also essential for normal expression of the BCR complex on functional B-cells are the Igα and Igβ membrane-bound heterodimers, which are expressed by the earliest committed B-cell progenitors and before expression of Ig-μ heavy chain [20]. The resultant complex is covalently linked to both the pre-BCR and BCR, which is critical since the cytoplasmic domains of Igα and Igβ contain ITAM motifs which connect the pre-BCR and BCR to downstream elements of the signal transduction cascade. It is important to distinguish that Igα and Igβ play different roles. Igα functions both in signal transduction and also operates as a chaperone, escorting the transmembrane domain of the μ heavy chain to the cell surface [21], a function not intrinsic to the Igβ protein [22]. Gene defects of Igα (OMIM: 112205) and Igβ (OMIM: 147245) are very rare and lead to autosomal recessive forms of agammaglobulinemia. Clinically, patients have recurrent sinopulmonary infections, but may also have chronic diarrhea with malabsorption and dermatomyositis-like manifestations and sometimes neutropenia [15,16].

Downstream from the BCR, B-cell linker (BLNK; OMIM: 604515), also known as SLP65 (SH2-binding leukocyte phosphoprotein of 65 kDa), is a 456-amino acid adaptor protein essential in the signaling pathway after antigen engagement of the BCR [23], resulting in the activation of BTK, and subsequently binding of phospholipase Cγ2 (PLCγ2) to BLNK, thus enabling BTK to phosphorylate PLCγ2. As a result, downstream signaling occurs, leading to recombination-activating gene (RAG) protein expression, light chain recombination and further differentiation of pre-B-cells [23]. Few patients with BLNK defects have been reported [17,23] making this a very rare form of agammaglobulinemia.

Two additional autosomal recessive forms of agammaglobulinemia have been described, PIK3R1 deficiency and E47 Transcription Factor/TCF3 deficiency. There are multiple isoforms of phosphatidylinositol 3-kinase (PI3K), a lipid kinase important in growth signaling pathways. This complex includes heterodimeric proteins consisting of p110α, p110β, and p110δ catalytic subunits which constitutively associate with a 85-kDa regulatory subunit. In humans, p85α is produced by the PIK3R1 gene, located on chromosome 5 (5q13.1). The clinical features of homozygous PIK3R1 deficiency (OMIM: 171833) were described by Conley and colleagues and include almost total loss of B-cells (1%) and agammaglobulinemia without abnormalities in the T-cell compartment. Bone marrow findings were consistent with an early block in B-cell development with minimal VDJ rearrangement [24].

The E47 Transcription Factor/TCF3 gene (OMIM: 147141) encodes and by alternative splicing, generates two broadly expressed members of the basic helix-loop-helix (bHLH) family of transcription factors, E12 and E47, collectively known as E2A proteins [25]. E2A is indispensable for commitment to the B-cell lineage and B-cell lymphopoiesis, DNA recombination, receptor editing, marginal/follicular zone development and class switch recombination [25]. Both autosomal dominant and recessive mutations in the *TCF3* gene have been reported. Boisson and colleagues reported identical heterozygous dominant negative *de novo* mutations in four unrelated male and female patients with no history of consanguinity [26]. Clinically, patients presented with autosomal dominant agammaglobulinemia and an unusual phenotype of B-cells characterized by the increased expression of CD19 but the absence of a BCR. Bone marrow evaluation demonstrated a profound reduction in the number of $CD19^+$ cells and a block in B-cell development at the common lymphoid precursor to pro-B-cell stage of differentiation. This blockade occurred earlier than that seen in patients with defects in *BTK* or BCR signaling components. In contrast, Ben-Ali and colleagues reported autosomal recessive mutations in *E2A* in a Tunisian male with a history of consanguinity, who presented with recurrent pneumonia and meningitis since early childhood [26]. He also had facial dysmorphic features, severe hypogammaglobulinemia with near undetectable peripheral B-cells, pancytopenia and splenomegaly with otherwise normal T- and NK-cells. He developed B-cell acute lymphoblastic leukemia (B-ALL), which was treated with chemotherapy, but an after an unfortunate relapse, died due to complications.

3. CVID phenotype: severe reduction in serum immunoglobulins with normal or low B-cells.

3.1. Common variable immune deficiency (CVID)

After early B-cell development with successful generation of cells bearing a functional BCR, B-cells move from the bone marrow to the spleen and peripheral lymphoid tissues, where additional maturational events occur which lead to plasma cell development. Failing any of these steps results in varying degrees of hypogammaglobulinemia. From the clinical point of view, patients are usually given the generic label, common variable immune deficiency (CVID). One of the essential issues in CVID is that B-cells either do not become fully activated, proliferate normally, and/or terminally differentiate into plasma cells and/or memory B-cells [27], which reflect the various blocks in B-cell development that lead to CVID. Although the majority of CVID cases have no identified genetic defect, in perhaps 10% of cases overall, the genetic basis has been determined. This has provided clues as to the stages of B-cell differentiation that are defective and the main forms will be discussed below.

As one of the most common symptomatic primary immunodeficiencies, CVID is estimated to affect between 1:25,000 and 1:50,000 of the population, with the majority of patients diagnosed between the ages of 20 and 45 with males and females being affected equally. This heterogeneous group of PIDs was first recognized in 1954 [28] and is characterized by decreased serum immunoglobulin IgG with a decrease in serum IgA and/or IgM, along with defective specific antibody production [1]. Although most CVID patients have low to normal numbers of circulating B-cell, the main characteristic is failure in the differentiation of B-cells into immunoglobulin-secreting plasma cells. Reduced numbers of isotype switched $CD27^+$ memory B-cells in CVID patients with increases in $CD21^{lo}$ or increased transitional B cells, has become a useful basis for sub-classification of patients [29]. However, CVID is often accompanied by reduced T-cell numbers, cytokine defects, defective lymphocyte proliferative to mitogens and antigens, abnormal lymphocyte trafficking, dysregulated cellular responses to chemokines [30], defective dendritic cell [31] and innate immune interactions [32], uncontrolled T-cell polarization and more recently described, an inflammatory role of innate lymphoid cells [33].

The clinical spectrum of CVID is broad and consists of mainly two phenotypes, one predominated by recurrent infections while in approximately 25–50% of patients, autoimmune and/or inflammatory features are present, including enteropathy, non-infectious immune-mediated lung disease and/or granulomatous disease, which lead to significant morbidity and mortality [34,35]. Bronchiectasis, an irreversible lung complication, has been reported in a significant proportion of patients [36]. Approximately 10% of patients have significant liver dysfunction, with nodular regenerative hyperplasia leading to portal hypertension, or in other cases, primary biliary cirrhosis and/or granulomatous disease. In contrast to patients with XLA, patients with CVID have normal sized or enlarged tonsils but approximately 25% of patients have splenomegaly and/or generalized lymphadenopathy leading to concern for lymphoma [37]. Individuals with CVID are susceptible to malignancy, particularly non-Hodgkins lymphoma, and have an estimated 1.8- to 5-fold increased risk of developing cancers of all types [38].

3.2. Genetic defects leading to the CVID phenotype

3.2.1. TACI deficiency

Transmembrane activator and CAML interactor (TACI) (OMIM: 604907), a product of the highly polymorphic gene *TNFRSF13B*, is located on the short arm of chromosome 17 at 17p11.2. TACI is expressed on mature B-cells, especially marginal zone B-cells, $CD27^+$ memory B-cells, and plasma cells [39] and binds both APRIL and BAFF only when presented in an oligomeric or membrane-bound form. Compared to the more rare gene defects described below, the relative frequency of TACI deficiency is more common, with TACI mutations found in 8–10% of CVID patients [40], usually in the heterozygous state, suggesting either a dominant-negative effect or haploinsufficiency [41,42]. TNFRSF13B haploinsufficiency or null alleles result in decreased TACI expression on memory B-cells and impaired antibody secretion, suggesting that during later stages of B-cell development, TACI supports class-switch recombination, plasma cell differentiation and antibody secretion [39]. Clinically, patients are found to have hypogammaglobulinemia with impaired antibody responses [39], however, a common feature is a propensity to autoimmune manifestations and lymphoid hyperplasia potentially due to lack of normal mechanisms of establishing tolerance [43].

TACI mutations are not entirely disease causing by themselves, but appear to confer increased susceptibility to CVID [40]. It is also important to highlight that TACI variants have been detected in 1% of individuals who otherwise are healthy [44] and asymptomatic family members of affected individuals [43]. This suggests either variable penetrance of the gene defect, other CVID-predisposing or causative genes not yet identified or unknown environmental factors. There is evidence that perhaps such polymorphisms might be an evolved adaptive response and might associate with CVID [45].

3.2.2. BAFF receptor deficiency

Maturation of splenic B-cells is regulated by interactions with B-cell activating factor of the tumor necrosis family (BAFF), acting on its receptor (BAFF-R) as well as activation of BCR by self-antigen [46]. These allow differentiation of transitional and mature B-cells, expression of Bcl-2 family members and downregulation of pro-apoptotic factors. BAFF receptor (BAFF-R, OMIM: 606269) is encoded by three exons of the TNFRSF13C gene located on chromosome 22q13 and produces a homotrimeric transmembrane protein of 184 amino acid residues. BAFF-R, together with the BCR, forms a complex receptor network, consisting of BAFF-R, TACI and B-Cell Maturation Antigen (BCMA), which is required for BAFF-mediated proliferation and survival. Autosomal recessive mutations in BAFF-R were identified in two siblings, leading to adult onset hypogammaglobinemia [47]. More common are polymorphisms in BAFF-R (especially the P21R variant) noted in subjects with CVID, which have modifying effects on either BAFF-R assembly or ligand binding, and thus may impair B-cell maturation [48].

3.2.3. TWEAK deficiency

TNF-like weak inducer of apoptosis (TWEAK) has also been described as having a role in BAFF signaling and B-cell survival (TNFSF12, OMIM: 602695) [46]. *TWEAK* is located on human chromosome 17p13.1 upstream of *APRIL*. TWEAK is widely expressed in many tissues and cell types, including monocytes/macrophages, dendritic cells, natural killer (NK) cells and T-cells, and its expression is increased during inflammation [49]. The precise role of TWEAK has not been fully elucidated, however, it may have a role in promoting proliferation in endothelial cells and modulating innate immunity [49]. An autosomal dominant mutation in *TWEAK* was identified in one CVID pedigree, associated with recurrent infections, reduced IgM and IgA with impaired antibody responses to protein and polysaccharide vaccines. This mutation appeared to affect B-cell survival by interacting with BAFF to form ineffective BAFF complexes [46,49].

3.2.4. ICOS deficiency

Autosomal recessive mutations in the gene encoding the inducible T-cell costimulator (*ICOS*; OMIM 604558; chromosome 2q33.2), a T-cell surface receptor, was one of the first genetic causes of CVID to be identified [50]. ICOS, a member of the CD28 and CTLA4 (cytotoxic T-lymphocyte associated protein 4, OMIM: 123890) family of proteins, is required for interaction with its cognate receptor on antigen presenting cells (B7) and is required for germinal center formation and terminal B-cell differentiation [51]. Patients with homozygous and compound heterozygous mutations have been reported and have a variable age of onset [50]. The severity of the immune defect is quite diverse and may include inflammatory bowel disease, abnormal liver enzymes, enteropathy and/or opportunistic infections [52].

3.2.5. B-cell costimulatory molecule deficiencies

B-cell development and differentiation is critically dependent upon signal transduction through the BCR and its co-receptors. Of these, CD19 (OMIM: 107265; chromosome 16p11.2), a cell-surface glycoprotein of the immunoglobulin superfamily protein exclusively expressed throughout B-cell development except at the plasma cell stage, forms a complex with CD21 (OMIM: 120650) and CD81 (OMIM: 186845) in the membrane of mature B-cells. Quite rare autosomal recessive mutations in these genes leading to defective B-cell activation and hypogammaglobulinemia have been identified [53–55]. Clinically, patients present with recurrent infections, however, in CD19 and CD81 defects, glomerulonephritis has been reported [3]. In CD21 deficiency, a reported case had low IgG with impaired anti-pneumococcal response. In addition to these, deficiency in another co-receptor, CD20 (OMIM: 112210), has been reported in a case of recurrent infections with hypogammaglobulinemia in the presence of normal B-cell numbers, but an inability to mount anti-polysaccharide responses [56]. Autosomal recessive mutations in an additional integral B-cell receptor, CD27, a marker of human memory B-cells, have also been described in patients with the CVID phenotype [57].

3.2.6. B-cell defects linked to immune dysregulation

An emerging theme in the study of human B-cell defects is that mutations in genes that control immune regulation are likely to present with the clinical phenotype of antibody deficiency, with hypogammaglobulinemia being an early and cardinal feature. These syndromes also commonly include autoimmunity, enteropathy, splenomegaly and generalized lymphoid hyperplasia.

3.2.6.1. LRBA and CTLA4 deficiency. The first of these immune dysregulation syndromes to be recognized were recessive mutations in lipopolysaccharide-responsive beige-like anchor protein (LRBA; OMIM 606453; 4q31.3), a cytosolic protein localized in the vesicles and endoplasmic reticulum of almost all cell types, including T- and B-cells [58,59]. Although the entire function is not fully understood, LRBA is involved in intracellular vesicle trafficking and internalization of ligand-activated receptors [59]. Mutations leading to loss or greatly reduced protein expression are linked to a severe phenotype with recurrent infections, autoimmune lymphoproliferative syndrome (ALPS)-like features in many and, with increasing evidence, has become a clinically variable syndrome with a wide spectrum of clinical manifestations [60]. The worldwide prevalence of LRBA deficiency is still unknown, however, currently, more than 80 patients have been diagnosed [58,60].

CTLA4, another member of the ICOS/B7 family mentioned above, is a negative immune regulator expressed on activated T cells and $FoxP3^+$ regulatory T cells (Tregs) and is essential for the maintenance self-tolerance and immune homeostasis [61]. Similar to defects of LRBA, but with more variable penetrance, CTLA4 heterozygous autosomal dominant mutations lead to hypogammaglobinemia, autoimmunity and recurrent infections [61]. Both LRBA and CTLA4 deficiencies have phenotypic similarities as LRBA co-localizes with CTLA4 in endosomal

vesicles and acts as a chaperone to modulate CTLA4 surface expression; thus mutations in either genes disrupt CTLA4 surface expression and result in downstream immune inhibitory dysfunction [62]. A consistent feature of both syndromes is that Tregs have markedly reduced suppressive functions [62].

3.2.6.2. Activated phosphoinositide 3-kinase delta syndrome (APDS). Other syndromes of antibody deficiency are due to mutations of Class IA phosphoinositide 3-kinase (PI3K), known as activated phosphoinositide 3-kinase delta syndrome (APDS), which are categorized as types 1 and 2. APDS1 is a primary immunodeficiency caused by autosomal dominant gain-of-function mutations in *PIK3CD,* the gene which encodes the catalytic subunit p110δ (OMIM: 602839) [63] while autosomal dominant gain-of-function mutations in *PIK3R1*(OMIM: 616005) encoding for the 85 kDa regulatory subunit p85α result in APDS2 [64,65]. Heterozygous gain of function mutations in *PIK3CD* (often E1021K) [66] and a subset of heterozygous mutations in *PIK3R1* have been described as clinically indistinguishable as both mutations lead to increased activity of the p110 subunit. Both syndromes include a predominant antibody deficiency frequently presenting as a CVID-like or hyper-IgM–like phenotype associated recurrent infections, progressive B- and naive T-cell lymphopenia and massive lymphoproliferation [67]. In addition, patients with APDS1 and APDS2 are at risk for developing malignancy, specifically B-cell lymphoma [68].

3.2.6.3. Nuclear factor kappa-B (NF-κB). Mutations in transcription factors of the Nuclear Factor Kappa-B (NF-κB) family have been increasingly identified in subjects with a CVID-like phenotype. First described were autosomal dominant, heterozygous *NFKB2* mutations (OMIM: 164012), which led to early onset hypogammaglobulinemia with recurrent infections, autoimmunity in some, but more commonly, endocrine abnormities were found [69]. Mutations in *NFKB1* (OMIM: 164011) appear to be rather common in subjects with a CVD-like phenotype, which also lead to a quite variable form of autosomal dominant antibody deficiency with autoimmunity, unusual infections and lymphoproliferative disease in some [70].

4. Hyper IgM syndrome: severe reduction in serum IgG and IgA with normal/elevated IgM and normal B-cell numbers.

Class-switch recombination (CSR) occurs downstream of T-cell dependent B-cell activation in germinal centers. Activated follicular B-cells receive help from cognate T follicular helper cells to undergo CSR and somatic hypermutation (SHM). Eventually, CSR and SHM result in high-affinity antibody production and the differentiation of B-cells into long-lived memory B-cells and plasma cells [71]. Immunoglobulin class switch recombination deficiencies, previously termed “hyper-IgM syndromes (HIGM)” are rare primary immunodeficiencies characterized by impaired production of switched immunoglobulin isotypes and normal or elevated IgM levels.

Some of the CSR deficiencies are caused by defects in CSR machinery and are predominately intrinsic B-cell defects, which include mutations in activation-induced cytidine deaminase (AID) and uracil-DNA glycosylase (UNG) [72]. In contrast, CD40 ligand (CD40L) and CD40 deficiencies are combined immune defects with impaired interaction between activated $CD4^+$ T-cells expressing CD40L and cell types expressing CD40 which include B-cells, dendritic cells, monocytes/macrophages, platelets, and activated endothelial/epithelial cells.

4.1. CD40L

Aruffo and colleagues mapped the CD40L gene to Xq26 [73], a region to which the clinical phenotype of the hyper-IgM syndrome type 1 (OMIM: 300386) had been mapped. CD40L on activated T-cells and cognate interactions with CD40 on B-cells results in B-cell proliferation, adhesion, and finally, differentiation. CD40L deficiency, which is inherited as an X-linked trait, is the most common form of HIGM, estimated frequency is 2:1,000,000 males [74]. CD40L deficiency often presents in infancy with increased susceptibility to recurrent sinopulmonary infections, primarily caused by encapsulated bacteria *Streptococcus pneumoniae* and *Haemophilus influenza*. In addition, patients are at a higher risk of developing early in life opportunistic infections, which include *Pneumocystis*, *Cryptosporidium*, and *Histoplasma* organisms. Patients can often have chronic and recurrent diarrhea. Infection with *Cryptosporidium parvum* is common and is associated with an increased risk of biliary tract diseases, including sclerosing cholangitis and cholangiocarcinoma [75]. Liver complications due to chronic viral hepatitis and cytomegalovirus (CMV) infections have been reported [75]. Cases of central nervous system infections with *Cryptococcus* and *Toxoplasma* infections have been reported as well as JC virus-related enteroviral meningoencephalitis and progressive multifocal leukoencephalopathy (PML) [74,76].

Mucosal disease is also common in CD40L deficiency such as recurrent oral ulcers and proctitis, often associated with chronic or cyclic neutropenia in half of patients [77]. Fewer cases of autoimmune complications have been reported and include thrombocytopenia and autoimmune hemolytic anemia [77]. Patients with CD40L deficiency also have an increased risk of malignancies of hepatobiliary origin including hepatocarcinoma, cholangiocarcinoma, peripheral neuroectodermal tumors of the gastrointestinal tract and with a lesser incidence of lymphoma [74,75]. Overall, long-term survival may be poor, due to early in life *Pneumocystis carinii* pneumonia, liver disease and/or malignancy [77].

4.2. CD40

Recessive mutations in the B-cell surface receptor CD40 (OMIM: 109535) leading in most cases to absence of surface expression, are additional but very rare causes of the HIGM phenotype with only few cases reported. CD40 deficiency has been described in patients with similar clinical features as CD40L deficiency including severe bacterial and opportunistic infections [78].

4.3. Activation induced cytidine deaminase (AID)

AID, a 198-amino acid 24 kDa protein encoded by the *AICDA* gene (OMIM: 605257) located on chromosome 12p13, deaminates deoxycytidine to deoxyuracil, which is a physiologic trigger for the base-excision repair pathway leading to the generation of DNA breaks which is required for CSR and SHM [79]. AID is only expressed in activated B-cells. Defects in function of AID protein are most often inherited as autosomal recessive with reports of autosomal dominant mutations in the nuclear export signal [80]. Patients can have symptoms as early as 2-years-old, however, diagnosis can be delayed by decades [81]. As for AID defects, patients have bacterial infections, mostly due to encapsulated bacteria. Other infectious complications include meningitis, cellulitis, lymphadenitis, and gastrointestinal infections mainly due to viruses and to *Giardia lamblia*. Unlike CD40L deficiency, patients with AID deficiency have enlargement of lymphoid organs such as the spleen, tonsils, and lymph nodes with reports of autoimmunity [82]. Autoimmune complications have been reported in patients and include cytopenias, hepatitis, inflammatory bowel disease, and arthritis [83].

4.4. Uracil-DNA glycosylase (UNG)

UNG, the enzyme that removes uracil on single-stranded DNA after deamination of deoxycytidine to deoxyuracil by AID, is required for CSR and SHM to generate high-affinity antibodies [84]. As for AID deficiency, UNG deficient B-cells cannot undergo CSR despite CD40-mediated activation. UNG deficiency (OMIM: 191525) is inherited as autosomal recessive and only few cases have been described [85].

Clinically, UNG deficiency is indistinguishable from AID deficiency, both of which defects leads to absence or very low levels of IgG, IgA associated with normal or elevated serum IgM levels [82].

5. Isotype, light chain, or functional deficiencies with generally normal numbers of B-cells

5.1. Selective IgA deficiency (SIGAD)

Selective IgA deficiency is the most common primary antibody deficiency, with worldwide incidence varying depending on the ethnic background (1:143 to 1:18,500) [86]. It affects males and females equally and is defined as a serum IgA level of less than 7 mg/dl and normal levels of serum IgG and IgM in a patient older than 4 years old [87]. Primary IgA deficiency must be distinguished from secondary causes due to medications such as anticonvulsants (phenytoin, carbamazepine, valproic acid), disease-modifying anti-rheumatic drugs (sulfasalazine, hydroxychloroquine), non-steroidal anti-inflammatory drugs and others [88]. Although an underlying gene defect has not been identified in SIGAD, impaired switching to IgA or a failure of IgA producing B-cell maturation into IgA secreting plasma cells has been intensively investigated. Clinically, two-third of patients with SIGAD remain asymptomatic [89], whereas symptomatic patients suffer from allergies, recurrent sinopulmonary and mucosal infections [90], both infectious and non-infectious gastrointestinal diseases [91] and gastrointestinal and lymphoid malignancies [92]. Autoimmunity also appears to also be increased [93]. While the pathophysiology of SIGAD remains unknown, associations with selected major histocompatibility (MHC) alleles and higher frequency within families with autoimmunity or other immune defects have been reported [94]. Patients with SIGAD have progressed to CVID, suggesting further monitoring.

5.2. IgG subclass deficiency with and without IgA deficiency

Human IgG is subdivided into four subclasses, IgG1, IgG2, IgG3 and IgG4, each encoded by a separate constant (C) region genes on chromosome 14 and constitute 65%, 25%, 7%, and 3% of total serum IgG, respectively [95]. Immunoglobulin heavy chain deletions (*IGHC*, OMIM: 147100) are autosomal recessive defects caused by chromosomal deletions of portions of the IgG heavy chain locus at 14q32. One or more IgG and/or IgA subclasses as well as IgE may be absent. Deletion of IgM is not involved. Ig heavy chain deletions are generally asymptomatic and do not require treatment, however, individuals can also present as an isotype deficiency, depending on the deleted part of the Ig locus. However, in most cases, IgG subclass deficiency not due to genetic defects were first described in 1970 [96], and is defined as an abnormally low level (2 standard deviations below the age-adjusted norm) of one or more IgG subclasses with an otherwise normal total IgG level [97]. The most common IgG subclass deficiency is IgG4 deficiency (40%), followed by IgG2 (28%), IgG3 (17%) and IgG1 deficiency (14%) [88]. IgG subclass deficiencies can be associated with other primary immunodeficiencies and other conditions such as atopic disorders, chronic airway diseases or autoimmunity. However, in the population, 2–20% of healthy individuals have lower than normal level of one or more IgG subclasses [98]. Thus, the clinical significance of IgG subclass deficiency in patients with recurrent infections is unclear. IgG subclass deficiency alone is generally not considered sufficient for a diagnosis of immunodeficiency unless antibody responses to vaccines or to natural exposure are also documented [97]. IgG subclass deficiency (especially IgG2) may be associated with IgA deficiency. Determination of IgG subclasses may be useful in patients with selective IgA deficiency with recurrent sinopulmonary infections, as IgG2 deficiency and impaired polysaccharide responses are found in approximately 10% of patients [97].

5.3. Selective IgM deficiency

Selective IgM deficiency (SIgMD) is a very rare immune disorder in which no serum IgM is detected and other isotypes are preserved. While it has been occasionally reported, the causes are unknown [99].

5.4. Kappa (κ) chain deficiency

Kappa (κ) light chain deficiency (*IGKC*, OMIM: 147200) is a quite rare autosomal recessive disease caused by mutations in Ig kappa (Igκ) constant region located on chromosome 2p11. κ light chains represent two-thirds of the light chains of total immunoglobulins, both circulating and surface bound on lymphocytes. The pathogenesis of the disease is failure to express κ chains and as a result all immunoglobulin molecules express only lambda (Igλ) light chains, but the reason is unknown [100]. Although this disease could be seen in association with other conditions, it can be asymptomatic. Deficiencies of Igκ have been reported in a few individuals with immune deficiencies [101].

5.5. Specific antibody deficiency with normal Ig levels and normal B-cells

Specific antibody deficiency (SAD) is characterized in patients over 2 years old who present with recurrent infections and are found to have impaired antibody response to polysaccharide antigens with usually intact protein antigen response, normal concentrations of immunoglobulins and IgG subclasses [102]. The prevalence of SAD is not well known as studies have estimated between 5 and 20% in children and adults [103]. The pathophysiology of this disorder is not established but there are studies suggesting a B-cell repertoire defect or defective splenic marginal zone interactions [104]. Clinically, patients with SAD have increased susceptibility to recurrent bacterial sinopulmonary and a subset of patients have a history of allergy, particularly allergic rhinitis [105]. In young children, repeat antibody testing is recommended at yearly intervals because spontaneous recovery can occur, however, symptomatic adults should be followed periodically for progression towards IgG subclass deficiency or CVID.

5.6. Transient hypogammaglobulinemia of infancy

By definition, patients with transient hypogammaglobulinemia of infancy (THI) have low IgG levels (2 standard deviations below the mean for age-match controls) with possible involvement of IgA and less frequently IgM [98] that spontaneously return to normal, usually within 2–3 years of age. However, the timing of normalization often varies [106]. Most subjects with THI remain asymptomatic, however in some patients, it can be associated with a higher rate of recurrent infections, especially of the upper respiratory tract. The pathophysiology of THI is unknown, however, a prospective study of infants with hypogammaglobulinemia showed that those with a low number of memory B-cells and inability to produce IgG *in vitro* were associated with persistence of hypogammaglobulinemia and an increased risk of infection beyond 2 years of age [106]. If THI is suspected, evaluation should include specific antibody responses to age-appropriate vaccines and flow cytometric quantitation of lymphocyte subsets to exclude more substantial immune defects. Specific antibody responses are often intact in patients with THI. As the name implies, the disease is self-limited and patients should be monitored over time until levels have normalized. However, medical intervention is indicated for some patients during this period and in others, the defect may be a harbinger to a more permanent immune defect [106].

6. Diagnosis

Diagnosing a primary B-cell defect relies first on clinical history and then on confirmatory laboratory evaluations. This includes a detailed family and infection history, age of onset, frequency and duration of

treatments and if known, organisms that might suggest a primary B-cell defect or a combined B- and T-cell immune defect. Laboratory evaluations include complete blood counts, full lymphocyte panels for T-cell, B-cell, and NK-cell subsets, quantitative serum immunoglobulin levels (IgM, IgG, IgA and IgE where indicated) and evaluation of specific antibody responses to both protein and polysaccharide antigens [98]. Interpretation of immunoglobulin levels should factor in the age of the patient. IgG subclasses can be useful but in general are interpreted only with regard to results of vaccine responses. Immunophenotyping of B- and T-cells is also a useful adjunct for subcategorization, prognostication and management [98]. Gene sequencing is commercially available for many of the known gene defects and include primary antibody deficiency panels. Molecular diagnosis can be important for treatment optimization and for accurate genetic counseling.

7. Treatment

The management of primary B-cell immunodeficiencies focuses largely on the prevention and treatment of infections and secondarily on controlling any complications that may develop. Adequate antibody replacement therapy for those with documented loss of functional IgG is key, with intravenous or subcutaneous immune globulin formulations being the primary cornerstone in the care of patients. Microbial therapy is used as needed for acute treatment, and in some cases, chronic antibiotic prophylaxis. For non-infectious complications associated with more severe B-cell defects such as chronic lung disease, gastrointestinal disease, autoimmunity and malignancy, surveillance and monitoring for disease progression continues to be an essential part of a multidisciplinary management; treating such complications early is critical.

Immunosuppressive, anti-inflammatory, cytotoxic, and anti-neoplastic therapies are all used for the treatment of autoimmune or malignant complications of primary B-cell defects. Newer therapies targeting defective pathways are becoming more widely accepted in practice. Current treatment strategies for select B-cell defects with immune dysregulation are prime examples. In addition to supportive therapy and immunosuppressive treatments, patients with APDS have benefited from treatment with rapamycin, used for targeted therapy to inhibit the biologically relevant downstream PI3K effector mechanistic target of rapamycin (mTOR) pathway [67,107]; however, course of treatment has not been free of off-target side effects. Emerging evidence for the use a selective PI3Kdelta inhibitor (Leniolisib/CDZ173) in APDS-causative p110delta variants is on the horizon [108]. Another example includes CTLA4-fusion protein replacement (Abatacept and Belatacept) used in reversing life-threatening infiltrative and autoimmune disease in CTLA4 and LRBA deficient patients [62,107,109]. Continued clinical studies are necessary to determine the effectiveness and safety of these targeted therapies.

Hematopoietic stem cell therapy (HSCT) has been regularly employed to treat a growing spectrum of immunodeficiencies and should be sought for combined immunodeficiencies and considered as a treatment option for patients with genetic mutations that lead to an impaired immune response. The mainstay of treatment for primary B-cell defects remains immunoglobulin replacement, however, in CD40L deficiency, the only curative option is HSCT, in which one of the biggest cohort achieved a cure rate of 58% [110]. Allogeneic stem cell transplantation has been used as a treatment option for CVID patients whose specific defect is known and it is clear that donor T- and B-cell engraftment can correct the defect with the intended to correct other manifestations, such as malignancy, treatment-refractory immune dysregulation or severe lung/gastrointestinal inflammatory disease [111,112]; however, experience is very limited. HSCT appears to be a treatment option for patients with severe APDS [67,113], severe immune dysregulation in CTLA4 mutation carriers [107,114] and LRBA deficient patients [60,115]. With growing indications for HSCT in primary immunodeficiency, a careful discussion of the risk/benefit ratio should take place despite potential benefit for whom conventional.

8. Conclusion

Murine models have illustrated the most basic principles of B-cell biology, but what is most solidly known for human B-cell immunity, has often been based on studies of primary immunodeficiencies (PID). X-linked agammaglobulinemia permitted the elucidation of cytoplasmic tyrosine kinase BTK, crucial for maturation of mature B-cells. Defects of all of the components of the BCR result in autosomal agammaglobulinemia, demonstrating that continuous BCR signals are essential for the maintenance of mature B-cell populations; similarly, the integrity of the BAFF receptor is essential [47,116]. Recessive mutations of CD19, CD20, CD81 and CD21 receptors required for amplification of BCR signaling, lead to versions of common variable immune deficiency (CVID) [53–56]. The X-linked HIGM syndrome revealed that CD40L is essential for Ig class switch, germinal center formation, and $CD27^+$ memory B-cells. Other HIGM defects illustrate the additional requirements for these functions: CD40, AID and UNG deficiency, PIK3R1 and INO80 chromatin remodeling complex [46,65,117,118]. Earlier work centered primarily on the adaptive immune system, but in the past decade, identifying mutations of genes of innate immunity, such as the Toll Like receptor and IL-1 Receptor signaling pathways (e.g. IRAK4, MyD88, UNC93B, TLR3), selected cytokines and receptors have illustrated that these defects lead to serious and curiously characteristic infectious diseases [119,120]. At the same time, these advances suggested important avenues for therapy [121]. While the field of PID has experienced remarkable advances in understanding the pathogenesis of some B-cell defects, from the point of view of the practicing immunologist, genetic and immunological exploration of the most common of these, CVID, IgA deficiency, Ig subclass and selective antibody deficiency, has only just begun. The advent of next-generation sequencing has greatly facilitated the search for novel genetic diseases [122,123], and our recent work has demonstrated that these methods can identify causative genes for the antibody defects being studied in this program [124].

Disclosure information

T. Smith and C. Cunningham-Rundles have no relevant conflicts of interest to disclose.

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