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ORPHAN DISEASES (B MANGER, SECTION EDITOR)

# Novel Developments in Primary Immunodeficiencies (PID)—a Rheumatological Perspective

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**Abstract**

**Purpose of Review** The purpose of this review is to provide an overview of the most relevant new disorders, disease entities, or disease phenotypes of primary immune deficiency disorders (PID) for the interested rheumatologist, using the new phenotypic classification by the IUIS (International Union of Immunological Societies) as practical guide.

**Recent Findings** Newly recognized disorders of immune dysregulation with underlying mutations in genes pertaining to the function of regulatory T cells (e.g., CTLA-4, LRBA, or BACH2) are characterized by multiple autoimmune diseases—mostly autoimmune cytopenia—combined with an increased susceptibility to infections due to hypogammaglobulinemia. On the other hand, new mutations (e.g., in NF-kB1, PI3Kδ, PI3KR1, PKCδ) leading to the clinical picture of CVID (common variable immmune deficiency) have been shown to increasingly associate with autoimmune diseases.

**Summary** The mutual association of autoimmune diseases with PID warrants increased awareness of immunodeficiencies when diagnosing autoimmune diseases with a possible need to initiate appropriate genetic tests.

**Keywords** CVID · NF-kB deficiency · CTLA-4 haploinsufficiency · LRBA indusfficiency · APDS · DADA2

## Introduction

With the advent of potent antirheumatic—mostly biological—drugs, rheumatologists are increasingly confronted with immunodeficiencies as sequelae of immunosuppression. Considering the expanding armamentarium of targeted immunosuppressive antirheumatic drugs, the problem of secondary immunodeficiencies will further increase, necessitating preoccupation and knowledge of *primary* immunodeficiencies to anticipate possible effects of our patient management similar to those found in PID.

The connection of *primary* immunodeficiencies and rheumatic diseases is a phenomenon less appreciated in rheumatology. Increasing pathogenic insight has led to the current understanding that autoimmune diseases (AID) and primary immunodeficiency syndromes (PID) are in fact two sides of the same coin, and the appearance of a disorder of "one side" should prompt alertness to possible manifestations of "the other side." It is in this mindset that this review of new developments in PID is written, keeping a rheumatologists' perspective.

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## General New Developments in PID

Epidemiological data on PIDs are scant, as diagnosis is often hindered by lack of awareness in general and underreporting of asymptomatic or mild (IgA deficiency) as well as symptomatic forms in particular. Throughout the last years, large national registries have provided more comprehension addressing demographic and clinical aspects of PID. Data collected across several registries suggest a current overall prevalence of PID of aproximately 4/100000 of the population in Europe [1–3], which may still be an underestimation, mainly

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due to the reporting system [4]. The largest PID registry to date is the ESID Registry with more than 28.000 patients entered in April 2019. (https://cci-reporting.uniklinik-freiburg.de/#/, accessed on April 6th 2019). It shows a clear predominance of antibody disorders (> 50%), followed by phagocytic diorders.

The link between PID and AID was recently corroborated and quantified in the french PID register [5], where 26.2% were suffering from at least 1 autoimmune or autoinflammatory condition; most AID were autoimmune cytopenias (anemia, thrombocytopenia) or gastrointestinal disorders, resulting in a 3- to 14-fold increased relative risk in general for AID, 6-fold risk for rheumatologic disorders, and a 120-fold risk for autoimmune cytopenias. A noteworthy association between occurrence of allergy and cancer, as well as mortality with autoimmunity/inflammation, was reported [5].

Interestingly, autoimmunity occurs with all PID disorders, including antibody disorders, the most prevalent PID.

In the last years, the field of PID has been propelled forward by next-generation sequencing, which led to the discovery of new disorders as well as the recognition of new phenotypes in already established PID. In 2017, the newest report of the IUIS (International Union of Immunological Societies) expert committee was published encompassing details of 354 different immunodeficiency disorders grouped according to genetic cause [6•]. To make the increasingly complex volume of disorders more palatable for clinician's needs, a flanking "Clinical Phenotypic Classification" was released, combining information about clinical features with genetic aberrancies [7••]; of this, a downloadable version for apple and android smartphones has been conceived, making the step to bedside even smaller [8]. Of the nine groups defined by the IUIS, particularly the groups comprising disorders of antibody deficiencies, immune dysregulation and autoinflammation are interesting for the rheumatologist. As the latter has been the topic of a recent review [9], we focus in this concise review on the most important antibody disorders and immune dysregulation disorders.

## Developments in Antibody Disorders

The hallmark of this heterogeneous group of disorders is an increased susceptibility to bacterial respiratory tract infections (e.g., by *Streptococcus pneumoniae* and *Haemophilus influenzae*), presenting as otitis media, sinusitis, and pneumonia. In a substantial minority, the predominant feature is autoimmunuity (mostly cytopenia) or autoinflammation presenting as enteropathy or granulomatous disease (e.g., in the lung). The most common antibody disorder is selective IgA deficiency (sIgAD), with a varying prevalence over the globe ranging from 1:163 in Spain [10] to less than 1:14.000 in Japan ( [11]; reviewed in [12]); most patients with sIgAD remain asymptomatic, but association with AID (celiac disease, thyroid disease, Juvenile Idiopathic Arthritis (JIA)) has long been established. On the other end of the spectrum is agammaglobulinemia with severe bacterial infections early in childhood; X-linked agammaglobulinemia (XLA), a rare disease caused by mutations in BTK leading to absence of B cells, has been known since 1952; the largest study of XLA -patients including 783 patients from 40 centers around the world, published in 2019, showed great differences in survival rates (> 20 years: 29% in Africa vs 75% in Europe) as well as comorbidities (mostly seen in European patients: 17.2% arthritis and 5.9% inflammatory bowel disease) [13].

Common variable immunodeficiency disorders (CVIDs) is the most frequent symptomatic antibody deficiency, with a variable prevalence in Europe between 6.6/100.000 inhabitants in Finland and 0.6/100.000 in Spain [14, 15]. CVID is characterized by the occurence of mostly respiratory infections due to a substantial decrease in IgG, and mostly also IgA and IgM, with a variable genetic background. The last years have seen the establishment of different diagnostic criteria sets for CVID (http://esid.org/Working-Parties/Registry/Diagnosis-criteria, [16••, 17]) with several important items: setting the age (> 4 years) and the gammaglobulin levels (< 5 g/l or < 2 SD) and allocating a new, important role for complications of CVID—namely autoimmune and granlumolamtous diseases—also in the diagnostic process; additionally, typical immunological changes such as reduced vaccination response and decreased memory B cell subsets and increased CD21 low B cells have been incorporated. CD21 low B cells have been ascribed a role as marker of autoimunity and splenomegaly in CVID [18], and therefore been included in the EUROClass system, which attempts to define clinical subgroups of CVID by immunological changes [19]. Their presence in other autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, and Sjögren's syndrom corroborates the putative role of this anergic memory B cell type in PID-associated autoimmunity [20–22].

The most important criteria sets are shown in Tables 1 and 2 and weighed against each other in [23].

The understanding of the genetic background of CVID has deepened in the last years, as more monogenetic causes have been discovered (to date > 20); however, the underlying genetic mutations of the vast majority of CVID patients (80%) are still not deciphered. Already established monogenetic causes include dysfunctional genes of the B cell co-receptor complex (CD19, CD21, CD81, and Leu13) regulating B cell receptor signaling [24–27] as well as genes encoding co-receptors needed for germinal center reaction as ICOS [28] and CD27. Additionally, mutations affecting members of the TACI/BAFF-R/BCMA/BAFF/APRIL system are well defined causes of CVID, as these cytokines and their receptors play an important role in B cell homeostasis [29, 30] (genetic causes of CVID are reviewed in [31], Table 3). Among the genes discovered only in the past years are genes encoding

**Table 1** ESID criteria of CVID: (http://esid.org/Working-Parties/Registry/ Diagnosis-criteria)

| |
|---|
| At least one of the following: |
| • Increased susceptibility to infection |
| • Autoimmune manifestations |
| • Granulomatous disease |
| • Unexplained polyclonal lymphoproliferation |
| • Affected family member with antibody deficiency |
| And |
| marked decrease of IgG and |
| marked decrease of IgA |
| with or without low IgM levels (measured at least twice; < 2 SD of the normal levels for their age); |
| And at least one of the following: |
| • Poor antibody response to vaccines (and/or absent isohemagglutinins); i.e.,: absence of protective levels despite vaccination where defined |
| • Low switched memory B cells (< 70% of age-related normal value) |
| And |
| secondary causes of hypogammaglobulinemia have been excluded |
| And |
| diagnosis is established after the fourth year of life (but symptoms may be present before) |
| And |
| no evidence of profound T cell deficiency, defined as two out of the following |
| • CD4 numbers/μl: 2–6 years (years of life) < 300, 6–12 years < 250, > 12 years < 200 |
| • % Naive CD4: 2–6 years < 25%, 6–16 years < 20%, > 16 years < 10% |
| • T cell proliferation absent |

**Table 2** New diagnostic criteria (Ameratunga et al., 2013) for CVID: sequential order is important

| |
|---|
| A Must meet all major criteria |
| • Hypogammaglobulinemia IgG < 5 g/l |
| • No other cause identified for immune defect |
| • Age > 4 years |
| B Sequelae directly attributable to immunesystem failure (ISF) (one or more) |
| • Recurrent, severe or unusual infections |
| • Poor response to antibiotics |
| • Breakthrough infections inspite of prophylactic antibiotics |
| • Infections inspite of appropriate vaccination, e.g., HPVdisease |
| • Bronchiectasis and/or chronic sinus disease |
| • Inflammatory disorders or autoimmunity |
| C Supportive laboratory evidence (three or more criteria) |
| • Concomitant reduction or deficiency of IgA (< 0.8 g/l) and/or IgM (0.4 g/l) |
| • Presence of B cells but reduced memory B cell subsets and/or increased CD21low B cells |
| • IgG3 deficiency (< 0.2 g/l) |
| • Impaired vaccine responses compared to age-matched controls |
| • Transient vaccine responses compared with age-matched controls |
| • Absent isohemagglutinins (if not bloodgroup AB) |
| • Serological evidence of significant autoimmunity, e.g., Coombstest |
| • Sequence variations of genes predisposing to CVID, e.g., TACI, BAFFR, MSH5 |
| D Presence of relatively specific histological markers of CVID (not required for diagnosis but presence increases diagnostic certainty in context with A and B criteria) |
| • Lymphoid interstitial pneumonitis |
| • Granulomatous disorder |
| • Nodular regenerative hyperplasia of the liver |
| • Nodular lymphoid hyperplasia of the gut |
| • Absence of plasmacells on gut biopsy |
| Probable CVID: ABC or ABD ➔ indication for IVIG/SCIG substitution |
| Possible CVID: A alone, AB or AC or AD, but not B ➔ possible indication for IVIG/SCIG substitution |
| Hypogammaglobulinemia of uncertain significance (HGUS): IgG > 5 g/l, no criteria met |

signaling molecules (e.g., NF-κB1, NF-κB2, PLCγ2, PI3Kδ, PI3KR1, PKCδ, and IKAROS, Table 3) and genes causing diseases with prominent immune dysregulation (CTLA-4 and LRBA deficiency, discussed in the next section, Table 4) in addition to hypogammaglobulinemia.

The burden of disease in CVID was investigated recently and placed autoimmunity (23.2%) as most prevalent problem, exceeding the occurence in the general population 7.6-fold and the prevalence of other complications (i.e., d: bronchiectasis, 21.9%; digestive disorders, 15.6%; solid cancers, 5.5%; lymphoma, 3.8%) [56]. Principally, complications of CVID can be divided due to their cause into consequences of repeated or severe infection resulting in organ damage (e.g., bronchiectasies) versus autoimmune/autoinflammatory complications arising from immune dysregulation; elevated rates of malignancies, solid, as well as lymphomas, contsitute a third group. Among the autoimmune manifestations, thrombocytopenia and hemolytic anemia are most prevalent, followed by autoimmune thyroid disease, autoimmune skin disease (alopecia and vitiligo), and arthritis.

The lung is the most frequent location of organ damage in CVID; apart from brochiectasies due to infections, diverse radiographical and histological pictures are seen and summarized under the term GLILD (granulomatous-lymphocytic interstitial lung disease (GLILD). This encompasses the namegiving granulomatous formations as well as multiple forms of pulmonary lymphoid hyperplasia. GLILD can be seen in up to 20% of CVID patients and is often seen in combination with other granulomatous/inflammatory changes in the spleen, lymph nodes, liver, and gastrointestinal tract. Typically diagnosed by HRCT (high-resolution CT scans), GLILD shows a variable picture of parenchymal consolidation, reticular respectively nodular changes, and/or fibrosis, possibly combined with ground-glass opacities [57]; the histological features of GLILD stretch from sarcoid-like non-caseating granulomas to peri-bronchiolar

**Table 3** Overview of important antibody immnodeficiencies

| Disease (gene) | Clinical picture | Immune cell composition | Immunoglobulines | Inheritance | Reference |
|---|---|---|---|---|---|
| CD19, CD20, CD21, CD81 – deficiencies (CD19, CD20, CD21, CD81) | Recurrent RTI, GI infections and diarrhea, cytopenia CD81 and CD19-Deficiency: glomerulonephritis possible | nl total B cells ↓↓ memory B cells, ↓↓ BCR-signaling nl total T cells and subsets | ↓ IgG, variable IgM/IgA ↓responses to protein and polysaccharide vaccines | all AR | [24–27] |
| CD27 deficiency (TNFRSF7) | Severe EBV infection (severe mononucleosis, pneumonia, meningitis/encephalitis, oral/perianal ulcers, uveitis), aplastic anemia, lymphoproliferation | nl or ↓ CD4, nl or ↓ memory CD8 nl or ↓ T cell proliferation and cytotoxicity | Variable IgG/IgM/IgA ↓ or nl responses to protein and polysaccharide vaccines | AR | [32] |
| ICOS deficiency (ICOS) | RTI, GI infections, opportunistic infections, bronchiectasis, AID (cytopenia, rheumatic disease, IBD), granuloma, lymphoproliferation malignancy | nl or ↓ total B cells, ↓↓ memory B cells, nl or ↓ total CD4, nl or↓ total CD8 | ↓ IgG, variable IgM/IgA ↓ or nl responses to protein and polysaccharide vaccines | AR | [28] |
| TACI deficiency (TNFRSF13B), BAFF-Receptor deficiency (TNFRSF13C) | RTI, GI infections, bronchiectasis, AID (cytopenia, rheumatic disease, IBD), granuloma, lymphoproliferation malignancy | nl or ↓ total B cells, nl or ↓ memory B cells, nl or ↓ total CD4, nl or ↓ total CD8 | ↓ IgG, variable IgM/IgA ↓ or nl responses to protein and polysaccharide vaccines | Mono/biallelic | [29] |
| NFkB2 deficiency (NFkB2) | RTI, GI infections, bronchiectasis, endocrinopathy (pituitary hormone deficiencies -mainly ACTH def), AID (alopecia, vitiligo) Lymphoproliferation | nl or ↓ total B cells, nl or ↓ memory B cells, nl or ↓ total CD4, nl or ↓ total CD8 | Variable IgG/IgM/IgA ↓ or nl responses to protein and polysaccharide vaccines | AD | [33] |
| NFkB1 deficiency (NFkB1) | RTI, GI infections, AID (Cytopenia, IBD, alopecia, thyroid gland), pyoderma gangrenosum, bronchiectasis, chronic lung disease, LIP, lymphoproliferation malignancy | nl or ↓ total B cells, nl or ↓ memory B cells, nl or ↓ total CD4, nl or ↓ total CD8 | Variable IgG/IgM/IgA ↓ or nl responses to protein and polysaccharide vaccines | AD | [34–38] |
| APDS 1 / PIK3CD mutation (PIK3CD) and APDS2 / PIK3R1 deficiency (PIK3R1) | RTI, GI infections, viral (warts, persistent CMV/EBV viraemia) infections, bronchiectasis, AID (cytopenia, IBD, (EBV/CMV-induced) lymphoproliferation, malignancy (mainly lymphoma) | nl or ↓ total B cells, nl or ↓ memory B- cells, nl or ↓ total CD4, nl or ↓ total CD8 | Variable IgG/IgM/IgA ↓ or nl responses to protein and polysaccharide vaccines | AD | [37, 38] |
| PLAID / PLCγ2-associated antibody deficiency and immune dysregulation(PLCγ2) | RTI, Cold urticaria, atopy, skin granuloma, blistering skin lesions, onychomycosis, varicella zoster infections, bacterial skin infections, AID (skin and thyroid) | nl or ↓ total B cells, nl or ↓ memory B cells, nl or ↓ total CD4, nl or ↓ total CD8 | Variable IgG/IgM/IgA ↓ or nl responses to protein and polysaccharide vaccines | AD gain of function | [39, 40] |
| IKAROS deficiency (IKZF1) | RTI, *Streptococcus pneumoniae* infections, GI infections, bacterial skin infections, apthous ulcers, AID (cytopenia), malignancy (ALL) | nl or ↓ total B cells, nl or ↓ memory B cells, nl or ↑ total CD4, nl or ↑ total CD8 | ↓ IgG variable IgM/IgA ↓ or nl responses to protein and polysaccharide vaccines | AD | [40] |
| PKCδ deficiency (PKCD) | Severe systemic AID: SLE-like, severe (EBV/CMV-induced) lymphoproliferation RTI, GI infections, urinary tract infections, failure to thrive | Variable total B- cells, ↓ memory B cells, nl or ↓ total CD4, nl or ↓ total CD8, ↑ CD21low B cells, ↑ CD4-CD8- T cells | Variable IgG/IgM/IgA ↓ or nl responses to protein and polysaccharide vaccines | AR | [41–43] |

This is an overview of primary immunodeficiencies predominantly affecting antibodies; immunologic changes and clinical phenotype are listed as well

*AD* autosomal dominant, *AID* autoimmune diseases, *ALL* acute lymphatic leukemia, *AR* autosomal recessive, *BCR* B cell receptor, *CMV* cytomegaly virus, *EBV* Ebstein Barr virus, *GI* gastrointestinal, *IBD* inflammatory bowel diseases, *Ig* immunoglobuline, *LIP* lymphocytic interstitial pneumonia, *nl* normal, *RTI* respiratory tract infection

and interstitial lymphocytic infiltration. Usually, the development of GLILD is insidious, only becoming clinically relevant in later stages, when a restrictive pattern in lung function tests becomes apparent, often with a decline in carbon monoxide diffusion capacity.

The treatment of CVID in general includes prophylactic antibiotics (mostly azithromycin), especially if bronchiectasies are already present, and substitution of immunoglobulins. The indication when to start substitution relies on the correct diagnosis and burden of disease; in this decision, the diagnostic criteria

**Table 4** Overview of important primary immunodeficiencies with predominant immune dysregulation

| Disease (gene) | Clinical picture | Immune cell composition | Immunoglobulines | Inheritance | Reference |
|---|---|---|---|---|---|
| Tregopathies | | | | | |
| IPEX / immune dysregulation, polyendocrinopathy, enteropathy, X-linked (FoxP3) | Enteropathy, T1D, eczema, cytopenia, thyroiditis, hepatitis | ↑ CD4 ↑ eosinophils variable FOXP3 + Treg | IgE ↑ | X-linked | [44] |
| CD25 deficiency (CD25) | Enteropathy, eczema, lympho- proliferation, recurrent infections (respiratory, cellulitis), T1D, thyreoiditis | Shifted CD4:CD8 ratio | IgE ↑ (one patient) | AR | [45] |
| CTLA-4 haploinsufficiency with autoimmune infiltration / CHAI (CTLA-4) | Enteropathy, T1D, cytopenia, respiratory disease, lympho- proliferation | Lymphopenia, nl or ↓ FOXP3+ Treg, ↓ total B cells, ↓ memory B- cells, ↓ total T cells, ↓ NK cells, ↑ CD21low cells | nl or↓ IgG/M | AD, haploinsufficiency | [46, 47] |
| LRBA deficiency with autoantibodies, Treg cell defects, autoimmune infiltration, and enteropathy / LATAI (LRBA) | Cytopenia, diabetes, enteropathy, GLILD, lympho- proliferation, hypogamma- globulinemia and recurrent infections | Leukopenia lymphopenia, ↓ FOXP3+ Treg, ↓ total B cells, ↓ sm B cells, ↓ plasmablasts | Defective specific antibody response | AR, homozygous or compound heterozygous | [48, 49] |
| BACH2-related immunodeficiency and autoimmunity / BRIDA | Enteropathy, lymphoproliferation, recurrent respiratory tract infections | ↓ FOXP3+ Treg, ↓ total B cells, ↓ sm B cells | ↓ IgG ↓ Ig M | AD | [50] |
| STAT5b deficiency (STAT5B) | Growth delay, severe intestitial lung diseases, eczema, respiratory infections | ↓ FOXP3+ Treg, ↓ Treg function | Normal or hyper-gamma-globulin--emia | AR | [51] |
| Autoimmune disease, multisystem, infantile-onset syndrome / ADMIO / STAT3 Gain of function mutation (STAT3) | Early polyautoimmunity (T1D, hypoparathyroidism), celiac disease, cytopenia, respiratory infections | Variably: ↓ Treg number and function, ↓ memory B cells, ↑ CD4-CD8 cells | Normal or hyper-gamma-globulin--emia | AD | [52, 53] |
| STAT1 gain of function mutation (STAT1) | Chronic mucocutaneous candidiasis (CMC), hypothyroidism, T1D, cytopenia | Mostly normal, lymphopenia (in 20%), ↓ memory B cells (in 50%) | Mostly normal | AD | [54, 55] |

This is an overview of primary immunodeficiencies predominantly characterized by immune dyregulation, including immunologic changes and clinical phenotype

*AD* autosomal dominant, *AR* autosomal recessive, *GLILD* granulomatous-lymphocytic interstitial lung disease, *Ig* immunoglobuline, *NK cells* natural killer cells, *nl* normal, *sm B cells* switched memory B cells, *T1D* type 1 diabetes

established by Ameratunga et al. can be helpful [16••]. The choice of immunosuppressive therapy for GLILD should be guided based on the underlying genetic abberancy, and if unknown, different approaches have been published.

Recently, a consensus of the British Lung Foundation/United Kingdom Primary Immunodeficiency Network was established regarding the therapeutical approach in the treatment of GLILD, advocating glucocorticoids as first-line therapy [58•]. The second-line therapy in this consensus paper consists of a combination of rituximab and azathioprine or mycophenolate mofetil. Yet, others promote early combined immunosuppression to prevent development of irreversible lung damage and side effects of prolonged therapy with Glucocorticoids [59, 60].

## Selected Genes Encoding Signaling Molecules: (Table 3)

### NF-kB1 and NF-kB2

The NF-κB (nuclear factor "kappa-light-chain-enhancer" of activated B cells) family of transcription factors comprises five members: NF-kB1, NF-kB2, RelA, RelB, and c-Rel. Various

combinations of these proteins influence diverse cellular processes, among which the expression of numerous cytokines, chemokines, growth factors, apoptosis regulators, and cell surface receptors. In B cells, NF-κB signaling influences maturation, survival, differentiation, class switching, and tolerance to self-antigens. Whereas, NF-κB2-deficient patients are known to present early in childhood with a CVID (-like) phenotype often displaying pituitary hormone deficiencies (an unusual feature in CVID) [33], variants inducing the loss of function of NF-κB1 show great variability in clinical manifestations and age of onset (first years of life to the 7th decade). In the first reported (5 generation) family with the same mutation of NF-κB1, the spectrum from light hypogammaglobulinemia (like sIgAD) to severe CVID with viral (Epstein-barr virus (EBV), JC virus, cytomegaly virus (CMV)), and bacterial infections, as well as autoimmune manifestations (autoimmune cytopenia, alopecia, vitiligo, and Hashimoto thyroiditis), malignancy (solid tumors and lymphoma), repiratory disease (e.g., lymphocytic interstitial pneumonia), and bronchiectasis was seen [34]; interestingly, NF-κB1 deficiency was the most commonly identified monogenic cause (4.1%) in a European cohort of 390 CVID patients associating with massive lymphadenopathy, splenomegaly, and autoimmune disease [35]. Therapeutic measurements include antibiotics and immunoglobulin replacement therapy. EBV-associated lymphoproliferative disease was treated succefully with rituximab (anti-CD20 antibody) [36].

### Activated PI3 Kinase Delta Syndrome

PI3Kδ (phosphoinositide 3-kinase-δ) is a key signal transduction node in immune cells controlling lymphocyte development and differentiation upon exposure of B and T cells to their antigen. This takes place in part via mechanistic target of rapamycin (mTOR) pathways. Mutations leading to a gain of function of genes encoding PI3Kδ result in APDS. Underlying mutations are located in the PIK3CD and the PIK3R1 gene and cause hyperactive PI3Kδ signaling and senescent T cells, lymphadenopathy, and immunodeficiency [37, 38, 61, 62]. The resulting diseases were named APDS1 and 2 and current data shows that activated PI3 kinase delta syndrome (APDS) mutations have high penetrance and have not been identified in large cohorts of healthy patients [63]. The majority of patients present with recurrent respiratory infections, often associated with bronchiectasis and ear and sinus damage. Severe, recurrent, or persistent infections with herpes family viruses, indicating defective T cell function, are also common and may cause early death in some affected individuals. Therefore, although classified in the IUIS as predominantly an antibody disorder [7••], APDS should be considered a combined immunodeficency disorder. Lymphoproliferation (benign lymphadenopathy, hepatosplenomegaly, focal nodular lymphoid hyperplasia), and a substantially increased risk of B cell lymphoma are seen as well as autoimmune manifestations (cytopenia, JIA, glomerulonephritis, thyroiditis, and sclerosing cholangitis). Growth retardation is common in APDS2, and mild developmental delay in both APDS.

Treatment regimes include antibiotic prophylaxis, immunoglobulin replacement therapy, and hematopoietic stem cell transplantation (HSCT) [63, 64]. Immunosuppressive therapies aimed at reducing lymphoproliferation have included treatment with rituximab and rapamycin to target the activation of the mTOR pathway [61]. Leniolisib, a small molecule selectively inhibiting PI3Kδ, which was developed for cancer, normalized PI3Kδ hyperactivation in cells of APDS patients in vitro prompting a clinical trial in APDS patients. In 6 patients reported to date treatment with leniolisib resulted in normalization of immuological and inflammatory markers, and a reduction of lymph node and spleen sizes [65]. Apart from an extension of the open-label study, also, a controlled trial NCT02435173 is currently recruiting patients.

### PKCδ Deficiency

Protein kinase C delta (PKCδ) is a key component of the BCR-mediated signaling cascade downstream of Brutons kinase and critical for regulation of cell survival, proliferation, and apoptosis of B cells. The first report of a patient with PKCD deficiency described a young patient with CVID-like features, namely recurrent infections of the respiratory, the urinary and the gastrointestinal tract, and otitis media, which improved in frequency and severity under immunoglobulin substitution. [41] Additionally, the patient experienced membranous glomerulonephritis, lymphoproliferation, antiphospholipid syndrome, and relapsing polychondritis indicating a problem of immune dysregulation. Interestingly, the other patients described in the literature so far exhibited features of immune dysregulation resembling SLE, without the CVID-like phenotype and with normal immunoglobulin levels [42, 43, 66]. Accordingly, the therapeutic regimen is imunosuppressive (hydroxychloroquine, mycophenolate mofetil, and rituximab).

## Disorders of Immune Dysregulation

The key problem in most diseases of this group—classified as such according to the IUIS classification—is the loss of tolerance. Tolerance (to autoantigens) is conveyed either centrally (in the thymus) or by peripheral measures (e.g., regulatory T cells, Tregs).

### Disturbed Central Tolerance: APECED/APS

Apart from the well-characterized DiGeorge syndrome, APECED, (autoimmune polyendocrinopathy candidiasis ectodermal dystrophy), also known as autoimmune polyendocrinopathy syndrome type 1 (APS1) causes a

deranged cenral tolerance. APS is a monogenic disorder imduced by diverse classically autosomal-recessive mutations in AIRE (autoimmune regulator gene). AIRE is a crucial mediator of central tolerance controlling the expression of tissue-specific (auto)antigens in the thymus [67].The prototypical manifestations of APS are autoimmune endocrinopathies with > 80–90% of patients exhibiting hypoparathyroidism and adrenal insufficiency; diabetes and gonadal dysfunction, extraglandular manifestations have been described as well. Additionally, the majority of patients with APS produce autoantibodies, of which some are directed against tissue antigens (e.g., GAD65 or TPO), whereas others are targeting IL-17, IL-22, and IFNω. These anti-IL17 antibodies are associated with the pathognomonic chronic mucocutaneous candidiasis (CMC). The "classical APS1" with an autosomal-recessive inheritance begins early in childhood and displays the clinical triad of CMC, hypoparathyroidism, and adrenal insufficiency. During the last few years, more features have been subsumed under the term "non-classical APS-1," which shows diversity in the underlying genetic mutations [68], as well as in the phenotypic spectrum [69]. North American patients, e.g., exhibit in 40–80% nonendocrine manifestations before the typical triad, e.g., urticarial eruption, hepatitis, gastritis, intestinal dysfunction, pneumonitis, and Sjögren's-like syndrome; the latter displays a typical histology of Sjögren's syndrome without the pathognomonic autoantibody profile [69]. Therapy relies on hormone replacement and immunosuppression (glucocorticoids, azathioprine, MMF, cyclosporine, tacrolimus, rapamycin, or methotrexate) where appropriate.

## Disturbed Peripheral Tolerance: "Tregopathies" (Table 4)

Peripheral tolerance greatly depends on the correct number and function of regulatory T cells (Treg). These cells are thymus-derived and characterized by the expression of the surface markers CD3, CD4, and CD25, and the transcription factor FoxP3. The first disorder described in humans based on the dysfunction of Treg was IPEX, which is caused by mutations in FoxP3, a gene located on the X chromosome [70]. The acronym stands for immune dysregulation, polyendocrinopathy, enteropathy, X-linked, summarizing the most important manifestations (diarrhea, early-onset organ-specific autoimmunity especially in the gut and pancreas leading to type I diabetes, T1D) as well as the inheritance. In the recent most comprehensive description of IPEX patients, more than 50 different mutations were defined in the entire FoxP3 gene, with no discernable correlation with certain phenotype, course, or outcome of the disease [44]. The 96 patients displayed manifestations including typical eczema, autoimmune thyroiditis, autoimmune cytopenia, nephropathy, autoimmune hepatitis, alopecia, and hyper-IgE (with or without eosinophilia) with onset at very early age. With a growing number of patients fitting the clinical classification without mutation in the FoxP3 gene, the idea of IPEX-like diseases or Tregopathies was introduced (reviewed in [71•]). These include (according to the latest IUIS phenotypic classification, ref. [7••]) diseases caused by loss of function mutations in CD25, cytotoxic T lymphocyte-associated antigen 4 (CTLA4), LPS-responsive and beige-like anchor protein (LRBA), and BTB domain and CNC homolog 2 (BACH2), summarized in Table 4, and a gain of function mutation in signal transducer and activator of transcription 3 (STAT3) (see next section). The common denominator of these genes is the contribution of their encoded proteins to the suppressive function of Treg. The suppression of effector cells by Treg is conveyed, among other mechanisms, by the constitutively expressed inhibitory protein CTLA4 on the Treg cell surface. CTLA4 binds to CD80 and CD86 on antigen presenting cells (APC), and these costimulatory molecules are susequently removed from the APC surface through transendocytosis [72]. This in turn prevents the interaction between CD80/86 on APC with CD28 on effector T cells, which is needed as *second signal* in T cell activation [73]. This mechanism also affects follicular helper T cells, which are key players in B cell stimulation, leading to deranged humoral immunity as well [74]. The haploinsufficiency of CTLA4 seen in humans is characterized by occurrence of autoimmune cytopenia, lung disease, enteropathy, skin disease, and neurological involvement [46, 47, 75•]. Additionally, lymphoproliferation manifesting as lymphadenopathy and hepato-splenomegaly is present and mostly non malignant, although incidental reports of lymphoma have been published. The effect on humoral immunity causes hypogammaglobulinemia with common respiratory infections. Noteworthy is the variable age at onset of disease, sometimes reaching into late adulthood.

A similar clinical phenotype is generated by homozygous or compound heterozygous mutations in LRBA, which binds to the cytoplasmic tail of CTLA4 preventing its degradation in lysosomes. Originally seen in patients with early-onset hypogammaglobulinemia, recurrent infections, autoimmune manifestations, and inflammatory bowel disease [48], the phenotype has been extended in the to date largest characterization of patients [49]. The most prevalent features of immune dysregulation are autoimmune cytopenia, diabetes, enteropathy and GLILD, paired with lymphoproliferation, mostly splenomegaly, and reduced IgG (IgA and IgM were decreased in approximately 1/3 of patients each).

In 2017, Afzali et al. were the first to describe BACH2-related immunodeficiency and autoimmunity (BRIDA) that results from BACH2 haploinsufficiency. BACH2 is a transcription factor regulating B cell class-switch recombination and somatic hypermutation as well as T cell differentiation, limiting the development into effector T cells and enhancing the development into Treg [76]. The BACH2 gene locus comprises superenhancers, which are large clusters of transcriptional enhancers promoting the expression of genes; superenhancers therefore decide cell identity [77] and render

the gene very sensitive to alterations. Accordingly, as with other genes comprising superenhancers, even single-nucleotide *polymorphism* is linked to multiple autoimmune and inflammatory conditions: rheumatoid arthritis, T1D, asthma, multiple sclerosis, vitiligo, Graves disease, Crohn disease, and celiac disease (reviewed in [78]). However, the main clincial phenotype of patients with BACH haploinsuffiency was CVID-like with hypogammaglobulinemia and recurrent infections, enteropathy, and lymphadenopathy [50].

## Immune Dysregulation Disorders Based on JAK-STAT Mutations: STAT5b, STAT3, STAT 1 GOF (Table 4)

Since the first descripition of the JAK-STAT signaling pathway in 1989, four Januskinases (JAK), JAK1, JAK2, JAK3, and TYK2, and 7 STATs have been discovered: STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6 (reviewed in [79]). Upon ligation of diverse cytokines, interferons (IFN), and growth factors, this signaling cascade comes into action; the composition of players in the individual signaling process depends on the respective ligand binding to its cognate receptor. In case of IL-2, the crucial cytokine for Treg generation and function, ligand binding leads via JAK1/JAK3 activation to phophorylation of STAT5b. As growth hormone (GH) receptor is also reliant on STAT5b, the main symptom of STAT5b mutation is a growth delay with normal levels of GH [51]. The immune system is also affected as recurrent skin and respiratory tract infections occur as well as progressive, possibly lethal interstitial lung disease; number and function of Treg are decreased.

STAT3 is implicated in the signaling processes of many cytokine receptors including IL-6 and IL-10. Whereas loss of function mutations result in the well-established hyper-IgE syndrome (characterized by the triad of eosinophilia, eczema, and recurrent skin and pulmonary infections [80]), gain of function mutations in STAT3 are characterized by very early-onset polyautoimmunity (T1D, autoimmune hypothyroidism, and celiac disease, ref. [81]). Following the description of more patients, also, enteropathy, autoimmune cytopenias, hepatitis, alopecia, scleroderma, lymphoproliferation, interstitial lung disease, short stature, and recurrent infections are recognized as symptoms as well as hypogammaglobulinemia, decreases in Treg number, and function [52, 53].

STAT1, a transcription factor used by all interferons, is associated with primary immunodeficiencies arising from mutations leading to loss *and* mutations leading to gain of function. STAT1 loss of function variants result in impaired IFN-α and IFN-γ responses manifesting as increased susceptibility to viral and mycobaterial infections. In contrast, gain of function mutations lead to a shift in the STAT3/STAT1 balance to the advantage of STAT1 and disadvantage of STAT3. The latter is crucial for IL-6 signaling and IL-6-dependent development of T helper 17 (TH17) cells. As Th17 are important in the fight against fungi, this results in a hightened susceptibility to fungi—clinically seen as chronic mucocutaneous candidiasis (CMC) [82]. As the dysbalance towards STAT1 increases IFNα levels, autoimmune manifestations such as hypothyroidism, autoimmune hepatitis, T1D, and cytopenia are part of the clinical picture [54, 55].

Concluding the section on immune dysregulation, it can be said that the main clinical features of this group are noninfectious gut pathology, cytopenia, endocrine abnormalities (especially T1D), and lung and skin inflammation, often arising as autoimmune diseases and acccompanied by lymphoproliferation.

Accordingly, therapeutic approaches include, apart from anti-infectious measures, unspecific immunosuppression as glucocorticoids and calcineurin inhibitors as well as newer, more targeted treatment options. Rapamycin/sirolimus, an mTOR inhibitor, selectively targets effector T cells, thus indiretly supporting Treg function, rendering it an option in these disorders [44]. CTLA4-Ig (abatacept) has been employed succfessfully in patients with CTLA4 haploinsufficiency and LRBA deficiency [75•, 83]. In LRBA deficiency, also, hydroxychloroquine has been employed due to its inhibitory effects on lysosomal degredation [49]. Abrogating the upstream events (cognate interaction of IL-6 and IL-6R) by the IL-6Ra tocilizumab has shown efficacy in the gain of function mutation of STAT3 in terms of ameliorating the dysbalance of Th17 and Treg as well as clinically [84]. The B cell depleting rituximab is considered a standard treatment of autoimmune cytopenia, and therefore has been used in several immune dysregulatory disorders involving mutations in FOXP3, CD25, CTLA4, LRBA, and STAT3 gain of function mutations to combat cytopenia, and also organ inflammation [44, 49, 53, 75•]. However, for all these monogenic diseases, the only curative option has been allogenic stem cell transplantations (HCT) with a substantial risk of transplant related mortality. To circumvent this risk, efforts to refine directed gene therapy have been undertaken in the last three decades. This lead to the 2016 approval of the EU to use a gamma-retrovirus encoding for the human *ADA* cDNA sequence in severe combined immunodeficiency patients caused by a mutation in the adenosine deaminase (ADA) gene [85] and research is ongoing for the use of gene therapy in Tregopathies. For the time being, in patients with severe disease manifestations, HCT, also at adult age, should be considered before the occurence of irreversible organ damage [86].

As outlined in the introduction, we feel that the group of autoinflammatroy disorders listed in the IUIS classification poses special interest for the rheumatologist; however, due to restrictions in space and the availability of recent reciews in this journal covering this group of disorders [9, 87], we only want to highlight the recently characterized ADA2 deficiency, which also manifests with symptoms of humoral immundoeficieny.

## Deficiency of Adenosine Deaminase 2 (DADA2)

ADA2 (adenosine deaminase 2) is highly expressed in myeloid cells and plays a role in the differentiation of macrophages;

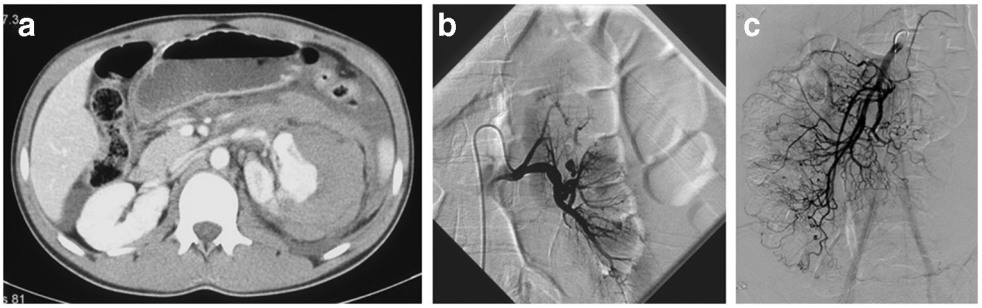


**Fig. 1** CT scan showing massive left-sided retroperitoneal hemorrhage in a patient with deficiency of ADA2 (**a**); conventional angiography revealed multiple aneurysms in the left kidney (**b**) as well as multiple aneurysms in the superior mesenteric artery (**c**) mimicking polyarteritis nodosa

however, its function is still largely undetermined. Biallelic deficiency of ADA2 by mutations in *CECR1* has been linked to an imbalance in differentiation of monocytes towards proinflammatory M1 macrophages. Deficiency in adenosine deaminase type 2 (DADA2) was initially described as a condition characterized by fever, polyarteritis nodosa (PAN), livedo racemosa, liver disease, early-onset—typically lacunar—stroke, and mild immunodeficiency by two independent groups [88, 89]. The predominant clinical presentation is small- and medium-sized arteritis affecting skin and central nervous system. Yet, DADA2 is a systemic disease, and vasculitis or inflammation of kidney, GI tract, and liver, as well as cytopenia, are important disease manifestations (Fig. 1), the latter sometimes seen as inital presenting symptom [90]; lymphoproliferation may span a spectrum from benign to malignant [90]. Apart from mild hypogammaglobulinemia and low IgM serum levels and occasional lymphopenia, an immunodeficient phenotype manifesting with recurrent sinopulmonary and herpes virus infections was reported in a subset of patients, often initially diagnosed as CVID [91, 92•]. Autoimmune phenomena in DADA2 are less common, yet some patients are reported to have systemic lupus, transiently positive lupus coagulans, associated with a type 1 interferon gene expression signature in peripheral blood [93]. To alleviate inflammation, several disease modifying antirheumatic drugs, including anti-IL1 therapy, have been tried, with no consistent success. Anti-TNF-agents (etanercept, adalimumab, infliximab) are the mainstay of treatment, although less effective for immunodeficiency or severe cytopenia. The latter are usually treated with rituximab. Supportive treatment with immunoglobulin substitution, antibiotics, and antiviral agents should be started upon indication. In refractory cases, HSCT is the best therapeutic option, as shown in 14 patients, with remission of immunological, hematological, and vascular manifestations [94].

## Conclusion

During the last years, the field of primary immunodeficiencies has seen great developments due to the discovery of new mutations on account of the empolyment of new techniques. This has led on one side to the characterization of new disorders like the "Tregopathies," which are characterized by immune dysregulation and on the other side to the extension of the clinical phenotype and underlying genetic mutations of already known disease entities like CVID. Many of the newly described diseases (or phenotypes) show features of immune dysregulation, spilling over into the primary scope of rheumatologists, and thus warranting the rheumatologists´ attention. The periodical reports of the IUIS and the associated Phenotypic Classification for Primary Immunodeficiencies [6•, 7••] help the clinician to process the multitude of new immune deficiencies; we have tried to integrate the most important discoveries listed in these reports in this review.

## Compliance with Ethical Standards

**Conflict of Interest** Dr. Leavis reports grants and other from Shire and personal fees and other from Novartis, other from Sobi, outside the submitted work.

Dr. Fritsch-Stork has nothing to disclose.

Dr. Zwerina has nothing to disclose.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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