



Novel Genetic Discoveries in Primary Immunodeficiency Disorders

Margaret T. Redmond¹ · Rebecca Scherzer¹ · Benjamin T. Prince¹

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Abstract

The field of Immunology is one that has undergone great expansion in recent years. With the advent of new diagnostic modalities including a variety of genetic tests (discussed elsewhere in this journal), the ability to diagnose a patient with a primary immunodeficiency disorder (PIDD) has become a more streamlined process. With increased availability of genetic testing for those with suspected or known PIDD, there has been a significant increase in the number of genes associated with this group of disorders. This is of great importance as a misdiagnosis of these rare diseases can lead to a delay in what can be critical treatment options. At times, those options can include life-saving medications or procedures. Presentation of patients with PIDD can vary greatly based on the specific genetic defect and the part(s) of the immune system that is affected by the variation. PIDD disorders lead to varying levels of increased risk of infection ranging from a mild increase such as with selective IgA deficiency to a profound risk with severe combined immunodeficiency. These diseases can also cause a variety of other clinical findings including autoimmunity and gastrointestinal disease.

Keywords Inborn errors of immunity · Immune dysregulation · Genetics · Genetic testing

Introduction

As the number of defined PIDDs increases, classification of the diseases remains important to those who care for these patients so that critical information can be easily disseminated [1, 2]. Additionally, a molecular diagnosis of those diseases provides a better understanding of infection risk and associated non-infectious comorbidities and allows for a more targeted treatment approach. Staying up to date with the ever-evolving number of PIDDs can be challenging as noted by Tangye et al. in their most recent update on novel inborn errors of immunity [2]. Due to a number of new diagnosable PIDDs since the last update just 1 year ago in 2020, the IUIS (International Union of Immunologic Societies) Committee released an interim update in 2021. That update included 26 novel monogenic gene defects leading to inborn errors in immunity. This article includes recently described monogenic gene defects that have been associated with PIDDs.

Severe Combined Immunodeficiencies

Understanding of the genetic basis of severe combined immunodeficiency (SCID) has changed rapidly in the last decade with expanded newborn screening and improved genetic testing. Infants with SCID have an absence of functioning T lymphocytes with variable involvement of B lymphocytes and NK lymphocytes. Early diagnosis of disease is critical to allow for appropriate treatment, which can include hematopoietic stem cell transplantation (HSCT) or gene therapy. While many genetic causes of SCID have been previously described, several new genetic causes of SCID have been recently identified.

SCID Due to Cellular Defects

LAT Deficiency

Linker for activation of T cells (LAT) is a transmembrane molecule that acts as a scaffold protein in the T cell receptor (TCR) signaling pathway. Different autosomal recessive mutations resulting in premature termination have been linked to immunodeficiency in two unrelated consanguineous families [3, 4]. One family had complete loss of protein expression, and those infants had very low T lymphocyte

✉ Rebecca Scherzer
rebecca.scherzer@nationwidechildrens.org

¹ Division of Allergy and Immunology, Department of Pediatrics, Nationwide Children's Hospital, The Ohio State University College of Medicine, Columbus, OH, USA

counts, with normal numbers of B lymphocytes and NK lymphocytes. Recurrent infections and failure to thrive were noted at presentation. In the second family, the protein retained some function, and those patients had a combined immunodeficiency clinical picture. These children had high numbers of $\gamma\delta$ T lymphocytes and progressive development of lymphopenia and hypogammaglobulinemia. Clinically, they presented with recurrent infections, autoimmune cytopenias, lymphadenopathy, and hepatosplenomegaly. In both family groups, several patients died due to disease and transplant complications.

SLP76 Deficiency

SH2 domain-containing leukocyte protein of 76kD (SLP76) associates with the Grb2 adaptor protein to act as a substrate for tyrosine kinases in the TCR activation pathway. One patient has been described with a homozygous mutation in the *SLP76* gene that presented skin abscesses, rash, and autoimmunity [5]. Notable lab findings were very low CD4+ cells, clonally expanded CD8+ cells, and impaired PHA proliferation. Numbers of B lymphocytes and NK lymphocytes were normal, but the population of switched memory B cells was reduced.

EXTL3 Deficiency

Exostosin-like glycosyltransferase 3 (EXTL3) is part of a group of glycosyltransferases that regulate glycosaminoglycan heparin sulfate. Nine patients from five unrelated families were identified with homozygous pathogenic variants in *EXTL3* [6]. All patients presented with skeletal abnormalities and most had neurodevelopmental delay. Interestingly, three of the five families had a T–B+NK–SCID phenotype while two families had no immune dysfunction. Those with T–B+NK+ phenotype also presented with erythroderma, eosinophilia, oligoclonal T cell expansions, and high risk of death in infancy.

RAC2 Gain-of-Function

RAC2 is required for the transfer of electrons in the NADPH oxidase pathway, and previous loss of function mutations were found in patients with impaired neutrophil chemotaxis. Ten patients from six different families were identified to have heterozygous GOF mutations [7–10]. Patients have been described with low T cells, B cells, and NK cells. IgG levels are low with impaired specific antibody development. Impairment can range from T–B–NK+ SCID to combined immune deficiency. Clinically, affected individuals have recurrent bacterial and viral infections with some

developing pulmonary failure and requiring lung transplant secondary to infections.

T–B+NK+ SCID Due to Defects in Thymus Development

PAX1 Deficiency

PAX1 is one of the paired box (PAX) families of transcription factors. PAX1 plays an important role in embryogenesis, specifically in the pharyngeal pouches that become the thymus. Homozygous mutations in *PAX1* had previously been identified as a cause of otofaciocervical syndrome type 2 which is associated with microtia and other facial development abnormalities. A subset of patients with *PAX1* mutations in three unrelated families has been described with a T–B+NK+ SCID phenotype related to absent thymus tissue [11, 12]. These patients have an Omenn syndrome–like phenotype with erythroderma, eosinophilia, and severe bacterial infections. Several infants have died following HSCT from infections. Testing revealed that even though most had evidence of at least partial donor chimerism, none were able to achieve T cell reconstitution. Thymic transplantation is required for treatment of these patients.

FOXN1 Haploinsufficiency

Forkhead box N1 (FOXN1) expression is required for development of thymic function as it is a transcription factor that regulates epithelial cells in the thymus. Homozygous loss-of-function (LOF) mutations in *FOXN1* have previously been identified as a cause of T–B+NK+ SCID. With expanded TREC testing in newborns, a population of infants with FOXN1 haploinsufficiency was identified [13]. A study of 25 infants and 22 adults identified with heterozygous *FOXN1* mutations revealed that prior to 2 years of age, these children have noted to have low T lymphocyte counts involving both CD4+ and CD8+ cells. During infancy, these children were noted to have recurrent bacterial and viral infections that were sometimes severe. The CD4+ T lymphocyte count improved after age two, but CD8+ T lymphopenia was noted in most of the adults studied. The risk of severe infection is present until normalization of CD4+ lymphocyte population, but HSCT did not lead to T lymphocyte reconstitution when pursued. The role of thymic transplant for infants with FOXN1 haploinsufficiency is not yet known. Many of the infants were noted to have eczema, and both age populations had nail dystrophy noted on exam.

Combined Immunodeficiencies

Combined immunodeficiency (CID), like SCID, results from impaired functions of both the cellular and humoral immune systems. Unlike SCID, they do not generally cause fatality from infection in the first year of life but can result in significant morbidity and mortality. Improved testing has provided new insight into the genetic cause of many CIDs, including those which share features with previously described CIDs.

Hyper IgE Syndromes

In recent years, many genetic mutations have been identified that are associated with most of the features classically associated with autosomal dominant hyper IgE syndrome (AD-HIES) which is caused by a dominant negative mutation in *STAT3*. Most of these diseases are triggered by an autosomal recessive inheritance, but other dominant negative mutations have also been described.

ZNF341 Deficiency

ZNF341 is a C2H2-zinc finger transcription factor that binds to the promoter region of the *STAT3* gene and is necessary for expression of *STAT3*. Patients in four unrelated families were described with autosomal recessive mutations in *ZNF341* leading to low *STAT3* expression and are phenotypically nearly identical to *STAT3* deficiency with facial dysmorphism, eczema, recurrent skin and respiratory infections, susceptibility to mucosal fungal infections, and skeletal and joint abnormalities [14, 15]. Patients are noted to have decreased T-helper (Th)17 and NK cells, normal numbers of B cells with reduced memory B cells, and impaired specific antibody production in the context of elevated serum IgE and IgG.

IL-6 Receptor Deficiency

Two patients were identified from unrelated families with homozygous mutations in the IL-6 receptor gene (*IL6R*) [16]. Both patients presented with eczema, recurrent skin abscesses, and pyogenic pneumonias beginning in infancy. Patients were found to have eosinophilia, elevated serum IgE, and slightly low IgG. Fevers are uncommon, and C-reactive protein (CRP) does not rise with infections. Patients have elevated serum levels of IL-6. In contrast to *STAT3* deficiency, these patients have reduced but sufficient Th17 function and have not been found to be prone to fungal infections. One patient is well controlled with prophylactic

antibiotics and intravenous IgG replacement, but the other has not had success with prophylactic antibiotics and continues to have frequent, pyogenic skin infections.

IL6 Signal Transducer Deficiency, Complete and Partial

The *IL6ST* gene encodes for a cytokine receptor subunit called GP130 that binds to multiple receptors including IL-6, IL-11, leukemia inhibitory factor (LIF), and oncostatin M. Two pathogenic, autosomal recessive variants have been identified in the *IL6ST* gene [17–20]. One defect inhibits signaling through all GP130-associated receptor pathways where the second defect inhibits signaling through all but the LIF receptor pathway.

The mutation that preserves LIF pathway signaling has been identified in two unrelated patients. Both patients have a phenotype remarkably like *STAT3* deficiency with early-onset pneumonias, elevated IgE, scoliosis, craniosynostosis, and eczema. These patients were shown to have absent *STAT3* response to IL6 stimulation. Patients can have decreased Th17 cells, reduced B cells, and eosinophilia.

The variant with complete LOF has been identified in seven patients from four families [19]. These patients were found to have a fatal Stuve-Weidemann-like syndrome. Many patients died *in utero* or in the early neonatal period with notable skeletal dysplasia and respiratory distress. One affected patient who lived to be 6 years of age developed eczema at 1 year of life and had scoliosis, short stature, and periods of hyperthermia. She died from cardiorespiratory arrest following scoliosis surgery.

IL6ST Dominant Negative

In addition to the two LOF variants in *IL6ST*, a dominant negative mutation has been described in 12 patients from 8 unrelated families [21]. This pathogenic variant leads to accumulation of mutant proteins in the cell surface. These patients have been shown to have significantly elevated IgE, eosinophilia, eczema, recurrent pyogenic skin and pulmonary infections, and scoliosis. However, unlike patients with *STAT3* deficiency and *IL6ST* partial deficiency, the Th17 cell population is normal.

ERBIN Deficiency

ERBB2-interacting protein (ERBIN) forms a cytoplasmic complex with *STAT3*, and phosphorylated SMAD2/3 that is integral to sequestering SMAD2/3 and ultimately has an inhibitory effect on transforming growth factor β (TGF- β). Unregulated TGF- β leads to an increase in T-regulatory (Treg) cells, increased IL-4R α expression, and increased Th2 cytokine expression. Three related patients were found to have an autosomal dominant mutation in ERBIN and

share many features with STAT3 deficiency related to this altered complex formation including recurrent infections, eczema, elevated serum IgE, eosinophilia, retained primary teeth, and skeletal and vascular abnormalities [22]. Interestingly, patients with ERBIN deficiency do not have the recurrent fungal infections, decrease in Th17 lymphocytes, or specific antibody defects that are seen in STAT3 deficiency.

Elevated IgE Not Associated with HIES

Several reported PIDDs can present with a notably elevated IgE but do not share the other features associated with HIES. The following disorders have been described over the past few years.

CARD11 Dominant Negative

CARD11 (also known as CARMA1) is a scaffolding protein that functions in lymphocyte receptor signaling pathways including Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF- κ B) and mechanistic target of rapamycin (mTOR) complex 1 pathways. Autosomal recessive mutations in *CARD11* have been previously described as a cause of CID leading to risk of opportunistic infections such as *Pneumocystis jirovecii* (PJP). A germline GOF mutation in *CARD11* has been shown to cause BENTA (B cell expansion with NF- κ B and T cell anergy). Recently, a dominant negative heterozygous mutation in *CARD11* was identified in four patients in three families [23]. These patients were found to have normal T cell numbers with defective proliferation that results in Th2 skewing, normal B cells, eosinophilia, and an elevated serum IgE. Clinically, affected patients present with notable atopy, cutaneous viral infections, recurrent respiratory infections, and lymphoma.

STAT5b Dominant Negative

Homozygous pathogenic variants in *STAT5B* are associated with T lymphopenia and impaired proliferation. Recently, a dominant negative mutation was identified in multiple patients from three unrelated families [24]. These patients share some features with those with autosomal recessive STAT5b deficiency, notably short stature, which is related to the role that STAT5b plays in growth hormone signaling. Patients with the dominant negative mutation did not have immune dysfunction or recurrent infections but did have associated eczema and an increased serum IgE.

Arp2/3-Mediated Filament Branching Defect

Defects in the Actin-related protein 2/3 complex subunit 1 B gene (*ARPC1B*) have been described to cause an autosomal recessive disease that shares some clinical features with patients who do not express Wiskott-Aldrich syndrome protein

(WASP) [25–27]. These patients had thrombocytopenia with small or normal platelet size and associated-bleeding episodes. Patients are at risk for invasive bacterial infections and significant cutaneous viral infections. They also have increased rates of atopic diseases including eczema, food allergy, and asthma, and frequently have associated eosinophilia and elevated serum IgE and IgA levels, though specific antibody function is normal. Inflammatory complications of vasculitis and colitis have been reported. Immunologic testing is notable for defective Treg function and defects in cytoskeleton function that impact the formation of the immunologic synapse.

Combined Immunodeficiencies Associated with DNA Repair Defects

NSMCE3 Deficiency

The *NSMCE3* gene (also known as *NDNL2*) encodes a subunit of the SMC5/6 complex that is necessary for DNA damage repair. Four children from two unrelated families with biallelic, pathogenic variants in *NSMCE3* were described to have severe pulmonary disease following viral respiratory infections [28]. All identified children died in early childhood from complications of severe lung disease. Patients presented with failure to thrive, and 50% had infantile eczema. Patients were noted to have thymic hypoplasia, T lymphopenia, impaired mitogen and antigen-related proliferation, and impaired-specific antibody responses. The DNA repair defect was in homologous repair, but VDJ recombination and B lymphocyte numbers were normal. Evidence of radiation sensitivity was also identified.

GINS1 Deficiency

The Go-Ichi-Ni-San complex subunit 1 (GINS1, aka PSF1) is necessary for DNA replication. Homozygous null mutations have been shown to be lethal for mice during embryogenesis. Five patients in four unrelated families were found to have compound heterozygous variants, with at least one hypomorphic mutation [29]. These patients presented with intrauterine growth retardation, viral infections, and malignancy. Immunophenotyping was notable for very low NK cell counts, neutropenia, and variable lymphocyte counts. Neutrophil counts were found to increase with bacterial infections and G-CSF treatment.

Humoral Immunodeficiencies

Humoral immunodeficiencies have primary defects in the B cell lineage. These defects can cause issues with B cell development and secondary abnormalities in immunoglobulin production. Associated autoimmunity is common in these diseases as

are mild impairments in T and NK cell populations. The most common symptomatic humoral immunodeficiency is common variable immunodeficiency (CVID) which involves low IgG, low IgM or IgA, and impaired antibody production to specific antigens. Many of these patients have defects in production or maintenance of switched memory B cells.

FNIP1 Deficiency

Six patients from five unrelated families were identified with homozygous or compound-heterozygous mutations in folliculin interacting protein 1 (*FNIP1*) [30, 31]. Some patients had complete absence of B cells and subsequent agammaglobulinemia. Patients presented clinically with recurrent sinopulmonary and gastrointestinal infections. In addition to infection-related complications like bronchiectasis, patients had Wolff Parkinson White syndrome, hypertrophic cardiomyopathy, myopathy, developmental delay, and neutropenia.

IRF2BP2 Deficiency

A father and his two children with CVID diagnoses were identified to have a heterozygous mutation in *IRF2BP2* [32]. *IRF2BP2* encodes a transcriptional co-pressor of the NFAT family. Homozygous LOF mutations in *IRF2BP2* are not viable in mice, and at this time it is not clear what role IRF2BP2 plays in the immune response. Heterozygous patients in the study presented in late adolescence with recurrent sinus infections, low IgG and IgM levels, absent IgA, and decreased switched memory B cell populations. One patient subsequently developed CVID-associated colitis.

NFE2L2 Autosomal Dominant

NFE2L2 encodes a transcription factor, NRF2. Four patients from unrelated families were found to have different autosomal dominant mutations that lead to loss of function of NRF2 [33]. Affected patients presented with recurrent lung, sinus, and skin infections, developmental delay, failure to thrive, and weakness. Laboratory studies were notable for hypogammaglobulinemia with reduced memory B cells, low homocysteine, and increased G6PD activity.

ATP6AP1 Deficiency

ATP6AP1 encodes a subunit of V-ATPase, which is necessary for acidification of both intracellular organelles and the extracellular space. Pathogenic variants in *ATP6AP1* are associated with disorders of glycosylation and lead to involvement of multiple organ systems. X-linked, pathogenic, hemizygous, variants in this gene have been identified in multiple unrelated families to cause an associated humoral immunodeficiency

[34–37]. Patients present with recurrent invasive infections, developmental delay, and hepatopathy. In infants, cutis laxa has also been described. The mutation is associated with mild to severe hypogammaglobinemia, leukopenia, and low copper. Fatality due to liver failure has been reported.

ARHGEF1 Deficiency

ARHGEF1 functions to activate guanosine triphosphate RhoA in the signaling of G protein-coupled receptors. In B cell-like diffuse large B cell lymphomas, homozygous somatic mutations in *ARHGEF1* are associated with an inability to signal with sphingosine-1-phosphate. Two related patients were identified with compound heterozygous germline mutations in *ARHGEF1* [38]. These patients presented with recurrent pneumonia and subsequent bronchiectasis. Both were found to have hypogammaglobinemia, absent specific antibody production, low total and switched memory B cell counts, and low CD8 + effector memory cells. One patient developed autoimmune thrombocytopenia and one developed bronchial mucoepidermoid carcinoma.

SH3KBP1 X-linked Deficiency

SH3KBP1, also known as CIN85, encodes a Cbl-interacting protein that forms a complex with SLP65. Two male siblings were identified with pathogenic germline mutations in *SH3KBP1*, located on the X chromosome [39]. One sibling died at age 15 from septic shock and had a history of recurrent pneumonia, otitis media, and sinusitis with very low immunoglobulin levels. The other brother had a history of recurrent infections until age 4 but no history of infections between 4 years of age and 12 years of age. He was found to have low serum IgM, low IgG4, and a non-protective response to unconjugated polysaccharide pneumococcal vaccination.

SEC61A1 Deficiency

SEC61A1 encodes for a subunit of the heterotrimeric Sec61 complex that forms a pore in the endoplasmic reticulum. Its function is necessary for the ability of the plasma cell to regulate endoplasmic reticulum stress. Ten people in one extended family and three people in an additional unrelated family, all with recurrent bacterial infections, were identified to have mutations in *SEC61A1* [40]. Affected patients had decreased serum IgG, IgM, and IgA levels and an impaired specific antibody response. The first family had a heterozygous missense mutation, while the second had a nonsense mutation leading to haploinsufficiency. Immunophenotyping showed normal T, B, and NK cell populations (including switched memory B cells); however, plasma cell development was impaired.

PIK3CG Deficiency

PIK3CG encodes for a subunit of PI3K γ , which is critical to regulating inflammation. Two unrelated patients have been identified with compound heterozygous mutations in *PIK3CG* [41, 42]. One patient presented in adolescence with a hemophagocytic lymphohistiocytosis (HLH)-like presentation. She had low T cell populations, but B cells and immunoglobulin levels were normal. The second patient presented with cryptogenic organizing pneumonia, hypogammaglobulinemia, specific antibody defects, lymphadenopathy, splenomegaly, and autoimmune cytopenias. She has subsequently developed enterocolitis.

CTNBL1 Deficiency

CTNBL1 encodes β -catenin-like protein 1, which binds to activation-induced cytidine deaminase (AID) to induce somatic hypermutations. One patient was identified with a homozygous mutation in *CTNBL1* [43]. The patient presented at age two with recurrent sinopulmonary and HSV infections, autoimmune cytopenias, and progressive hypogammaglobulinemia. She was found to have low T, B, and NK cell counts with absent switched memory B cells.

APRIL (TNFSF13) Deficiency

TNFSF13 encodes a proliferation-inducing ligand (APRIL) which works alongside B cell activating factor (BAFF) in B cell maturation and maintenance. One patient, born to consanguineous parents, was found to have a homozygous mutation in *TNFSF13* that was associated with hypogammaglobulinemia [44]. His history was notable for unremarkable infections in childhood. He was monitored without IgG replacement for 10 years; replacement was started following mild infection. He had subsequent development of alopecia areata. Immunophenotyping showed normal T and NK cells with decreased switched memory B cells.

Disorders of Immune Dysregulation and Autoimmunity

Advances in DNA sequencing technologies have expanded the historical definition of what constitutes a primary immunodeficiency. Instead of presenting with a more classic picture of severe or recurrent infections, molecular defects impacting immunologic tolerance, T cell signaling, and responses to cellular/pathogen debris can lead

to immune disorders that present with more prominent features of autoimmunity and immune dysregulation [45].

Disorders of Regulatory T cells

Since the initial identification that immune dysregulation, polyendocrinopathy, enteropathy, with X-linked inheritance (IPEX) syndrome was caused by pathogenic variants in *FOXP3* leading to a Treg cell defect, many other disorders have been described as the result Treg deficiency or dysfunction [46].

CD122 Deficiency

The interleukin-2 receptor subunit beta (CD122) is an important part of both the high-affinity IL-2 receptor (formed by CD25, CD122, and CD132) and the intermediate IL-2 receptor (formed by CD122 and CD132). While pathogenic variants in both *CD25* and *CD132* have been well described, autosomal recessive mutations in *CD122* were independently described in five separate kindreds [47, 48]. Patients presented with early-onset autoimmunity, including enteropathy, skin abnormalities, and autoimmune hemolytic anemia, similar to patients with IPEX syndrome, but additionally showed increased susceptibility to cytomegalovirus (CMV) and Epstein-Barr virus (EBV). This increased herpes virus susceptibility is thought to be secondary to the expression of the intermediate IL-2 receptor that binds both IL-2 and IL-15 on CD8+ T cells and NK cells. Subsequently, patients with CD122 deficiency had increased amounts of immature NK cells with decreased CD122 expression.

Bach2 Deficiency

The BTB and CNC homolog 2 (*BACH2*) super-enhancer transcription factor is expressed in both T and B lymphocytes and is crucial for the differentiation and maturation of these cells as well as for the development of Treg cells [49]. Genetic variations within *BACH2* have been previously associated with many immune-mediated diseases including multiple sclerosis, rheumatoid arthritis, chronic pancreatitis, asthma, inflammatory bowel disease, and type 1 diabetes. More recently, autosomal dominant, missense mutations within *BACH2* were described in three individuals from two separate families with early-onset autoimmunity and immunodeficiency [50]. Patients presented with autoimmune lymphocytic colitis and sinopulmonary infections and developed a progressive T cell lymphopenia. Immunophenotyping was notable for impaired memory B cell development, variable hypogammaglobulinemia, and decreased expression of Foxp3 within Tregs as a result of Bach2 haploinsufficiency.

DEF6 Deficiency

DEF6 is a unique guanine nucleotide exchange factor that acts downstream of the TCR to activate small GTPases and promote Ca²⁺ signaling, NFAT1 activation, and T cell adhesion. Recently, biallelic variants in *DEF6* were described in seven individuals from three separate families with early-onset autoimmunity and recurrent infections [51, 52]. Patients presented with a variable phenotype of enteropathy, autoimmune cytopenias, lymphoproliferation, and increased susceptibility to EBV infection/lymphoma. Immunologic evaluation was notable for mild T and B cell lymphopenias with an expansion of Foxp3 + CD25 – Treg cells and significantly decreased expression of CTLA4 on both stimulated and unstimulated-memory Treg cells. The authors go on to demonstrate that memory Treg cells from DEF6-deficient individuals showed impaired trafficking and expression of the checkpoint inhibitor CTLA4 that could be contributing to the autoimmune phenotype.

Defective T cell Signaling Resulting in Systemic Autoimmunity

Cellular signaling downstream of the TCR and a variety of cytokine receptors is necessary for normal T and B cell development. It is also required for initiating a coordinated immunologic response and returning to a state of homeostasis once a threat has been eliminated. This often involves a delicate balance of activation and inhibition mechanisms that when altered can lead to unchecked inflammation and subsequent autoimmunity.

SOCS1 Haploinsufficiency

Suppressor of cytokine signaling 1 (SOCS1) is an important negative regulator of type 1 and type 2 interferon (IFN) signaling through its inhibition of Janus kinase (JAK) activity and subsequent downregulation of STAT1 and STAT2. Dominant mutations in *SOCS1* have recently been described in several patients presenting with variable, early-onset, multisystemic autoimmunity including cytopenias, systemic lupus erythematosus, glomerulonephritis, psoriasis, arthritis, thyroiditis, hepatitis, and lymphoproliferation [53, 54]. Patient immunophenotyping was notable for T cell lymphopenias, decreased switched memory B cells, increased CD21 low B cells, and hypogammaglobulinemia with increases in STAT1 phosphorylation and expression of type I and type II interferon (IFN)-stimulated genes. One patient with SOCS1 haploinsufficiency was reported to develop SARS-CoV-2-triggered autoimmunity, which was thought to be related to increases in type 1 and type 2 interferon signaling [55].

ZAP 70 Mixed LOF and GOF

ZAP 70 is necessary in TCR signaling and homozygous LOF mutations cause a SCID with notable decreases in CD8 + T cells. A sibling pair was identified that had compound heterozygous mutations, one mutation that caused reduced function, and one that caused gain of function of ZAP 70 [56]. These siblings had severe autoimmunity that began in early infancy including bullous pemphigoid, colitis, and autoantibody to factor VIII triggered hemophilia. Symptoms were resolved in both patients following HSCT.

Immunodysregulatory Disorders Associated with Hemophagocytic Lymphohistiocytosis

Defects in cytotoxic CD8 + T cells, NK cells, or inflammatory regulation can result in severe systemic inflammation, macrophage activation, and subsequent hemophagocytosis. Many primary immunodeficiencies have been identified where HLH is either the predominant feature or a described complication, often in the context of infection [57].

Hermansky-Pudlak Syndrome Type 10

Biallelic defects in *AP3D1*, which encodes the delta subunit of the adaptor protein 3 (AP3) complex involved in lysosome trafficking, were recently identified in a single patient as an additional cause of Hermansky-Pudlak syndrome (HPS), classified as HPS type 10 [58]. The clinical presentation was similar to HPS type 2 with oculocutaneous albinism, mild facial dysmorphism, microcephaly, hip dysplasia, chronic neutropenia, persistent hepatosplenomegaly, reduced cytotoxic lymphocyte degranulation, and susceptibility to airway infections. Additionally, the index patient developed early-onset neurologic symptoms including microcephaly, severe neurodevelopmental delay, generalized seizures, and hearing impairment not seen in HPS2. The authors demonstrate that a deficiency of the delta subunit destabilizes the AP3 complex and was associated with degradation of all other subunits. The patient ultimately died after turning 3 years old from septic pneumonia.

TIM3 Deficiency

T cell immunoglobulin and mucin domain-containing protein-3 (TIM3) encoded by the hepatitis A virus cellular receptor 2 (*HAVCR2*) gene is an inhibitory receptor expressed on T cells, B cells, dendritic cells, and macrophages and is thought to be important for inducing T cell exhaustion. Biallelic pathogenic variants in *HAVCR2* have now been identified as a cause of subcutaneous panniculitis-like T cell lymphoma (SPTCL) and associated HLH [59–62]. Affected patients are more likely to manifest with

HLH and require HSCT compared to those with other variants of SPTCL and have also been reported to have recurrent, clonally unrelated lymphoma [60, 61].

MCM10 Deficiency

Biallelic LOF variants in *MCM10*, which is important for cell replication, were described in one patient who presented with very low NK cell counts, fever, and CMV infection [63]. His course was consistent with HLH with elevated ferritin and low fibrinogen levels. He underwent HSCT but died from CMV complications. A separate family was identified that had three intrauterine fatalities related to restrictive cardiomyopathy [64]. These fetuses were also found to have compound heterozygous LOF mutations in *MCM10*.

HEM1 Deficiency

Hematopoietic protein-1 (HEM1) is a member of the WASP-family verprolin-homologous protein (WAVE) regulatory complex that stimulates F-actin polymerization in response to activation of several immune receptors and is important for activation, migration, and synapse formation. Recently, biallelic LOF variants in *NCKAP1L*, the gene that encodes for HEM1, were shown to be associated with a novel primary immunodeficiency associated with lymphoproliferation, hyperinflammation, and features of HLH [65–67]. Affected patients manifested with sinopulmonary infections and skin infections coupled with cytoskeleton abnormalities, autoantibody production, increases in exhausted memory T cell populations, abnormal T cell activation, and an overproduction of Th1 cytokines.

Immunodeficiencies Associated with Hyper eosinophilia

JAK1 Gain of Function

Four patients from two different families have been identified to have germline GOF mutations in the inhibitory, pseudokinase domain of Janus kinase 1 (*JAK1*) [68, 69]. Increased basal phosphorylation of STAT proteins and active target gene transcription in both stimulated and unstimulated patient T and B cells was seen in vitro. Unlike biallelic, *JAK1* LOF mutations that are associated with increased susceptibility to atypical mycobacterial infections, patients with autosomal dominant, *JAK1* GOF present with severe atopic dermatitis, profound hyper eosinophilia with associated eosinophilic gastrointestinal disease, hepatosplenomegaly, and failure to thrive. Patients were successfully treated with JAK inhibitors.

STAT5b GOF

STAT5B GOF mutations have been previously described in patients with leukemia and lymphomas [70, 71]. Recently, somatic mutations in *STAT5B* have been identified to cause a hyper eosinophilic syndrome. Two patients with non-clonal eosinophilia, atopic dermatitis, urticaria-like rash, and diarrhea who were found to have *STAT5B* GOF mutations were recently reported [70]. Functional T cell studies in these patients confirmed a marked increase in STAT5b responsiveness to a variety of cytokines. Affected patients also had minimally increased baseline activity compared with cells from their parents and unrelated controls.

Immunodeficiencies with Early-Onset Enteritis/Enteropathy

Autoimmune and inflammatory gastrointestinal disease is a common manifestation in patients with underlying PIDDs. Although the overall incidence of traditional, polygenic inflammatory bowel disease (IBD) appears to be increasing among younger children, early manifestation of enteritis and/or enteropathy should raise one's suspicion of an underlying monogenic immunodeficiency [72].

TGF-β1 Deficiency

Transforming growth factor beta 1 (TGF-β1) is a member of the TGF-β family of proteins that controls embryogenesis, development, and homeostasis. Recently, biallelic LOF variants in the *TGFB1* gene were described in three individuals with very-early-onset IBD and neurologic abnormalities [73]. Patients presented in the first few months of life with bloody diarrhea, failure to thrive, microcephaly, encephalopathy, seizures, and recurrent viral infections, and two of the three affected individuals died before the age of four. Immunologic evaluation was notable for decreased T cell proliferation to antigens, anti-CD3, and anti-CD28.

RIPK1 Deficiency

Receptor-interacting serine/threonine kinase 1 (RIPK1) is an important regulator of inflammation and cell death responses downstream of tumor necrosis factor (TNF) receptor 1. Biallelic LOF variants in this key signaling molecule have been described in patients presenting with very-early-onset IBD, lymphopenia, and arthritis [73, 74]. Patients also have recurrent viral, bacterial, and fungal infections secondary to impaired innate and adaptive immunity. Immunophenotyping was notable for impaired activation of MAP kinase and NFκB pathways, increased inflammasome activity, and impaired TNF-α-mediated cell death.

ALPI Deficiency

Intestinal alkaline phosphatase (ALPI) is a metalloenzyme that catalyzes phosphate hydrolysis of bacterial lipopolysaccharide (LPS) and is important for maintaining homeostasis by reducing Toll-like receptor (TLR) 4 activity. Recently, biallelic LOF mutations were described in two unrelated patients presenting with early-onset, severe IBD with pancolitis and ulcerations [75]. Affected individuals had undetectable ALPI activity in their stool and required bowel resections after having poor responses to anti-TNF therapy.

TRIM22 Deficiency

Tripartite motif-containing 22 (TRIM22) is a RING finger E3 ubiquitin ligase that has been shown to have antiviral activity and activate NF- κ B signaling. Biallelic LOF variants in *TRIM22* have been described in eight patients with early-onset IBD characterized by granulomatous colitis and severe perianal disease [76, 77]. Described variants were shown to disrupt NOD2-dependent IFN- β and NF- κ B signaling.

CD55 Deficiency

CD55 or CHAPLE disease is an autosomal recessive disease caused by mutations of the complement regulator *CD55* gene leading to a loss of protein expression [78, 79]. CD55 deficiency is associated with hyperactivation of complement, angiopathic thrombosis, and severe protein-losing enteropathy (PLE). There have been 11 patients reported with abdominal pain and diarrhea caused by early-onset PLE with primary intestinal lymphangiectasia. Other manifestations of this genetic mutation can include edema due to hypoproteinemia, malabsorption, bowel inflammation, recurrent infections, and angiopathic thromboembolic disease [78, 79].

Autoinflammatory Syndromes

There has been an incredible expansion in our knowledge about autoinflammatory disorders which has been in conjunction with our ability to find genetic causes of these diseases. A number of these diseases are associated with arthritis/arthralgias.

Type I Interferonopathies

Type I IFNs are widely expressed cytokines that are important for antiviral immunity and cancer immunosurveillance. Several inborn errors of immunity have now been described that are characterized by constitutive activation of the type I

INF pathway, resulting in an autoinflammatory and autoimmune phenotype [80].

USP18 Deficiency

Biallelic LOF mutations in ubiquitin-specific peptidase 18 (*USP18*) have been described in six patients that were born with a pseudo-TORCH syndrome [81, 82]. USP18 acts as an important negative regulator of type I IFN signaling by blocking the interaction between JAK1 and the type I IFN receptor 2 and by enzymatically removing the ubiquitin-like protein ISG15. USP18-deficient fibroblasts showed enhanced induction of IFN-stimulated gene transcripts after IFN stimulation in vitro. Patients presented perinatally with intracranial hemorrhage, calcifications, brain malformations, liver dysfunction, thrombocytopenia, and a septic-shock like picture with respiratory failure and seizures. While most infants did not survive beyond the perinatal period, one was able to be successfully treated with JAK inhibition therapy and was last reported to be in remission at 2 years of age [82].

STAT2 GOF (Phenocopy of USP18)

While LOF mutations in *STAT2* are known to cause an inborn error of immunity predisposing to severe viral infections, a homozygous GOF mutation in *STAT2* was recently described in a single infant born to consanguineous parents [83]. The patient presented with an early-onset, fatal, severe inflammatory picture, similar to USP18 deficiency. Interestingly, the described variant exerted a GOF effect through a loss of STAT2's ability to appropriately traffic USP18 to IFNAR2, resulting in impaired, negative regulation of type I INF signaling.

OAS1 GOF

Five patients from three different families who presented with infantile-onset pulmonary alveolar proteinosis and hypogammaglobulinemia were identified to have heterozygous GOF mutations in the IFN-induced antiviral protein 2'-5' oligoadenylate synthetase 1 (*OAS1*) [84]. All children developed symptoms after respiratory tract infections. While the exact mechanism of the defect has not yet been elicited, the authors speculate that the defect leads to an exaggerated response to viral infections leading to alveolar macrophage dysfunction and impaired lung surfactant catabolism. HSCT was associated with improvement of pulmonary alveolar proteinosis in two patients.

LSM11 and RNU7-1 Deficiency

Since Aicardi-Goutières syndrome (AGS) was initially described in 1984, as a "progressive disorder of the central nervous system with bilateral spasticity and dystonia,

acquired microcephaly, and a rapid course toward profound deterioration and death,” pathogenic variants in several genes that lead to upregulation of type I INFs have been described to cause an AGS-like phenotype [85]. Recently, biallelic LOF variants in both *LSM11* and *RNU7-1* were identified as novel genetic causes of an AGS interferonopathy [86]. The authors demonstrate that LOF of either of these two components of the replication-dependent histone pre-mRNA-processing complex results in a disturbance of histone mRNA expression and protein status in affected fibroblasts in vitro that lead to aberrant interferon signaling by the double-stranded DNA sensor cyclic GMP-AMP synthase (cGAS).

CDC42

The cell division control protein 42 homolog (*CDC42*) gene encodes a Rho family GTPase that is important for a wide variety of cellular pathways including: cell polarity and migration, adhesion, actin polarization, cytoskeletal structure, and cell-cycle progression. Several patients have now been described with heterozygous variants in *CDC42* that have displayed a broad clinical phenotype, which is somewhat related to the location of the variant within the gene [87–98]. Pathogenic variants in the switch II domain of the gene generally result in Takenouchi-Kosaki syndrome, which is characterized by neurodevelopmental delay, dysmorphic facies, macrothrombocytopenia, musculoskeletal anomalies, lymphedema, and frequent infections [87, 88, 90–92]. Variants that affect the association with CDC42/RAC-interacting binding motifs can have profound effects on development resembling RASopathies [89]. More recently, pathogenic variants in the C-terminus region of the gene were reported to cause a severe, autoinflammatory syndrome characterized by neonatal onset of pancytopenia, autoinflammation, rash, and episodes of hemophagocytic lymphohistiocytosis (NOCARH syndrome) secondary to aberrant subcellular localization of CDC42, enhanced NF- κ B signaling, dyshematopoiesis, and NK cell dysfunction [94–97]. In these patients, IL-1 blockade with anakinra, IFN- γ inhibition with emapalumab, and HSCT have been successful.

Inflammasome Defects

The inflammasome is a multimeric protein complex that initiates inflammation through the activation of caspase-1 and subsequent release of IL-1 β and IL-18 in response to microbial or endogenous danger signals [99]. Although inflammasome activation is an important part of innate immunity, there are now several monogenic defects relating to the inflammasome that lead to aberrant autoinflammation.

NLRP1 Deficiency and GOF

NLRP1 was the first NOD-like receptor that was described but the most recent to be associated with human disease. It is the largest inflammasome sensor, and its activation is thought to be uniquely dependent on proteasomal degradation [100]. Pathogenic GOF variants in the PYD domain have been associated with palmoplantar carcinoma, familial keratosis lichenoides chronica, and corneal intraepithelial dyskeratosis without significant systemic inflammation [101, 102]. In contrast, a more autoinflammatory phenotype with periodic fevers, arthritis, and dyskeratosis has been described in patients with pathogenic variants between the NACHT and LRR domains and in the FIIND domain, which is unique to NLRP1 [103]. Treatment involves IL-1 blockade to control the systemic inflammation and retinoic acid and vitamin A for the skin manifestations.

RIPK1 GOF

In addition to the autosomal recessive immune dysregulation and early-onset IBD that is associated with LOF variants in *RIPK1*, an autosomal dominant autoinflammatory disorder with periodic fevers, lymphoproliferation, arthralgias, and microcytic anemia has been described [104, 105]. The autoinflammatory phenotype that is seen in these patients is the result of missense mutations that prevent the caspase cleavage of RIPK1, an important regulative mechanism to inhibit necroptosis and maintain inflammatory homeostasis. Five of the six described patients had a good treatment response to steroids and anti-IL-6R therapy but not IL-1 or TNF blockade.

Non-inflammasome-Related Defects

OTULIN Deficiency

OTULIN is a deubiquitinating enzyme that removes methionine 1-linked polyubiquitin signals conjugated by the linear ubiquitin chain assembly complex (LUBAC) and plays an important role in negatively regulating TNF-related NF- κ B signaling. Patients with biallelic LOF variants in *OTULIN* present with a severe, OTULIN-related autoinflammatory syndrome (ORAS) characterized by recurrent fevers, diarrhea, panniculitis, and arthritis [106–109]. OTULIN was also recently shown to be important for liver homeostasis, with progressive steatotic liver disease being reported in an OTULIN-deficient patient [110]. Affected patients have enhanced LUBAC induction of NF- κ B activation leading to increases in proinflammatory cytokines. Both TNF inhibition and HSCT have been reported as possible treatment strategies [106–108].

A20 Haploinsufficiency

An association between mutations in the gene *TNFAIP3*, encoding the NF- κ B regulatory protein A20, and autoinflammatory disease has been described with symptoms that often start in early childhood [111]. The main clinical findings associated with this diagnosis are recurrent oral, genital, or gastrointestinal ulcers. There have also been arthralgias, cutaneous lesions, episodic fever, ocular inflammation, and recurrent infections associated with the disease. Clinical phenotypes can vary between patients, even those within the same family. The inheritance pattern for this disorder is autosomal dominant.

Congenital Defects of Phagocyte Number or Function

Congenital Neutropenia

SMARCD2 Deficiency

Biallelic LOF variants in *SMARCD2* (SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily D, member 2) have recently been described in five individuals from unrelated families as a cause of abnormal neutrophil development and function similar to the phenotype of specific granule deficiency caused by LOF mutations in the transcription factor CCAAT-enhancer-binding protein ϵ (C/EBP ϵ) [112, 113]. *SMARCD2* has been shown to interact with C/EBP ϵ and is important for myeloid differentiation and granulopoiesis. Clinically, affected patients presented with delayed separation of the umbilical cord, severe bacterial infections, developmental aberrations (learning difficulties), misaligned teeth, brittle nails, and progressive myelodysplasia. *SMARCD2*-deficient neutrophils were found to have absent granule proteins, functional defects of chemotaxis, and impaired bacterial killing with a reduced neutrophil oxidative burst response to platelet-activating factor and N-formylmethionyl-leucyl-phenylalanine.

Shwachman-Diamond Syndrome

Shwachman-Diamond syndrome is a congenital multisystem disorder characterized by exocrine pancreatic dysfunction, skeletal abnormalities, neutropenia, and associated bone marrow failure. Over the last few years, pathogenic mutations in three additional genes important for ribosome biogenesis have been described to cause a Shwachman-Diamond phenotype. Biallelic LOF mutations in *DNAJC21* and *EFL1* were reported to cause short stature with metaphyseal dysplasia, developmental delay, exocrine pancreatic dysfunction, and neutropenia with *DNAJC21* deficiency presenting

with more profound global bone marrow failure by 12 years of age [114–118]. Additionally, heterozygous mutations in *SRP54*, which codes for a key protein in the ribonucleoprotein complex that mediates the co-translational targeting and translocation of secretory and membrane proteins to the ER, have been described to cause a Shwachman-Diamond-like syndrome [119, 120]. Affected patients develop a profound neutropenia with a maturation arrest at the promyelocytic stage occurring within the first months of life and variable neurodevelopmental delay and exocrine pancreatic dysfunction. The clinical phenotype is thought to be the result of mutation-specific dominant negative effects [121].

HYOU1 Deficiency

Biallelic defects in hypoxia upregulated 1 (*HYOU1*), a chaperone protein that localizes to the endoplasmic reticulum and mitochondria and participates in cell stress responses, were recently reported as a cause of a novel immunometabolic syndrome [122]. The single patient presented with congenital neutropenia, recurrent respiratory and herpes viral skin infections, stress-induced hypoglycemia, and relapsing Takayasu arteritis. Immunophenotyping demonstrated low B cells with a memory predominance but reduced switched memory cells. Responses to polysaccharides were absent; however, the patient was receiving concurrent low-dose immunosuppression.

Defects in Phagocyte Motility

WDR1 Deficiency

Biallelic LOF variants in *WDR1*, which encodes the protein actin interacting protein 1, were recently described to cause a novel immunodeficiency with mild neutropenia, poor wound healing, recurrent bacterial skin, and sinopulmonary infections as the result of defective regulation of the neutrophil cytoskeleton [123]. Patients also developed characteristic stomatitis and oral stenosis severe enough to warrant gastrostomy tube placement in some instances. An autoinflammatory syndrome with recurrent fevers and associated thrombocytopenia and T and B lymphocyte abnormalities secondary to aberrant actin regulation of the inflammasome has also been reported [124, 125]. *WDR1*-deficient neutrophils have a distinctive neutrophil herniation of the nuclear lobes and agranular regions within the cytosol with markedly impaired chemotaxis and chemokinesis.

CEBPE GOF

In contrast to the autosomal recessive neutrophil specific granule deficiency that is seen with LOF mutations in the transcription factor C/EBP ϵ , homozygous gain of function variants affecting the DNA binding domain was recently shown

to be associated with non-canonical inflammasome activation caused by decreased association with transcriptional repressors in three individuals from one family [126]. This novel primary immunodeficiency, which the authors term CAIN syndrome (C/EBPε-associated autoinflammation and immune impairment of neutrophils), presents clinically with recurrent, 4–5-day episodes of abdominal pain, fevers, and systemic inflammation with frequent upper respiratory tract and skin infections, lymphangitis, buccal ulcerations, and mild bleeding abnormalities. Affected patients had normal neutrophil and platelet morphology but significant alterations in the transcriptome of unstimulated granulocytes compared to controls and enhanced non-canonical, caspase-4/5-mediated inflammasome activation.

Defects of Phagocyte Function/Respiratory Burst

CYBC1 Deficiency

LOF mutations in *CYBC1* were recently identified in eight individuals as an autosomal recessive cause of chronic granulomatous disease (CGD) [127]. Affected patients had an abnormal, PMA-induced neutrophil oxidative burst assay similar to CGD patients with *NCF1* biallelic mutations and presented with the pathognomonic infections, IBD, and pro-inflammatory responses all characteristic of CGD. *CYBC1* is thought to co-localize and interact with gp91^{phox} in the endoplasmic reticulum where it likely acts as a chaperone for dimerization of gp91^{phox} and p22^{phox}.

Immunodeficiencies with Specific Pathogen Susceptibilities

While most primary immunodeficiencies present with a global increase in the frequency or severity of infections to a broad category of pathogens, some immunologic defects predispose the affected individual to a restricted number of pathogens or even a single microorganism. When this occurs, a tremendous amount of insight is often gained about either the virulence strategies utilized by the invading organism or the mechanisms implemented by the immune system to protect the host. Recently described PIDDs with specific pathogen susceptibilities discussed herein are summarized in Table 1.

Immunodeficiencies with EBV-Associated Lymphoproliferation/Lymphoma

CD70 Deficiency

The CD70–CD27 axis is important for immune surveillance of B cells by promoting antigen specific T cell expansion and is critical for proper immune response against EBV. Patients with a deficiency in CD27, a T cell co-stimulatory molecule, have previously been identified to develop EBV-associated lymphoproliferative disorders. More recently, defects in CD70, the ligand for CD27, were described in six patients from 4 different families that had similar susceptibilities to EBV [128–130]. Patients present with recurrent EBV-driven

Table 1 Recently described PIDDs with specific pathogen susceptibilities

Name of disease (<i>gene</i>)	Inheritance	OMIM #	Susceptible organism/disease
CD70 deficiency (<i>CD70</i>)	AR	602,840	EBV (lymphoproliferation, lymphoma)
CD137 deficiency (<i>TNFRSF9</i>)	AR	602,250	EBV (lymphoproliferation, lymphoma)
FAAP24 deficiency (<i>FAAP24</i>)	AR	610,884	EBV (lymphoproliferation, lymphoma)
RASGRP1 deficiency (<i>RASGRP1</i>)	AR	603,962	EBV (lymphoproliferation, lymphoma)
TET2 deficiency (<i>TET2</i>)	AR	619,126	EBV (lymphoproliferation, lymphoma)
RLTPR deficiency (<i>CARMIL2</i>)	AR	610,859	EBV (lymphoproliferation, smooth muscle tumors)
TBX21 deficiency (<i>TBX21</i>)	AR	604,895	Mycobacterium
IFNG deficiency (<i>IFNG</i>)	AR	618,963	Mycobacterium
JAK1 deficiency (<i>JAK1</i>)	AR	147,795	Mycobacterium
SPPL2a deficiency (<i>SPPL2A</i>)	AR	608,238	Mycobacterium and <i>Salmonella</i>
TIRAP deficiency (<i>TIRAP</i>)	AR	614,382	<i>Staphylococcus aureus</i>
IRF9 deficiency (<i>IRF9</i>)	AR	147,574	Influenza (severe disease)
IFNAR1 deficiency (<i>IFNAR1</i>)	AR	107,450	Vaccine related disease (yellow fever, measles)
IFNAR2 deficiency (<i>IFNAR2</i>)	AR	602,376	Vaccine related disease (measles)
RNA polymerase III deficiency (<i>POLR3A</i> , <i>POLR3C</i> , <i>POLR3F</i>)	AD	614,258, 617,454, 617,455	VZV
<i>SNORA31</i>	AD	NA	HSV1 (encephalitis)
<i>ATG4A</i>	AD	300,663	HSV2 (Mollaret's meningitis)
<i>MAP1LC3B2</i>	AD	NA	HSV2 (Mollaret's meningitis)

lymphoproliferation, EBV-positive lymphoma, and autoimmune-inflammatory features including uveitis, arthritis, and periodic fevers. Immunophenotyping was notable for decreased memory B cells and hypogammaglobulinemia. Patients also had sub-optimal responses to vaccination. While lymphocyte proliferation was intact to PHA, anti-CD3, and anti-CD28, affected CD8+ T cells demonstrated defective cytotoxicity against EBV-infected B cells in vitro.

CD137 Deficiency

The TNF receptor family member 4-1BB (CD137) is expressed on the surface of activated T cells and when bound, can preferentially promote the expansion, survival, and cytotoxicity of CD8+ T cells. Six patients from different families have been reported with biallelic, loss of function defects in *CD137* [131, 132]. Clinically, they presented at a young age with recurrent sinopulmonary and herpes viral infections with the majority developing EBV-associated lymphoproliferation or lymphoma. Their immunologic evaluation was consistent with a combined immunodeficiency with hypogammaglobulinemia, poor responses to T cell-dependent and independent antigens, and impaired T cell proliferation. Defective T cells also showed decreased expression of IFN γ and perforin.

FAAP24 Deficiency

Fanconi anemia-associated protein 24 (FAAP24) is a part of the Fanconi anemia core complex and plays a crucial role in DNA repair through its role in the Fanconi anemia signaling pathway and the ATR/Chk1 signaling pathway. Homozygous LOF variants in *FAAP24* were recently described in two siblings with fatal EBV-associated lymphoproliferative disease [133]. Using immortalized patient T cells, the authors show impaired cell cycle activation after DNA damage as well as an impaired FANCD2 monoubiquitination as evidence that the mutation leads to a functional defect of FAAP24.

RASGRP1 Deficiency

RASGRP1 is a diacylglycerol-regulated guanidine exchange factor (GEF) for the small GTPase Ras that is highly expressed in T and NK cells. It is considered to be the main GEF responsible for activating the Ras-MAP kinase/ERK kinase pathway. Over the last few years, several patients with biallelic LOF mutations in *RASGRP1* have been described to develop a CID with impaired cytoskeleton dynamics, and EBV-associated lymphoproliferation and lymphoma [134–138]. Patients are susceptible to severe viral (CMV, HPV), fungal, and bacterial infections and often have associated-hepatosplenomegaly and autoimmune cytopenias. Their immunologic evaluation is significant for decreased

percentages of naïve T cells, TCR clonality, NK cytotoxic function abnormalities, and impaired T and B cell activation, proliferation, and motility.

CARMIL2 Deficiency

Capping protein regulator and myosin 1 linker 2 (*CARMIL2*) is essential for T cell CD28 cosignaling and can modulate signaling in B cells, NK cells, and some myeloid cells. It also orchestrates actin polymerization and is important for cytoskeletal organization, endocytosis, and cell migration. There have now been several reports of patients with biallelic LOF variants in *CARMIL2* that present with characteristic EBV+ smooth muscle tumors, recurrent bacterial, fungal, and mycobacterial infections, persistent dermatitis, viral skin infections, and early-onset IBD [139–147]. Immunophenotyping is notable for a significant reduction in Treg cells, reduced mucosal-associated invariant T cells, reduced memory B cells, poor responses to both T cell-dependent and independent antigens, and impaired activation of the canonical NF- κ B pathway in a CD28-dependent manner.

TET2 Deficiency

Ten-eleven translocation methylcytosine dioxygenase 2 (TET2) is an important epigenetic regulator through its role in DNA demethylation and interactions with histone-modifying enzymes and transcription factors. TET2 is highly expressed in hematopoietic progenitor cells, and somatic TET2 LOF mutations are often seen in hematopoietic disorders, myeloid and lymphoid malignancies, and clonal hematopoiesis of indeterminate potential. Recently, germline LOF mutations were reported to cause an autosomal recessive primary immunodeficiency in three individuals with EBV-associated lymphoproliferative disease, recurrent sinopulmonary infections, and FTT [148]. Immunophenotyping was notable for an autoimmune lymphoproliferative syndrome-like phenotype with increased double-negative T cells, soluble CD25, soluble Fas ligand, and IL-10 and decreased Th1, Th17, and follicular helper T cells, and memory B cells. Affected individuals had variable hypogammaglobulinemia, and impaired Fas-dependent apoptosis. Interestingly, all three patients had autologous T cell reconstitution after HSCT despite T lymphoid depleting conditioning and subsequently died of complications.

Immunodeficiencies with Other Severe Viral Infections

IRF9 Deficiency

Defects in IRF9 can put the host at risk of recurrent and severe viral infections including influenza [149, 150]. Hernandez et al. described a 5-year-old female with a history of

recurrent viral infections. This included a severe influenza infection in addition to past respiratory syncytial virus, adenovirus, and parainfluenza virus infections. A pathogenic, homozygous variant in *IRF9* was found on WES and confirmed with Sanger sequencing [150]. A family who had multiple members with increased susceptibility to severe viral infections who were found to be IRF9 deficient has also been reported [149].

IFNAR1 Deficiency

Live attenuated vaccines do not cause life threatening disease in immunocompetent hosts, but patients with certain inborn errors in immunity can experience vaccine-driven disease. Recently, mutations causing autosomal recessive IFNAR1 deficiency were reported in children with live vaccine-related life-threatening infections [151]. In these patients, there is a decrease in INFAR1-dependent responses to IFN- α/β . One child was noted to have vaccine strain measles with symptoms starting under 2 weeks from when he was given the vaccine. Interestingly, that child had younger sibling who died 4 weeks after receiving the MMR vaccine, but genetic testing was not possible to confirm a specific diagnosis. Another child with this mutation was reported to have yellow fever vaccine-related disease including hepatic and renal dysfunction along with respiratory failure requiring intubation [151]. Both children recovered from their vaccine-related infections and were noted to be in good health at the time that article was published.

IFNAR2 Deficiency

Like IFNAR1 deficiency, there have been reports of vaccine-related disease in children with autosomal recessive INFAR2 deficiency after receiving live vaccines [152, 153]. There is a decrease in INFAR2-dependent responses to IFN- α/β with this genetic mutation. One patient was reported to have a fatal encephalitis felt to be secondary to his MMR vaccination. There was evidence of sustained viral replication along with HHV6 in brain samples obtained as part of the diagnostic work-up [152]. A second child with *INFAR2* mutations was reported to have HLH 5 days after his MMR vaccine along with recurrent viral infections [153].

RNA Polymerase III Deficiency

Though varicella zoster virus (VZV) usually causes chicken pox with a primary infection, there are those with a primary immune defect in which that infection can cause life-threatening symptoms of disease. Ogunjimi et al. reported

four cases of acute severe VZV infections in children who were found to be heterozygous for rare missense mutations in *POLR3A*, *POLR3C*, or both [154]. Variations in *POLR3F* can cause similar disease and with all three of the possible genetic defects, there is abnormal recognition of the varicella virus and a secondary decreased induction of IFN. The children in the previously mentioned report were all healthy prior to their VZV infection and had not experienced other recurrent viral infections [154].

SNORA31 Variations in *SNORA31* have been recently reported to decrease cortical neuron-intrinsic (CNS-intrinsic) immunity to herpes simplex virus (HSV-1) and put the host at risk of herpes simplex encephalitis [155]. Five unrelated patients with a history of HSV-1 encephalitis were found to have *SNORA31* variants thought to cause disease in an autosomal dominant pattern.

ATG4A and MAP1 LC3B2

Herpes simplex virus 2 (HSV2) can cause a recurrent form of viral meningitis, Mollaret's meningitis, in patients with specific genetic variations. Hait et al. described two adult patients with recurrent HSV2 lymphocytic Mollaret's meningitis [156]. One patient was noted to have a rare monoallelic variant in the autophagy protein ATG4A and the second in the autophagy protein LC3B2 [156].

Immunodeficiencies with Mycobacterial Susceptibility

There are a group of immune defects that lead to an increased Mendelian susceptibility to mycobacterial disease (MSMD). These patients can be susceptible to even weakly virulent mycobacterial infections. While some of these diseases have been described in the past, new genetic defects have been documented over the past several years. Recently, in the 2021 update of the IUIS Committee, LOF defects in both *TBCX21* and *IFNG* have been described to cause autosomal recessive PIDDs with decreased IFN- γ production [2]. Additional diseases recently described can increase MSMD.

JAK1 Deficiency

The JAK1 is involved in a pathway which is critical in immune responses, and its dysregulation can cause cancer or disorders of the immune system [157]. JAK 1 deficiency is a LOF defect, which results in an autosomal recessive disease that is notable for decreased IFN- γ production. Patients with JAK1 LOF have shown an increased susceptibility to mycobacterial disease, viruses, and early-onset urothelial carcinoma [158, 159].

SPPL2a Deficiency

A recently described disorder, which is associated with an inborn error in IFN- γ immunity, is SPPL2a deficiency. This diagnosis confers an increased susceptibility to mycobacterial and Salmonella infections [160]. It has been determined that SPPL2a-deficient memory Th1 cells, when stimulated with mycobacterial antigens in vitro, will not produce IFN- γ [160]. In one study, three patients with this disorder were described to have a significant defect of mycobacterium-specific IFN- γ production by specific CD4 + memory T cells. All three children were diagnosed with mycobacterial infections and subsequently found to have LOF mutations in *SPPL2A* [160].

Immunodeficiencies with Susceptibility to *Staphylococcus aureus*.

TIRAP Deficiency

TIRAP, which encodes a TIR-domain-containing adaptor of TLR2 and TLR4, can play a critical role in host defense. In patients with TIRAP deficiency, an autosomal recessive disorder, there is an impaired cellular response to specific TLR (including TLR2 and TLR4) stimulation [161, 162]. Though in humans, TIRAP can be redundant for protective immunity against many pathogens, patients with this disorder can be predisposed to severe staphylococcal infections. In a family with this defect, only one of the eight individuals with TIRAP deficiency had a serious staphylococcal infection noted [161]. This could be secondary to mixed penetrance of the disease, virulence of the staphylococcal strain, total bacterial load, or a combination of these factors [161].

Conclusion

This review provides an update on the more recently described inborn errors of immunity. The rise in the number of identifiable genes is secondary to our increasing ability to perform genetic testing on patients with known or suspected disease. As we continue to improve our genetic testing techniques, and they become more generally available, we will likely continue to see an increase in the identifiable causes of PID.

Author Contribution 1. Each author made substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of data; or the creation of new software used in the work.

2. Each author drafted the work or revised it critically for important intellectual content.

3. Each author approved the version to be published.

4. Each author agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Availability of Data and Material Material is found online and referenced accordingly.

Declarations

Ethics Approval This is a review study and contains information previously published on the topic.

Consent for Publication Appropriate use of references is completed throughout the manuscript.

Conflict of Interest The authors declare no competing interests.

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