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PIRD: Primary Immune Regulatory Disorders, A Growing Universe of Immune Dysregulation

Alice Y. Chan[1], **Troy R. Torgerson**[2]

[1]Division of Pediatric Allergy, Immunology, and BMT, Division of Pediatric Rheumatology, Department of Pediatrics, University of California San Francisco, San Francisco, California, USA

[2]Allen Institute for Immunology and Department of Pediatrics, University of Washington, Seattle, Washington, USA

Structured Abstract

Purpose of review—Primary Immune Regulatory Disorders (PIRD) are a growing subset of diseases referred to as inborn errors of immunity. Unlike classical primary immune deficiency disorders that typically present with severe, recurrent, or unusual infections, the clinical manifestations of PIRD are dominated by immune-mediated pathology (autoimmunity, autoinflammation/hyperinflammation, lymphoproliferation, malignancy, and severe atopy). This review introduces the concept of PIRD including clinical phenotypes, treatments, and new PIRD-associated gene defects.

Recent findings—The number of genetic defects associated with PIRD is rapidly growing. The identified genes often encode proteins that play critical roles in regulating the immune response to various triggers. Understanding the molecular mechanisms underlying PIRD has shed light on the clinical phenotypes and has helped to identify targeted therapies. In some cases, hematopoietic cell transplant (HCT) has been successfully employed as a cure.

Summary—It is important to recognize the broad clinical manifestations of PIRD as patients may have symptoms atypical of classical “immunodeficiency”. Because of their diverse immune dysregulation problems, they are often primarily managed by other subspecialists. Immunologists can help connect the diverse immune-mediated pathologies to a gene defect. This, in turn, can play a significant role in directing clinical management, selecting effective therapy, and deciding on appropriateness of HCT.

Keywords

autoimmunity; autoinflammation; immunodeficiency; non-malignant lymphoproliferation; hematopoietic cell transplantation

Corresponding Author: Alice Chan, Address: Division of Pediatric Allergy, Immunology, and BMT; University of California San Francisco; 550 16th Street; San Francisco, CA, 94143, USA., Telephone: +1 415-476-2171, alice.chan1@ucsf.edu.

Conflicts of interest

AC is a consultant for Invitae. TRT is a consultant for Takeda, Grifols, and CSL Behring.

Introduction

A recent update from the International Union of Immunological Societies (IUIS) Expert Committee on inborn errors of immunity, lists 430 genes associated with disorders of the immune system (1). Among these, 129 have clinical manifestations predominantly resulting from immune-mediated pathology rather than infections (1). This pathology arises from a breakdown in immune regulation resulting in clinical phenotypes such as autoimmunity, autoinflammation/hyperinflammation, lymphoproliferation, malignancy, and severe atopy. This group of disorders is rapidly expanding and is collectively termed Primary Immune Regulatory Disorders or "PIRD" (Figure 1) (2). This review focuses on the defining PIRD, highlighting new PIRD genes, and discussing general treatment considerations.

Overview of Primary Immune Regulatory Disorders

PIRD are a group of diseases with clinical phenotypes mainly caused by immune-mediated pathology and less prominent pathology from severe, recurrent, or unusual infections. Immune Dysregulation, Polyendocrinopathy, Enteropathy, and X-linked (IPEX) syndrome is a prototypical PIRD. Due to mutations in *FOXP3* causing defective T regulatory cells (Tregs), the clinical features are prominently autoimmune-mediated including autoimmune enteropathy, type I diabetes, thyroiditis, autoimmune cytopenias, and immune-mediated dermatitis (3,4). Infections occur in IPEX but are less prominent (3,4). Common Variable Immunodeficiency (CVID) and CVID-like diseases can also have a PIRD phenotype with severe autoimmune, inflammatory, or lymphoproliferative manifestations that dominate their clinical presentation. Several genetic defects in immunoregulatory genes have been identified in these patients including *CTLA4*, *NFKB2*, *PIK3CD,* and others.

Diversity of PIRD Phenotypes

PIRD encompasses a broad range of disease categories stemming from defects in various immune regulatory pathways (Table 1). One disease category called tregopathies is caused by defective Tregs which includes IPEX and IPEX-like disorders (5). PIRD can also develop from exaggerated innate and adaptive inflammatory responses as seen in autoinflammatory syndromes and hyperinflammatory disorders (8), and amplified atopic phenotypes in congenital atopic hypersensitivity is another PIRD phenotype. Additionally, PIRD can develop from aberrant inflammatory signals generated from improper sensing and clearance of cell debris (i.e. debris defects). PIRD can also present with non-malignant lymphoproliferation due to uncontrolled immune cell activation and proliferation like Autoimmune Lymphoproliferative Syndrome (ALPS) or ALPS-like disorders (7). Some PIRD genes can result in hematopoietic malignancies (7). Two other PIRD categories include monogenic inflammatory bowel diseases (IBD) which arise from a dysfunction in intestinal immune regulation (6), and rheumatologic diseases which arise from a breakdown in self-tolerance. Lastly, PIRD patients can have a combination of these phenotypes if the gene defect is at the intersection of multiple immune regulatory pathways.

Evaluating and Diagnosing PIRD

Given the wide clinical spectrum of PIRD, evaluation is focused on identifying the predominant immune-mediated pathology such as enteropathy, dermatitis, endocrinopathy,

and cytopenias. A multidisciplinary team approach is essential for gathering clinical data, assessing tissue pathology, and monitoring disease activity. Routine immunological labs are often limited in their ability to identify the specific genetic cause but can be informative to predict which aspect of the immune system needs bolstering or suppressing. Broad-based genetic testing (e.g. exome sequencing, targeted gene panel) is often the most informative and should be considered early in the evaluation. The absence of a positive family history does not eliminate a genetic cause since PIRD can be associated with heterozygous defects causing dominant gain- or loss-of-function so can arise *de novo*. Lastly, different mutations in the same gene can lead to widely discordant phenotypes. As a result, identification of a defect in a PIRD-associated gene should be considered based on its immunologic function and not discounted solely on previously described phenotype with that gene.

New PIRD Genes

Several recent correlations have been made between new gene defects and a PIRD phenotype. Some of these genes were previously described but only recently associated with PIRD features (Table 2).

CDC42—CDC42 (Cell division cycle 42) is a Rho GTPase family member that functions in controlling various cellular functions including actin cytoskeleton and vesicle trafficking. It is known to interact directly with the Wiskott-Aldrich Syndrome protein (WASp). Mutations in *CDC42* have previously been linked to Takenouchi-Kosaki syndrome (OMIM 116952), characterized by neurodevelopmental disorders and thrombocytopenia but no reported immune-mediated pathology. Recent reports describe four heterozygous mutations in *CDC42* from ten families with PIRD phenotypes (9–12). Three of the mutations had a clinical picture resembling the IL-1-mediated Neonatal-Onset Multisystem Inflammatory Disease with symptoms of recurrent fevers, urticarial-like rashes, hepatosplenomegaly, and cytopenias that started as a neonate (10–12). Some patients developed recurrent bacterial and viral infections, and one developed lymphoma (9,12). Patients had elevated inflammatory markers including elevated IL-18. Most patients responded to IL-1 inhibitors, and one improved with emapalumab, an anti-interferon-gamma (IFNγ) antibody. Recurrent HLH prompted HCT in two cases, with one successful outcome (10).

DEF6—Mutations in *DEF6* (Differentially expressed in FDCP 6 homolog) have been found in three consanguineous families with seven affected patients (13,14). All patients had homozygous mutations that included two missense mutations and one truncation mutant (13,14). DEF6, also called IRF4 binding protein (IBP) or SWAP-70-like adaptor of T cells (SLAT), is a guanine nucleotide exchange factor that interacts with Rab11 GTPase, which plays an important role in vesicular trafficking of CTLA4 (13). Mutant DEF6 protein reduces binding to RAB11 and thus decreases the surface availability of CTLA4 upon T cell activation (13). This reduced CTLA4 level results in a clinical phenotype similar to CTLA4 haploinsufficiency and LRBA deficiency with recurrent infections (viral and bacterial infections), autoimmunity predominantly autoimmune cytopenias, and lymphoproliferation (13,14). One family did develop early-onset enteropathy though also had a homozygous variant in *SKIV2L* that was predicted to be pathogenic and may be contributing to a blended phenotype (13). One patient developed Hodgkin's lymphoma (14). Immune phenotyping

showed reduced naïve T cells and variable Treg numbers. Immunoglobulin levels were predominantly normal with variability in vaccine response (13,14). Patients with severe disease were treated with a variety of immunomodulating medications including abatacept, which successfully treated the enteropathy (13,14). Some milder cases had symptom resolution without treatment.

***HEM1* or *NCKAP1L*—**HEM1 (Hematopoietic protein 1), encoded by the gene *NCKAP1L* (NCK associated protein 1 like), plays a role in both the reorganization of the actin cytoskeleton and mTOR2 signaling (15,16). Two publications reported seven patients from five families with biallelic mutations resulting in reduced protein levels or disruption of a critical binding site for other protein partners (15,16). Mutant HEM1 led to impaired T cell function and aberrant B cell development and function (15,16). The disease started in infancy, and patients developed recurrent infections, autoimmunity, and lymphoproliferation (15,16). Clinical labs include variable antibody levels, poor antibody responses, and elevated proportion of memory T cells (15,16). Patients were treated with a variety of immunomodulatory medications including azathioprine, mycophenolate mofetil, rituximab, cyclosporin, and sirolimus. At least two patients have been controlled on long-term immunomodulatory therapies (15,16). No reported patients have undergone HCT.

IL2RB—Two recent papers reported ten patients from five unrelated consanguineous families who presented with clinical features resembling IPEX with enteropathy, eczematous dermatitis, autoimmunity, lymphadenopathy, and recurrent bacterial and viral infections (17,18). Affected patients had homozygous mutations in the *IL2RB* (Interleukin-2 Receptor Beta Subunit) gene. IL2RB is the core subunit of the IL-2 and IL-15 receptor complexes that also include the common gamma chain (IL2RG) and a cytokine-specific alpha chain (IL2RA or IL15RA). IL-2 and IL-15 signals are critical for the development and function of T cells and NK cells, respectively. Tregs are particularly dependent on IL-2 signaling for their proliferation and ongoing competitive fitness. The four mutations resulted in reduced or complete loss of IL2RB protein (17,18). The most severe patients had complete loss of IL2RB and led to intra-uterine growth retardation with skin-like floating membrane in the amniotic fluid similar to prenatal IPEX patients (17). The other three mutations altered the extracellular domain leading to dysregulated IL-2/IL-15 signaling and function. Clinical labs in the patients showed elevated immunoglobulin levels, reduced to absent Treg numbers, and an expansion in NK cells (17,18). Patients were treated with various immune modulatory medications for their autoimmune manifestations (17,18). Four patients underwent HCT with one succumbing to respiratory failure (likely from CMV) and the other from multiorgan failure (17,18).

RIPK1—RIPK1 (Receptor-Interacting Serine/Threonine-Protein Kinase 1) has been previously linked to biallelic mutations in patients who developed predominantly very-early onset inflammatory bowel disease (19–21). Two new reports highlight a new hyperinflammatory syndrome, referred to as Cleavage-resistant RIPK1-Induced Autoinflammatory (CRIA) syndrome, due to a dominant mutation found in five unrelated families (22,23). RIPK1 plays an important role in controlling inflammation and cell death and is inactivated when it is cleaved by caspase-8. Interestingly, all mutations linked to the

hyperinflammatory syndrome affected amino acid p.D324 which is the critical cleavage site for caspase-8 thus rendering RIPK1 non-cleavable and persistently active (22,23). This leads to uncontrolled inflammatory signaling with excessive production of inflammatory cytokines such as IL-6. Patients present in infancy with recurrent high fevers every 1-4 weeks lasting 1-7 days in addition to lymphadenopathy and hepatosplenomegaly (22,23). Patients had elevated inflammatory gene signatures and inflammatory cytokines (22,23). Treatment with the IL-6 inhibitor, tocilizumab, showed the most benefit compared to steroids, IL-1 inhibitors and TNF inhibitors (23).

TET2—TET2 (Ten-Eleven Translocation methylcytosine dioxygenase 2), a member of the TET family, is an epigenetic regulator that plays a direct role in DNA demethylation and interacts with other partners to affect epigenetic modifications (24). While somatic *TET2* mutations have previously been linked to malignancy and myelodysplastic syndromes, a recent paper reported germline mutations in patients with recurrent bacterial and viral infections, autoimmunity, lymphoproliferation, and lymphoma (25). Three patients from two unrelated consanguineous families were found to have two different homozygous mutations. One was a missense and the other was a nonsense mutation that both resulted in loss of function and DNA hypermethylation (25). Patients showed elevated double negative alpha-beta T cells and most had decreased Fas-mediated apoptosis similar to ALPS patients (25). Patients also had reduced class-switch memory B cells, and two were placed on immunoglobulin replacement (25). All three developed lymphoma and underwent HCT with only one surviving with mixed chimerism. Interestingly, all 3 developed autologous T cell reconstitution (25).

TNFRSF9—*TNFRSF9* (Tumor Necrosis Factor Receptor Superfamily, member 9) gene mutations were found in six unrelated families that develop clinical manifestations including lymphoproliferation associated with EBV viremia, lymphoma, autoimmune cytopenias, and recurrent bacterial and viral infections (26,27). All patients had homozygous mutations in the *TNFRSF9* gene which encodes the protein called CD137 or 4-1BB. The mutations were all clustered in the extracellular domain and resulted in reduced or absent protein expression (26,27). Interestingly, there are three asymptomatic homozygous family members suggesting incomplete penetrance in this disease (26). CD137/4-1BB is a cell surface protein that functions as a coreceptor to modulate immune cell activation (28). It gets upregulated in activated T cells and promotes CD8 expansion and cytotoxic function. In B cells, it plays a role in activation, maturation, and class switch recombination. Cells from patients showed defective T cell activation and reduced B cell differentiation and function (26,27). Clinical immune labs include reduced T cell proliferation, variable T and B cell subsets, and variable immunoglobulins and specific antibodies (26,27). Most patients were treated with immunoglobulin replacement and/or anti-microbial prophylaxis (26,27). Some patients were also treated with immunomodulatory medications such as sirolimus, mycophenolate mofetil, and B cell therapies (26,27). One patient underwent a HCT with HLA-matched sibling though the outcome was not reported (27).

Overview of Treatments for PIRD

Management of PIRD patients is particularly challenging with balancing immune modulatory therapies in the setting of a potential increased risk for infection (29). Ideal therapy for PIRD patients is targeted at the specific genetic defect. Fortunately, there are a growing number of immune modulatory medications targeted at specific immune pathway, and some PIRD patients may be controlled on such therapies lifelong although data on long-term use and risk of infection is lacking in many cases. Some patients with insufficient clinical response and/or unacceptable side-effects require more definitive therapy such as HCT, gene therapy, or gene editing as these become available.

Immunomodulatory Therapies

Understanding the specific immune pathway defect can help identify drug targets to control disease manifestations. For example, CTLA4 haploinsufficiency and LRBA deficiency are diseases that reduce CTLA4 or alter itsintracellular trafficking. CTLA4 soluble fusion proteins composed of the Fc fragment of human IgG1 linked to the extracellular domain of CTLA4, such as abatacept and belatacept, are directed therapies that have been helpful in controlling CTLA4-like diseases (30,31). Jak inhibitors have been successfully used to control the inflammatory processes in gain of function mutations in STAT3 and STAT1 (32,33). Ruxolitnib, a Jak inhibitor, is also being used to treat HLH (34). Rapamycin is also shown to be effective for treating patients with Treg defects such as IPEX (35) and patients with ALPS or ALPS-like disease (36). Phosphoinositide 3-kinase (PI3K) inhibitors as well as rapamycin have also been effective in the treatment of PIK3CD disease (37,38). As more targeted therapies are developed, precision therapies can be aligned to the specific gene mutation. However, it is unclear whether lifelong immunomodulatory therapies will be sufficient. Thus, more long-term data is needed to better understand who can be maintained on such therapies versus those that need more definitive therapies like an HCT.

Hematopoietic Cell Transplant

HCT can be a successful treatment option for PIRD patients depending on the genetic defect and other transplant conditions (2,39). First, the genetic defect must be expressed in the hematopoietic compartment. If the gene also functions in non-hematopoietic cells, then HCT may only be partially beneficial. For example in NF-κB essential modulator (NEMO) deficiency, the gene functions in both immune and epithelial cells so HCT can resolve some, but not all, of the clinical manifestations (40). Second, control of the hyperinflammatory process prior to transplant may help decrease the risk for alloreactivity and potentially improve engraftment of donor cells (41). Third, it is important to have a conditioning regimen that maximizes donor engraftment with the lowest degree of toxicity. The optimal regimen will likely vary depending on the genetic mutation and prior disease activity causing organ dysfunction. At present, data is lacking about the best conditioning regimens for PIRD patients. Fourth, identifying a suitable donor is critical. While a matched-related donor without the gene mutation is ideal, it is not always possible. In some conditions, a family member, who is a carrier for the genetic defect, may be an acceptable donor but in other cases it is not an option (42). Lastly, HCT outcomes for these patients depend on the level of stable donor chimerism (i.e. the percent of stem cells derived from the donor). Some

PIRD may successfully be treated with mixed donor chimerism whereas others require full donor chimerism to prevent disease relapse post-HCT. Overall, HCT can be a potential therapy for PIRD but significant questions remain.

Conclusion

The PIRD disorders account for a growing subset of inborn errors of immunity. They present with dominant features of autoimmunity, autoinflammation/hyperinflammation, lymphoproliferation, malignancy, severe atopy, and immunodeficiency. The genes associated with PIRD are typically central modulators of immune regulation. Knowing the exact molecular defect can help identify effective therapies. HCT can be a potential curative treatment in some diseases whereas others may be successfully managed on long-term immunomodulatory therapies. Overall, the current understanding of the natural history of PIRD is limited, and more studies are needed to advance our knowledge of how best to manage and treat these patients.

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Key Points

- Primary immune regulatory disorders (PIRD) predominantly have clinical features of autoimmunity, hyperinflammation, lymphoproliferation, malignancy, and severe atopy with less dominant features of immunodeficiency and infection.
- Genetic causes of PIRD function in immune pathways that regulate the various types of immune responses.
- Treatment for PIRD are directed at the specific genetic defect, and HCT can be a curative therapy for some cases.

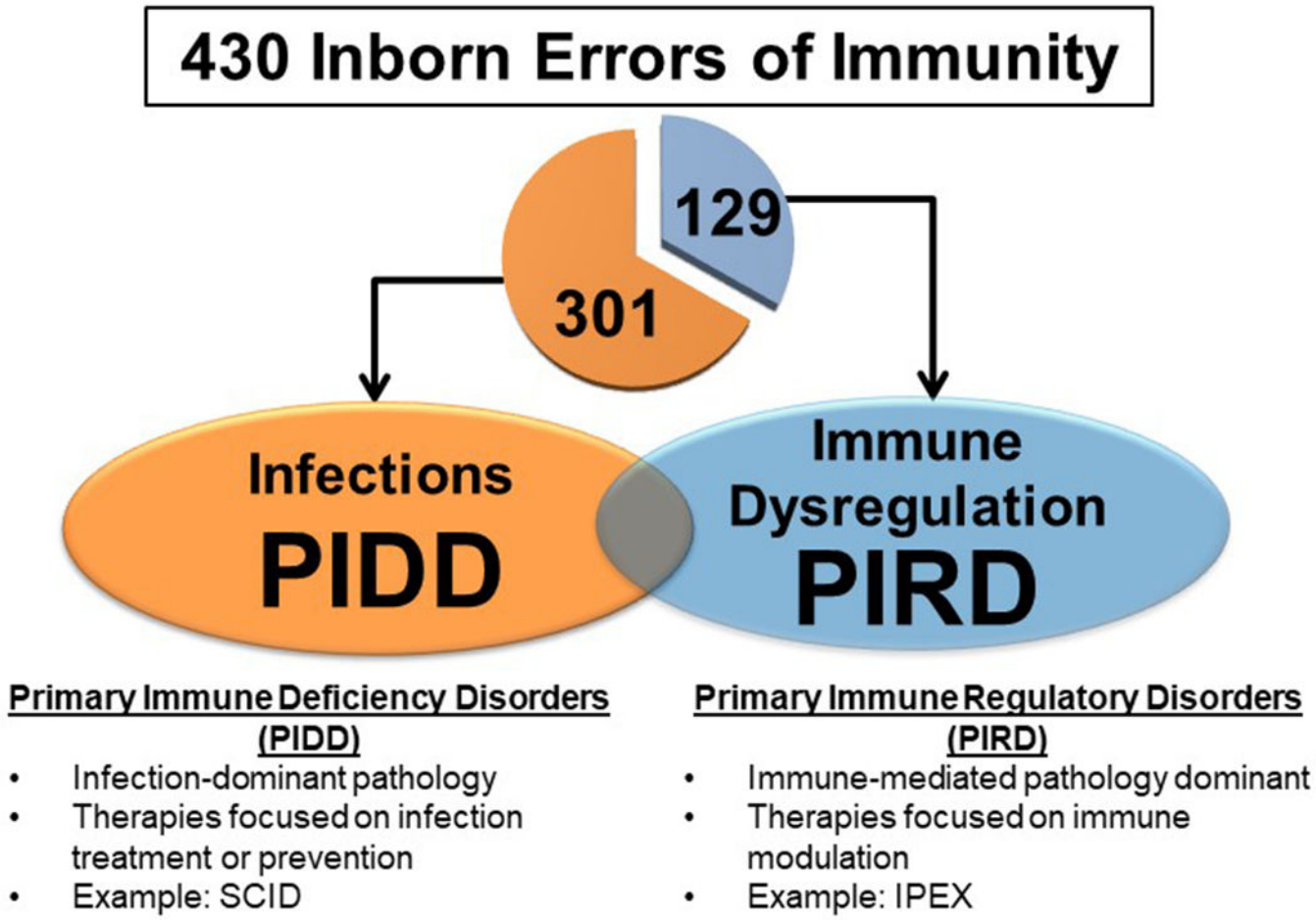

Figure 1:

Inborn Errors of Immunity (IEI). A total of 430 genes IEI were reported in the IUIS of which 129 are considered a primary immune regulatory disorder (PIRD).

Table 1:

PIRD Phenotypes

PIRD Phenotypes	Diseases/Pathways	Example Genes (Protein)*
Tregopathies	IPEX (Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-linked)	FOXP3
	IPEX-Like	CD25 CTLA4, LRBA, DEF6 IL2RB STAT1-GOF STAT3-GOF STAT5B
Autoinflammatory Syndromes	TRAPS (Tumor Necrosis Factor Receptor Associated Periodic Syndrome)	TNFRSF1A TNFRSF11A
	CAPS-like (Cryopyrin-Associated Autoinflammatory Syndromes)	CDC42 NLRP3
	FMF (Familial Mediterranean Fever)	MEFV
	DAD2 (Deficiency of Adenosine Deaminase 2)	ADA2
	DIRA (Deficiency of the Interleukin-1 Receptor Antagonist)	IL1RN
	CRIA (Cleavage-resistant RIPK1-Induced Autoinflammatory) syndrome	RIPK1
Hyperinflammatory Disorders (predisposition to HLH)	Cytolytic Defects	LYST PRF1 RAB27A UNC13D (MUNC13-4)
	Signaling Defect	CDC42 ITK MAGT1 SH2D1A STAT1-GOF
	Inflammasome Defects	NLRC4 XIAP
Debris Defects	Complement deficiency	C1q, C2
	Interferonopathies	COPA DNAse I IFIH1 (MDA5) STING TREX1
	PRAAS (Proteasome-Associated Autoinflammatory Syndrome)	PSMB8
Non-Malignant Lymphoproliferation	ALPS (Autoimmune Lymphoproliferative Syndrome)	CASP10 FAS, FASL
	ALPS-Like/ALPS-U	CTLA4, LRBA, DEF6 PIK3CD, PIK3R1 STAT3-GOF TNFRSF9 (CD137, 4-1BB) TET2
	RALD (Ras Associated Autoimmune Leukoproliferative Disease)	KRAS, NRAS
Hematopoietic Malignancies	SPTCL (Subcutaneous panniculitis-like T-cell lymphoma)	HAVCR2 (TIM3)
	LGL (Large Granular Lymphocytic Leukemia)	STAT3-GOF
	DLBCL (Diffuse Large B-Cell Lymphoma)	CARD11, BCL10, MALT1 PIK3CD
	AML (Acute Myeloid Leukemia) / MDS (Myelodysplastic Syndromes	GATA2

PIRD Phenotypes	Diseases/Pathways	Example Genes (Protein)*
	Various Types of Lymphomas	TET2
Congenital Atopic Hypersensitivity		JAK1-GOF PGM3 STAT5-GOF
Inflammatory Bowel Disease (IBD)	Infant Onset-IBD	IL10, IL10RA, IL10RB SKIV2L TTC7A
	VEO-IBD (Very early Onset Inflammatory Bowel Disease)	CYBB, NCF1 RIPK1 XIAP
Rheumatologic Diseases	Bechet's Disease	TNFAIP3 WDR1
	Lupus	C1q, C2 FAS NCKAP1L (HEM1)
	JIA (Juvenile Idiopathic Arthritis) subtypes	LACC1

GOF = Gain of Function, HLH = Hemophagocytic Lymphohistiocystosis

*genes listed together function in the same pathway or complex

Table 2:

Newly Described PIRD Genes

Gene	Onset (years)	Mode of Inheritance	Immune Clinical Manifestation						Immune Labs	Treatment			Outcomes (Alive/ Dead)
			Immunodeficiency	Autoimmunity	Auto-/Hyper-inflammation	Non-Malignant Lympho-proliferation	Malignancy	Atopy		Infection Ppx	Immune Modulatory Therapies	HSCT	
CDC42	0-2	AD	YES • Bacterial: pseudomonas, staphylococcus, group A streptococcus • Viral: varicella, EBV • Organs: GI, sinopulmonary	NR	YES • Recurrent fevers • NOMID-like • HLH	YES • LAD, HM, SM	YES • Hodgkin's lymphoma	YES • Hyper-eosinophilia • Hyper IgE from skin	↑ ESR, CRP, Ferritin ↑ IL-18 ↓ Ig ↓ memory B cells + HLH labs	• Ig replacement	• IL-1 inhibitors • Emapalumab	1 (alive) 1 (dead)	5/5
DEF6	0-10	AR	YES • Bacterial • Viral: CMV, EBV • Organs: respiratory, sepsis	YES • AIHA, ITP • AutoAb present • Enteropathy	YES • Recurrent fevers	YES • HM, SM	YES • Hodgkin's lymphoma	NR	Treg variable ↓naïve CD4 Nl to ↓ Ig Nl to ↓ specific ab + AutoAb	• Ig replacement	• B cell tx • Abatacept • Azathioprine	NR	6/1
Il2RB	0-1	AR	YES • Viral: CMV, EBV • Fungal Candida • Organs: GI, GU, sinopulmonary	YES AIHA Grave's Vasculitis Enteropathy Celiac	YES • Colitis	YES • LIP • LAD, HM, SM	NR	YES • Eczema • Food allergy	↑ NK ↓ Tregs ↑ g	• Viral ppx	• Sirolimus • Steroids • B cell tx	2 (alive) 2 (dead)	3/7
NCKAPL (HEM1)	0-1	AR	YES • Bacterial: pneumococcal, staphylococcus, pseudomonas • Viral: EBV, HSV1 • Organs: meningitis, skin, sinopulmonary	YES • ITP • Celiac disease • Lupus GN • AutoAb present	YES • Recurrent fevers	YES • LAD, HM, SM • ALPS-like • Rosai-Dorfman disease • HLH	NR	YES • Asthma • Allergic rhinitis • Food allergy	Nl subsets ↑ T memory ↓ proliferation Variable IgG/A/M ↑ IgE ↓ specific ab + AutoAb	• Ig replacement • Microbial ppx	• Steroids • Sirolimus • MMF • B cell tx • CsA • Azathioprine	NR	7/0
RIPK1	0-1	AD	NR	NR	YES • Recurrent fevers	YES • LAD, HM, SM	NR	NR	↑ inflammatory cytokines + AutoAb	NR	• Tocilizumab	NR	9/0
TET2	0-1	AR	YES • Viral: CMV, EBV, RSV • Organs:	YES • AIHA • AutoAb present	NR	YES • LAD, HM, SM	YES • Hodgkin's lymphoma • PTCL	NR	↑ DN alpha/ beta T cells ↓ FAS-mediated, apoptosis	• Ig replacement • Microbial ppx	• B cell tx • IVIG • steroids	1 (alive) 2 (dead)	1/2

Gene	Onset (years)	Mode of Inheritance	Immune Clinical Manifestation						Immune Labs	Treatment			Outcomes (Alive/ Dead)
			Immunodeficiency	Autoimmunity	Auto-/Hyper-inflammation	Non-Malignant Lympho-proliferation	Malignancy	Atopy		Infection Ppx	Immune Modulatory Therapies	HSCT	
			sinopulmonary, meningitis, skin				• Benign skin tumors • PMBCL		↓ class-switch memory B cells Ig variable Specific ab variable				
TNFRSF9 (41BB, CD137)	2-8	AR	YES • Bacterial: pneumococcal • Viral: Adeno, EBV, HSV • Organs: sinopulmonary, sepsis	YES • AIHA, ITP • AutoAb present	YES • HLH	YES • LAD, SM • ALPS-like	YES • Hodgkin's lymphoma • Burkitt's • DLBCL	YES • Eczema	↓ proliferation ↓ memory B Ig variable Specific ab variable + AutoAb	• Ig replacement • Microbial ppx	• B cell tx • Sirolimus • MMF	1 (ongoing)	6/0
										•	•		

Ab=antibody, Adeno=adenovirus, AutoAb=autoantibodies, CsA=cyclosporin A DLBCL= Diffuse large B-cell lymphoma, GN=glomerulonephritis, HLH=hemophagocytic lymphohistiocytosis, HM=hepatomegaly, Ig=immunoglobulin, LAD=lymphadenopathy, LIP=lymphocytic interstitial pneumonitis, LPD=lymphoproliferative disorder, MMF=mycophenolate mofetil, Nl=normal, NOMID=Neonatal Onset Multisystem Inflammatory Disease, NR=none reported, PMBCL=primary mediastinal B cell lymphoma, PTCL=Peripheral T-cell lymphoma, Ppx=prophylaxis, SM=splenomegaly, Tx=therapies