REVIEW

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Autoimmunity as a continuum in primary immunodeficiency

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Purpose of review
Primary immunodeficiency disorders (PIDs) are no longer defined by infections alone. First clinical sign or sequelae of PID may include autoimmunity, such as cytopenias, arthritis or enteropathy. This review addresses the latest in multidisciplinary approaches for expanding clinical phenotypes of PIDs with autoimmunity, including new presentations of known entities and novel gene defects. We also discuss diagnostic tools for identifying the distinct changes in immune cells subsets and autoantibodies, mechanistic understanding of the process, and targeted treatment and indications for hematopoietic stem-cell transplantation (HSCT).

Recent findings
In the past years, increased awareness and use of genetic screening, confirmatory functional studies and immunological biomarkers opened the door for early recognition of PIDs among patients with autoimmunity. Large cohort studies detail the clinical spectrum and treatment outcome of PIDs with autoimmunity with specific immune genes (e.g., *CTLA4*, *LRBA*, *PI3Kδ*, *NFKB1*, *RAG*). The benefit of early recognition is initiation of targeted therapies with precise re-balancing of the dysregulated immune pathways (e.g., biologicals) or definitive therapy (e.g., HSCT).

Summary
Clinical presentation of patients with PID and autoimmunity is highly variable and requires in-depth diagnostics and precision medicine approaches.

Keywords
autoimmunity, immune dysregulation, primary immunodeficiency, targeted therapy, tolerance

INTRODUCTION

Primary immunodeficiencies (PIDs) are no longer defined by tendency for infections alone. PID patients with noninfectious complications are increasingly recognized with features of 'immune dysregulation' including autoimmunity, inflammation, lymphoproliferation or malignancy (Fig. 1) [1].

However, identifying an underlying PID in a heterogenous group of patients with a variety of autoimmune disorders can be a daunting task. Most pediatricians or specialists taking care of patients with autoimmune disorders may not consider immune evaluation in the initial workup and assume low probability. Therefore, it is not uncommon that the specific diagnosis of highly vulnerable patients with genetic immune deficiency disease is delayed.

In this review, we will focus on recent understanding of the most common clinical entities with PID where autoimmune complications dominate and highlight features that may distinguish these patients from the general population of autoimmune patients. We will also introduce a basic description of immune and genetic diagnostic tools that are essential for understanding the underlying immune defect. We will discuss the pathomechanism of autoimmunity in immune-deficient background, including both intrinsic and extrinsic factors. Lastly, we will

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KEY POINTS

- PIDs are no longer defined by infections alone: autoimmunity, such as cytopenias or early-onset inflammatory bowel disease can be first clinical signs.
- Accumulation of multiple autoimmune manifestations with age 'and family history of variable clinical presentation of immune dysregulation' should increase clinical suspicion for underlying PID.
- Autoimmunity in PID emerges secondary to altered balance in immune pathways shaped by intrinsic and extrinsic factors that generate and/or sustain survival of autoreactive clones of lymphocytes.
- With the revolution of early genetic screening, specialties following patients with immune dysregulation can diagnose an underlying PID in increasing numbers.
- Treatment of PID patients with autoimmunity is most successful with narrow-spectrum immune modulation using biologicals specifically targeting immune pathways.
- Allogeneic HSCT and autologous HSCT with gene therapy are considered for genetically defined PID with autoimmunity and poor prognosis.

cite current literature on the decision-making process for targeted therapy and importance of a multidisciplinary approach for autoimmune disorders.

INCREASING AWARENESS FOR AUTOIMMUNITY: THE JANUS FACE OF PRIMARY IMMUNODEFICIENCY DISORDER

In the latter half of the 20th century, two rare classical endocrine monogenic autoimmune disorders were described. These two very early onset disorders are specific defects in regulatory T cells and/or elimination of autoreactive T cells, and are known as the syndromes of IPEX (immunodysregulation, polyendocrinopathy, enteropathy, X-linked) and APECED (autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy) (Fig. 2). APECED and IPEX are examples when pediatricians partnered in a multispecialty approach with endocrinologists and gastroenterologists for the care for complex monogenic autoimmune diseases. Once the underlying immune defect of autoimmune regulator (AIRE) (causing APECED) [2,3] and forkhead box P3 (FOXP3) (causing IPEX) [4,5] were discovered in 1997 and 2000 respectively, studies were initiated for insight into the disease biology, which informed clinical immunologists for both diagnosis and management of large numbers of patients [6] and eventually enabled transplant specialists to justify the use of HSCT for IPEX cases [6,7]. Similarly, clinical and research collaboration between pediatric hematologists/oncologists and immunologist began to properly care for patients with persistent multilineal cytopenias, lymphoproliferation, and tendency for malignancy with defects in immune cell apoptosis now termed as ALPS (autoimmune lymphoproliferative syndrome). Once genetic defects, biomarkers, and pathomechanism were better understood, diagnostic approaches and targeted therapies were developed successfully [8].

The need for a multidisciplinary approach for immune dysregulation among patients with autoimmunity continues on. Beyond IPEX, APECED, and ALPS, disorders with similar presentations ('IPEX- or ALPS-like') but different genetic causes have been steadily resurfacing (Fig. 2). This group of Mendelian multiorgan autoimmune diseases are now coined as primary immune regulatory disorders (PIRD) with subgroups of dominantly regulatory T-cell defects (T-regopathies) [9], and late-onset or profound combined immunodeficiency disorders (LoCID, P-CID) [10,11] where both T and B cells compartments are intrinsically autoimmune prone (Fig. 2). An excellent case-based review by Chandrakasan *et al.* [12▪] brings us close to the stories of immune dysregulation in PID patients with intricacies on the varying features of IPEX, ALPS, and/or LoCID-like disease. This report highlights the fact that isolated clinical autoimmune manifestations present early (even before infections) and the clinical course worsens with age [12▪].

A recent French national study, which is the largest to date and includes all types of PID and autoimmune manifestations, has been published by Fischer *et al.* [13▪▪]. One or more autoimmune and inflammatory manifestations were noted in 26.2% of 2183 retrospectively screened PID patients. In particular, immune manifestation of dysregulation, such as autoimmune cytopenias, enteropathy, and skin disease, occurred in 50% of PID patients with T-cell deficiency (CID) by 40 years of age and 10–30% of children below 18 years of age depending on the underlying immunodeficiency (innate, B-cell or T-cell defects). The study highlighted increased risk for autoimmune hemolytic anemia (AIHA) (830 times), inflammatory bowel disease (80 times), and arthritis (40 times) in children with PID compared with the general population. Although autoimmune manifestations occurred in patients with all types of PIDs, those with T-cell defects or common variable immunodeficiency (CVID) tended to have the highest risk for autoimmunity. Overall, this study well demonstrates that autoimmunity is a significant component of clinical presentation of all types of PIDs [13▪▪].

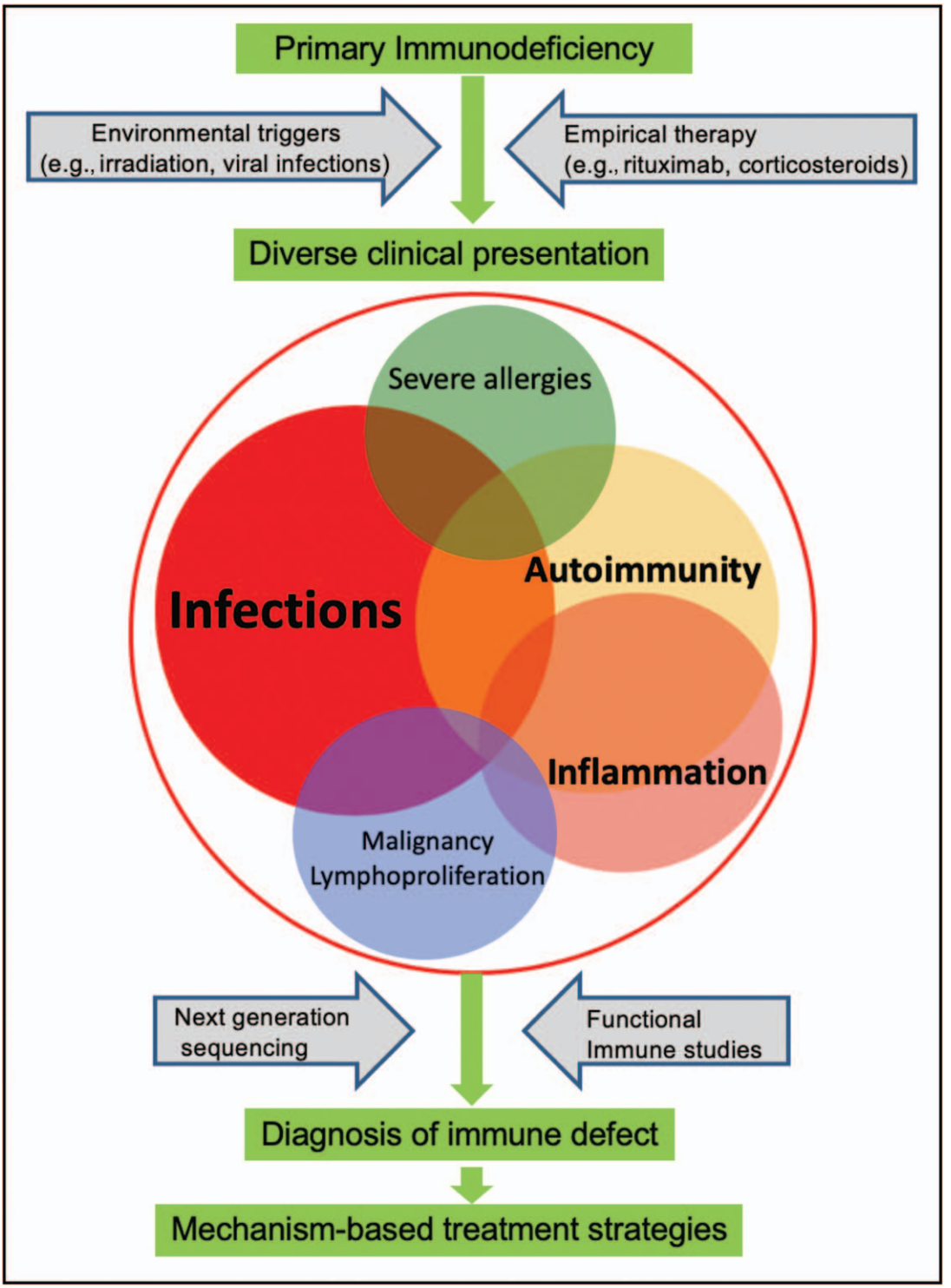
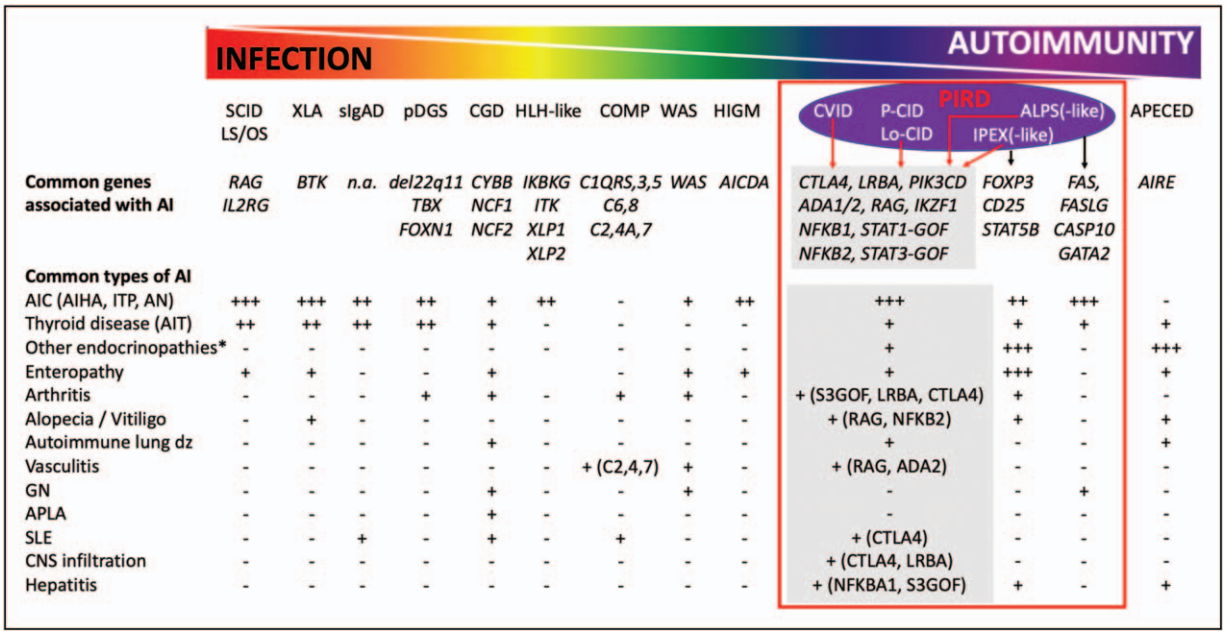


FIGURE 1. Precision medicine therapy for the diverse disease spectrum of primary immunodeficiency (PID). The variable clinical presentation of PID is influenced by environmental triggers as wells as empirical therapy. For instance, rituximab therapy eliminates B cells and thus reduces autoantibodies but also increases risk of infections, whereas viral infections can stimulate dysregulated B cells and result in autoimmunity. The use of next-generation sequencing and functional immune studies can identify the precise molecular basis of disease and enable optimal treatment which targets the molecular defect and minimizes adverse effects.

Clinically the most vulnerable group of young patients with PID and autoimmunity are those with reduced but not absent T-cell immunity. Unlike in severe combined immunodeficiency (SCID), these patients with LoCID and P-CID may only emerge after external triggers (viral infections or live



	SCID LS/OS	XLA	sIgAD	pDGS	CGD	HLH-like	COMP	WAS	HIGM	CVID / P-CID / Lo-CID / PIRD / ALPS(-like) / IPEX(-like)	APECED
Common genes associated with AI	*RAG IL2RG*	*BTK*	*n.a.*	*del22q11 TBX FOXN1*	*CYBB NCF1 NCF2*	*IKBKG ITK XLP1 XLP2*	*C1QRS,3,5 C6,8 C2,4A,7*	*WAS*	*AICDA*	*CTLA4, LRBA, PIK3CD ADA1/2, RAG, IKZF1 NFKB1, STAT1-GOF NFKB2, STAT3-GOF* / *FOXP3 CD25 STAT5B* / *FAS, FASLG CASP10 GATA2*	*AIRE*
Common types of AI											
AIC (AIHA, ITP, AN)	+++	+++	++	++	+	++	-	+	++	+++ / ++ / +++	-
Thyroid disease (AIT)	++	++	++	++	+	-	-	-	-	+ / + / +	+
Other endocrinopathies*	-	-	-	-	-	-	-	-	-	+ / +++ / -	+++
Enteropathy	+	+	-	-	+		-	+	+	+ / +++ / -	+
Arthritis	-	-	-	+	+	-	+	+	-	+ (S3GOF, LRBA, CTLA4) / + / -	-
Alopecia / Vitiligo	-	+	-	-	-	-	-	-	-	+ (RAG, NFKB2) / + / -	+
Autoimmune lung dz	-	-	-	-	+	-	-	-	-	+ / - / -	+
Vasculitis	-	-	-	-	-	-	+ (C2,4,7)	+	-	+ (RAG, ADA2) / - / -	-
GN	-	-	-	-	+	-	-	+	-	- / - / +	-
APLA	-	-	-	-	+	-	-	-	-	- / - / -	-
SLE	-	-	+	-	+	-	+	-	-	+ (CTLA4) / - / -	-
CNS infiltration	-	-	-	-	-	-	-	-	-	+ (CTLA4, LRBA) / - / -	-
Hepatitis	-	-	-	-	-	-	-	-	-	+ (NFKBA1, S3GOF) / + / -	+

FIGURE 2. The genetic basis for infections versus autoimmunity (AI) within PIDs. An inverse gradation of infectious and autoimmune complications exists for different primary immunodeficiencies. For example, SCID patients with complete RAG deficiency or loss of IL2RG function are plagued with infections but minimal autoimmunity whereas APECED have high autoimmunity but relatively few infections. Multiple primary immune dysregulation disorders (PIRD) can be caused by the same set of genetic mutations although particular mutations favor specific diseases such as FOXP3 mutations causing IPEX-like disorder. ∗Other endocrinopathies include Addison's disease, type 1 diabetes mellitus, adrenal corticotropic hormone insufficiency, and growth hormone deficiency. *COMP*, complement defects; *ADA1/2*, adenosine deaminase 1 and 2; *AIC*, autoimmune cytopenia; *AICDA*, activation induced cytidine deaminase; *AIHA*, autoimmune hemolytic anemia; *AIRE*, autoimmune regulator; *AIT*, autoimmune thyroid disease; *AN*, autoimmune neutropenia; *ALPS*, autoimmune lymphoproliferative syndrome; *APECED*, autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy; *APLA*, antiphospholipid antibodies; *BTK*, Bruton tyrosine kinase; *CASP10*, caspase 10; *CD25*, cluster of differentiation 25 (interleukin-2 receptor α chain); *CGD*, chronic granulomatous disease; *CNS*, central nervous system; *CVID*, common variable immunodeficiency; *CTLA4*, cytotoxic T-lymphocyte antigen 4; *CYBB*, cytochrome B-245 β chain; *FAS*, FS-7 associated surface antigen; *FASLG*, FAS ligand; *FOXN1*, forkhead box N1; *FOXP3*, forkhead box P3; *GATA2*, GATA binding protein 2; *GN*, glomerulonephritis; *HIGM*, hyperimmunoglobulin M syndrome; *HLH*, hemophagocytic lymphohistiocytosis; *IKBKG*, inhibitor of nuclear factor κ B kinase subunit gamma; *IKZF1*, IKAROS family zinc finger 1; *IL2RG*, interleukin-2 receptor gamma subunit; *ITP*, immune thrombocytopenia; *LS*, leaky severe combined immunodeficiency; *Lo-CID*, late-onset combined immunodeficiency; *LRBA*, lipopolysaccharide responsive beige-like anchor protein; *NCF1/2*, neutrophil cytosolic factor 1 and 2; *NFKB1/2*, nuclear factor κ B subunits 1 and 2; *OS*, Omenn syndrome; *P-CID*, profound combined immunodeficiency; *pDGS*, partial DiGeorge syndrome; *PIK3CD*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta; *RAG*, recombinase activating gene; *SCID*, severe combined immunodeficiency; *sIgAD*, secretory immunoglobulin A deficiency; *SLE*, systemic lupus erythematosus; *STAT5B*, signal transducer and activator of transcription 5B; *STAT1/3-GOF* (*S1/3GOF*), signal transducer and activator of transcription 1 and 3 gain-of-function mutations; *TBX*, T-box transcription factor; *WAS*, Wiskott Aldrich syndrome; *XLP1/2*, X-linked lymphoproliferative disease 1 and 2; *XLA*, X-linked agammaglobulinemia.

vaccinations) have delayed diagnosis and may not be identified by newborn screening for SCID that is now implemented nationwide in the United States. Speckmann *et al.* [11] have published an interim analysis of an international prospective study on natural history of 51 patients with P-CID. The age of diagnosis was delayed as late as 15 years of age, especially among those with undefined genetic cause. Curiously, within the first year of clinical presentation, over 50% of patients presented with signs of immune dysregulation and autoimmunity, especially autoimmune cytopenias (21%), which was a dominant feature and continued throughout their life [11]. Importantly, severe events of immune dysregulation resulted in hospitalizations in over half of the P-CID cases. Although autoimmune cytopenias are often dominant in the first clinical presentation, patients may eventually progress to autoimmune enteropathy, interstitial lung disease with or without granulomas or develop arthritis, alopecia, and lesions in the central nervous system. Two brief reports by Goda *et al.* [14] and Wu *et al.*

[15] illustrates well the autoimmune clinical presentation of young children with P-CID secondary to partial deficiency of recombinase activating gene (RAG). In the first case, the infant developed autoimmune thrombocytopenia (ITP) after varicella infection prompted the clinicians to screen for immunological biomarkers and genetic cause for presumed P-CID [14]. The second case describes a child with history of Kawasaki-like disease, arthritis, and alopecia followed by infections [15]. Both cases highlighted the importance of immune evaluation and biomarkers, to promote early genetic diagnosis in children who have early-onset autoimmune disease [14,15].

With the advance of genetic testing, we have the ability to group PIRD patients based on the underlying immune defect (Fig. 2). In recent years, several large studies have published on clinical characteristics of specific PIRD cohorts, in particular those with cytotoxic T-lymphocyte-associated antigen 4 (CTLA4), lipopolysaccharide (LPS)-responsive and beige-like anchor protein (LRBA), nuclear factor κ-light-chain-enhancer of activated B cells 1 and 2 (NFκB1/NFκB2), activated phosphoinositide 3-kinase delta syndrome (APDS) and hypomorphic (partial) RAG and adenosine deaminase 2 (ADA2) deficiencies.

An international cohort of 133 patients with CTLA4 deficiency [16▪▪] shows unprecedented diversity of first symptoms of presentation including autoimmune cytopenia (33%), respiratory manifestations (21%), enteropathy (IBD) (17%), type 1 diabetes (T1DM) (8%), neurological symptoms (seizures, headache, and nausea; 6%), and in less than 5% of cases autoimmune thyroid disease (AIT), arthritis, alopecia, primary biliary cirrhosis and Addison disease. Only 61% of cases had history of infections (bacterial disease, herpes reactivation, and tuberculosis). Most autoimmune manifestations (cytopenia, gastrointestinal, and lung disease) were progressive and severe. Unlike other patients with CVID, there were a high fraction of cases (28%) with involvement of the central nervous system (CNS) either secondary to lymphocytic infiltration or hematological cause (e.g., bleeding, ischemia secondary to anemia, thrombosis). Beside the presence of multiple autoimmune disorders, CNS involvement may be a clinical diagnostic clue for CTLA4 deficiency. As inheritance is autosomal dominant, subsequent generations may be involved with variable penetrance of the clinical disease.

A systematic review of clinical features of 109 cases with LRBA deficiency also highlighted that the first presentation was often autoimmunity (42%) [17▪]. Multiple autoimmune diseases occurred in 77% of patients, which were dominated by AIHA and ITP, followed by T1DM, AIT and IBD. Infections (16%) and chronic diarrhea (27%) were less frequent first signs of disease manifestation of PID. The primary clinical diagnosis of these LRBA deficient patients were CVID (43%), autoimmunity (28%), ALPS-like (8%), IPEX-like PID (7%), and LoCID (4%) [17▪]. Lastly, a systematic review of 243 APDS patients also had autoimmune complications (28%); however, infections and lymphoproliferation (70%) were more dominant [18▪].

In the LoCID group, loss-of-function NFκB1 variants were published as most common monogenic cause of CVID in Europeans [19▪▪]. Common clinical features included massive lymphadenopathy (24%), unexplained splenomegaly (48%), and autoimmune disease (48%) mainly AIHA and ITP, followed by alopecia, vitiligo, and AIT were also associated with worse prognosis. Among CID patients with immune dysregulation and hypomorphic SCID-associated genes, partial RAG deficiency tends to be the most common genetic cause. Two recent reports summarize the clinical presentation and treatment outcome of autoimmune complications. Both Delmonte *et al.* [20▪] and Farmer *et al.* [21▪] report broad clinical autoimmune presentations including autoimmune cytopenias, vitiligo, alopecia, vasculitis, and neurological disease. Farmer *et al.* [20▪] showed that there is significant delay in molecular diagnosis (5 years or more) and often clinical decision for HSCT is made before full understanding of underlying cause. Overall, both studies emphasize that optimal bridge therapy is yet to be defined among partial RAG deficient patients [20▪,21▪].

Unique cohorts are now described with ADA2 deficiency and may also present with CVID-like disease [22]. This is the first monogenetic vasculitis syndrome with highly pleiotropic clinical features of autoinflammation, autoimmunity (ITP, arthritis), vasculopathy, vasculitis and strokes [22,23]. Some of the earliest onset PIRDs are those with *STAT3* gain-of-function (GOF) or *NFκB2* variants. As high as 80% of NFκB2 deficient patients develop autoimmunity (alopecia, arthritis, cytopenia) with unique features of adrenocorticotropic hormone deficiency (44%) [24]. Fabre *et al.* [25] have published a comprehensive review of 42 children with STAT3 GOF pathogenic variants and very early onset autoimmunity (0.5–5 years of age) including cytopenias, interstitial lung disease, and endocrine complications (diabetes, thyroiditis, and growth failure). Lastly, Chinn *et al.* [26] have summarized in an excellent comprehensive review of the genetic causes of specific clinical autoimmune presentations among patients with PIDs managed by multiple specialists (hemotologist, endocrinologist, dermatologist).

In summary, PIRD groups with specific gene defects share similar features (IPEX, ALPS, CVID/CID-like) with combinations of multiple autoimmune diseases. Referral to the immunologist and diagnosis of PID is often delayed as the presenting symptoms are often autoimmunity-related with no significant history of infections.

GENETIC AND IMMUNOLOGICAL DIAGNOSTIC TOOLS

A genetic revolution has occurred in recent years regarding PID diagnosis. Panels with 200–300 PID genes are now more affordable and broadly available on clinical grounds. These panels are helpful to identify the most common PIDs linked to autoimmunity and discover 'new face of old disorders' (such as RAG deficiency). However, the quest often needs to continue in 'PID-panel' negative cases with whole exome and/or genome sequencing approaches as novel genes are being discovered. For example, Fernandez *et al.* [27▪] recently described a homozygous *IL2RB* pathogenic variant from two infant siblings, which manifested as multisystem autoimmunity (enteropathy, lymphocytic interstitial pneumonitis, Coombs+) and susceptibility to cytomegalovirus (CMV) infection. There are specific clinical target groups with autoimmunity where genetic testing proved to be fruitful. Among pediatric patients with Evans syndrome, there is a high probability of finding an underlying PID based on recent studies from France [28▪▪,29]. In a prospective cohort of 203 pediatric patients with Evans syndrome, 80 patients underwent genetic testing, which revealed 32 (40%) had an underlying pathogenic mutation. The affected genes included *TNFRSF6*, *CTLA4*, *STAT3*, *PIK3CD*, *CBL*, *ADAR1*, *LRBA*, *RAG1*, and *KRAS* [28▪▪]. One of the largest studies on genetic defects in PID patients has been the 'Houston project' by the teams of Jordan Orange and James Lupski (2017). They investigated 278 families from 22 countries by whole-exome sequencing. This project highlighted that 5% of patients had two distinct PID disease genes shaping their clinical and immune phenotype (mixed phenotype). Genes linked to autoimmune diseases spanned several categories (autoimmune disease, CID, CVID, defects of innate immunity) and were identified in more than 23 cases (8%). Genetic causes included *COPA*, *CTLA4*, *FOXP3*, *STAT1*, *STAT3*, *RAG1*, *CCDC40*, *CASP10*, *PLCG2*, *FALG*, and *CBL* [30]. Lastly, an eloquent case report of a mother and child by Le Coz *et al.* [31] highlights CD40L duplication in human autoimmune diseases including autoimmune cytopenias (AICs) and AIT, and discusses the relevance of epigenetic control in disease progression, CD40L overexpression and CD40/CD40L interaction as previously seen in lupus.

In case of variants of uncertain significance, functional studies are needed to confirm the link between the clinical phenotype and genetic findings. Therefore, immunologists and other specialists need to be prepared to initiate evaluation for protein expression and function such as CTLA4 or LRBA expression, STAT1 or STAT3 phosphorylation, B or T-cell repertoire or *in vitro* recombination activity testing (RAG and DNA deficiencies). Unfortunately, most of these assays are only available on a research basis in collaboration with expert centers. A practical approach to genetic testing for PID has been recently summarized by the Clinical Immunology Society [32,33].

Immune phenotyping is of utmost importance in identifying or confirming the underlying PID among the heterogenous group of patients with autoimmunity. Immunoglobulin levels can identify patients with CVID and CID, and a simple test of the ratio of naïve and memory T cells (CD45RA/CD45RO) may distinguish those with LoCID or P-CID [10,11,34].

There are specific subsets of T and B cells that have been linked to PID with autoimmunity. These include the expansion of TCRαβ $CD4^{-}CD8^{-}$ (double negative) T cells in ALPS, $CD19^{hi}21^{lo}$ B cells in CVID with autoimmunity, abnormal count of regulatory T cells (Treg) in Tregopathies, Th17 cells in STAT1 GOF patients, and expanding follicular helper T cells (Tfh) in CTLA4 and LRBA deficiency [35▪▪]. Changes in these subsets may also predict progression of autoimmune complications or response to therapy.

Patients with PID tend to have broad selection of autoantibodies as seen in RAG deficiency with AICs [20▪]. Further, in some PIDs, particular antibodies with unique self-reactivity occur and may serve as biomarkers. Beyond antibodies to IFNα, IFNω and IL-12 in patients with partial RAG deficiency [14,36] and APECED [37], Rosenberg *et al.* [38] reported neutralizing anti-IFNα antibodies among patients with IPEX in two large cohorts from Seattle Children's Hospital and San Rafaelle Hospital (Milan, Italy). Anti-IFNω antibodies were recently described in a patient with NFκB2 deficiency after herpes virus infection [39]. In addition, novel autoantibodies against lung-specific bactericidal/permeability-increasing fold-containing protein B1 (BPIFB1) and the potassium channel regulator protein (KCNFG), have been linked to onset of autoimmune pneumonitis in disorders of central T-cell tolerance (APECED, RAG deficiency, and thymoma) [39]. It is intriguing that presence of anticytokine antibodies are also proposed as markers of prognosis in APECED, as they noted negative correlation of anti-IFNα antibodies and the incidence of T1DM [40,41].

PATHOMECHANISM OF AUTOIMMUNITY IN IMMUNE-DEFICIENT BACKGROUND

Many patients with immunodeficiency harbor autoreactive T and B cells secondary to abnormal pruning of naturally occurring polyreactive clones in the bone marrow (B cells) or thymus (T cells). As these autoreactive cells fail central tolerance checkpoints secondary to intrinsic abnormalities, they spill to the periphery. If peripheral tolerance checkpoints are intact, these clones can become dormant. Additional triggers (extrinsic factors) may revive these clones (Fig. 3). In particular, autoreactive B cells have a second chance to undergo somatic hypermuation (SHM) of their B-cell receptor (BCR) during a process known as clonal redemption and lose self-reactivity [42]. If this process is impaired, autoreactive B cells remain activated and convert into plasma cells to generate autoantibodies. In particular, among patients with CVID and AIC, translocated microbiome or its components (e.g., LPS) have been proposed as triggers for self-reactive immunoglobulin heavy chain variable gene segment 4-34 (IgH-V4-34) expressing B-cell clones capable of binding both commensal bacteria and red blood cells [43▪▪]. Likewise, herpes virus infections as triggers are also well described and linked to onset of autoimmune complications [14,20▪]. In many of these patients, germinal centers are hyperplastic but likely inefficient as B cells display low SHM of BCR suggestive of abnormal clonal redemption [43▪▪]. Tfh cells are being recognized as important cellular players in immune dysregulation [44], as overproduction of Tfh cells has been associated with the generation of autoantibodies and autoimmunity. The phenomenon of Tfh expansion has been highlighted in a mouse model [45] and among patients with CVID with AIC [43▪▪], LRBA [35▪▪], CTLA4 deficiencies [46] and APDS [47]. Thauland *et al.* [47] have highlighted the importance of a new pathway for expansion of Tfh cells in APDS, which involved intracellular osteopontin and p85α.

AUTOIMMUNITY INCREASES MORTALITY IN PRIMARY IMMUNODEFICIENCY DISORDER: HOW TO OPTIMIZED TREATMENT

Cunningham-Rundles *et al.* [48] have established high mortality among CVID patients with noninfectious complications. Recently, Farmer *et al.* [49] at Massachusetts General Hospital studied 142 patients with genetically undefined CVID and concluded that both presence of AIHA and/or ITP increase risk of mortality. Similarly, Fisher *et al.* [13▪▪] in the French national study discussed above concluded that any types of PID with autoimmunity have increased mortality and complications post-HSCT. Even carriers can be at risk. Schwab *et al.* [16▪▪] described that both affected CTLA4 patients and their carrier family members ('unaffected' or not seeking medical attention) had decreased survival compared with the general population.

It has been described that many PID patients are seen and receive immune modulatory treatment for immune dysregulation before full evaluation or discovery of the underlying immune defect [20▪]. As

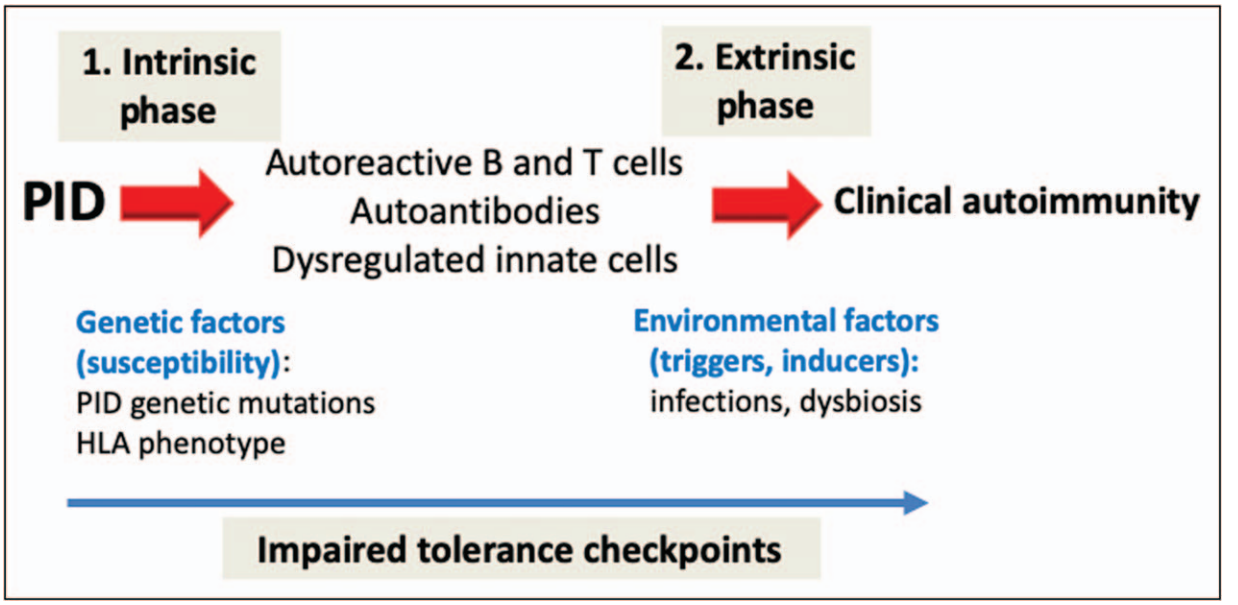


FIGURE 3. Intrinsic and extrinsic phases of autoimmunity in PID. Autoimmunity in PID arises because of impaired tolerance checkpoints resulting from both intrinsic (genetic susceptibility) and extrinsic (environmental) causes.

these treatments result in an altered immune status, it is often unclear to the specialists if immunodeficiency is induced by immune modulation or preexisted before therapy. This enigma can only be resolved if a pathogenic genetic defect causing an aberrant immune response is identified and proven by functional studies (as discussed in the genetic and diagnostic tool section). These variants may result in low (loss of function) or excessive response (gain of function) of a specific immune signaling pathway. The identification of pathogenic genetic defects can facilitate the use of targeted agents specific for the defect or group of defects that share similar pathophysiologic mechanisms.

Immune modulation is a major therapeutic challenge in the PID population and reflects the importance of precision medicine where narrow-spectrum immune modulation delicately balances infectious susceptibility. Most of biologicals are developed and received approval of the Federal Drug Administration for patients with cancer or rheumatologic conditions where safety profile is established (Table 1). In contrast, these biologicals are used off label with unclear safety profile in the PID population. There are excellent recent reviews in the literature discussing targeted therapies for immune dysregulation in PIDs [1,50–54]. Recent cohort studies highlight the use anti-IL-6 receptor and Janus kinase inhibitor biologics in STAT3GOF patients [25], CTLA4 Ig in CTLA4 deficiency [16▪▪], and a small molecule inhibitor, leniolisib, in activated protein I3 kinase delta syndrome (APDS or PI3Kδ) deficiency [55▪]. Monitoring Tfh cells is proposed as a cellular marker to assess control for immune dysregulation [35▪▪]. In patients with deficiency of adenosine deaminase 2 deficiency, TNFα blockade is first-line therapy for vasculopathy and autoinflammation [22,23].

In the era of genetic revolution, genetically defined PID patients with immune dysregulation are increasingly considered for definitive therapy with the ultimate goal to correct the underlying defect, primarily by HSCT. Hematopoietic stem cells (HSCs) may originate from a healthy donor (allogeneic) or the patient itself when genetic defect is repaired by viral transduction of the correct gene (autologous gene therapy). Furthermore, genetic defect in HSC may also be corrected via guide RNA that interacts with the cell's own DNA repair machinery [Clustered Regularly Interspaced Short Palindromic Repeats and CRISPR associated protein 9 (CRISPR-Cas9) gene editing]. Conditioning regimens need to consider the inflammatory state of the patient as the risk of graft failure is high in these circumstances. Targeted therapy for immune dysfunction serves as a bridge until the definitive treatment with HSCT can be pursued safely. Indication to pursue HSCT in a child with autoimmune complications and underlying PID has not been fully delineated. Only a few large cohort studies and case series on HSCT for autoimmune complications have been published among patients with partial RAG and ADA2 deficiencies [20▪,22,23,56,57]. A recent report of allogeneic HSCT for chronic arthritis in children is intriguing. In a retrospective study by Silva *et al.* [58], allogeneic HSCT was performed in 11 patients with systemic and five with polyarticular rheumatoid factor negative juvenile idiopathic arthritis after patients failed multiple medications considered to be the standard of treatment or failed autologous HSCT, or developed life-threatening complications such as macrophage activation syndrome. Eleven of 14 surviving patients were reported to be in drug-free remission at the last follow-up. Common complications were severe infections (viral reactivation) and even autoimmunity during and after the transplant. Notably, in these reports, there was no search for underlying PID on immunological or genetic grounds. The authors argued that identifying the predictive markers of medical treatment failure in these patients would allow for early selection of candidates for HSCT, fewer HSCT-related complications and less disability.

Preventing development of autoimmunity in PID is a far-reaching goal, as it is unclear, which PID patients will progress into clinical autoimmune disease even among those with a genetic defect linked to immune dysregulation. Monitoring prognostic biomarkers of development to autoimmunity could improve early interventions and slow or reverse disease progression. These may be cellular (e.g., Tfh/Treg ratio, autoimmune prone B-cell subsets) or serum markers (e.g., antibodies targeting self-antigens including cytokines).

CONCLUSION

The face of PID is rapidly changing with increased awareness, availability of genetic testing, and in-depth immune phenotyping. A multidisciplinary approach is needed to expedite prompt diagnosis. Once multiple autoimmune complications are present, care of these patients is likely shared by multiple specialists (e.g., in hematology, rheumatology, neurology). At that point, reevaluation of the patient's immune system is of high importance. The primary pediatrician needs to advocate for prompt immune evaluation and genetic testing in this multidisciplinary setting to optimize the diagnostic and treatment approach for these vulnerable patients.

Table 1. Current biologicals inlcuding those most commonly used in autoimmune complications of PID

Target	Agent	Structure	Approved indication by FDA	Used in PID patients off label or in clinical trials
Cellular lymphocytes				
CD52	Alemtuzumab	anti-CD52 mAb	MS	pt with HLH
B cells				
CD20	Rituximab	chimeric mouse/human anti-CD20 mAb	RA, polyJIA	ITP, AIHA, GLILD (pts with CVID/CID, APDS/PASLI)
	Ofatumumab	human anti-CD20 mAb	adult refractory CLL	
	Obinutuzumab	humanized anti-CD20mAb	adult *de novo* CLL	
CD22	Epratuzumab	humanized anti-CD22mAb	B cell malignancies	
BAFF	Belimumab	human anti-BAFF mAb	SLE	
CD38	Daratumumab	human anti-CD38 mAb	MM	AIHA (pts with WAS s/p HSCT)
Proteosome inhibitor	Bortezomib	pyrazine and boronic acid derivative	MM, MCL	
	Carfilzomib	epoxomicinderivate	MM	
	Ixazomib	second generation boron containing peptide	MM, MCL	
T cells				
m-TOR	Sirolimus (rapamycin)	S6K/m-TOR inhibitor	LAM, T/OR	ITP, AIHA (pts with CTLA4/ LRBA def, ALPS, APDS)
m-TOR	Everolimus	S6K/m-TOR inhibitor	BrCA, TS, T/OR	CTLA4/LRBA def
IMD	Myocphenolic acid	reversible inhibitor of IMD	kidney, heart, liver transplant	ITP, AIHA (pts with CTLA4/ LRBA def, ALPS, APDS)
CD28	Abatacept	human CTLA4-IgG fusion protein with extracellular domain of CTLA4 and IgG1 Fc	RA, polyJIA	pts with CTLA4, LRBA def
p110δ	Leniolisib (CDZ173)	small-molecule inhibitor of p110δ	n.a.	pts with APDS/PASLI
Complement				
Complement C5	Eculizumab	recombinant humanized IgG2 anti-C5 mAb	generalized MG, PNH	
Cytokines and receptors				
TNFα	Etanercept	soluable TNFα receptor IgG Fc fusion protein	RA	AInD (pts with TRAPS)
	Infliximab	human mouse chimeric anti-TNFα mAb	RA, UC	CVID with GLILD
	Adalimumab	Fully human anti-TNFα mAb	RA, UC	
	Golimumab	Fully human anti-TNFα mAb	RA, UC	
	Certolizumab pegol	Humanized pegylated Fab' fragment	RA, CD	
IL-1β pathway	Anakinra	Recombinant IL-1R antagonist	RA, CAPS	CGD and AInD (pts with CAPS, FMF, TRAPS, HIDS, DIRA)
	Rilonacept	fusion of IL-1R and IL-1R accessory protein	CAPS	AInD (CAPS such as FCAS, MWS, less effective in NOMID)
	Canakinumab	mAb to IL-1β	JIA, CAPS	
IL-6R	Tocilizumab	Humanized IL-6R antagonist	RA, JIA	pt with STAT3 GOF
IL-12/IL-23	Ustekinumab	Fully human anti-IL-12/IL-23 mAb (anti-p40)	PsA	CGD, LAD-1
IL-17	Secukinumab	Fully human anti-IL-17 mAb	PsO	

Table 1 (*Continued*)

Target	Agent	Structure	Approved indication by FDA	Used in PID patients off label or in clinical trials
IFNγ	Emapalumab (NI-0501)	Fully human anti-IFNγ mAb	n.a.	AInD with HLH and NLRC4 mutation
JAK1/2	Ruxolitinib	small molecule JAK (1-2) inhibitor	RA, PV	STAT1 and STAT3 GOF
JAK1/2	Baricitinib	small molecule JAK (1-2) inhibitor	RA	STAT1 GOF and CANDLE syndrome
JAK1/3	Tofacitinib	small molecule JAK (1-3) inhibitor	RA, PsA, UC	STAT3-GOF STAT1-GOF CANDLE syndrome
JAK3	Decernotinib	small molecule JAK3 inhibitor	n.a.	RA
PD-1	Nivolumab	human anti-PD-1 mAb	M	
PD-1	Pembrolizumab	human anti-PD-1 mAb	UC, M, CA	
CXCR4	Plerixafor	small molecule inhibitor (bicylam)	T for MM or NHL	WHIM syndrome
CXCR4	Mavorixafor (X4P-001)	n.a.	n.a.	WHIM syndrome

AInD, autoinflammatory disorder; BAFF, B cell acivating factor; BrCA, breast cancer; CA, cancer; CD, Crohns disease, CGD, chronic granulomatous disease; CTLA, cytotoxic T lymphocyte antigen; FDA, Food and Drug Administration; GLILD, granulomatous lymphocytic interstitial lung disease; IMD, inosine monophosphate dehydrogenase; JAK, janus kinase; JIA, juvenile idiopathic arthritis; IL-6R, interleukin 6 receptor; LAD-1, leukocyte adhesion defect 1; LAM, lymphangioleiomyomatosis; LRBA, lipopolysaccharide-responsive and beige-like anchor protein deficiency; m-TOR, mechanistic target of rapamycin; MCL, mantle cell lymphoma; MG, myasthenia gravis; MM, myeloma multiplex; M, melanoma; MS, mulitple sclerosis; PNH, paroxysmal nocturnal hemoglobinuria; PsA, psoriatic arthritis; Pso, psoriasis; S6K, Serine/threonine protein kinase; Pts, patients; PV, polycythemia vera; T/OR, transplant and organ rejection; TS, tuberous sclerosis; UC, ulcerative colitis.

Treatment of PID patients with autoimmunity is most successful when fine-tuned immune modulation is achieved using biologicals specifically targeting the imbalanced immune pathway. Definitive therapy with HSCT or gene therapy should be considered for treatment of refractory cases.

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Conflicts of interest

J.E.W. has been an advisory board member, speaker bureau participant and site-principal investigator for a trial funded by Takeda (former Shire) outside of the submitted work.

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