

New Genetic Discoveries and Primary Immune Deficiencies

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Abstract The field of immunology has undergone recent discoveries of genetic causes for many primary immunodeficiency diseases (PIDD). The ever-expanding knowledge has led to increased understanding behind the pathophysiology of these diseases. Since these diseases are rare, the patients are frequently misdiagnosed early in the presentation of their illnesses. The identification of new genes has increased our opportunities for recognizing and making the diagnosis in patients with PIDD before they succumb to infections that may result secondary to their PIDD. Some mutations lead to a variety of presentations of severe combined immunodeficiency (SCID). The myriad and ever-growing genetic mutations which lead to SCID phenotypes have been identified in recent years. Other mutations associated with some genetic syndromes have associated immunodeficiency and are important for making the diagnosis of primary immunodeficiency in patients with some syndromes, who may otherwise be missed within the larger context of their syndromes. A variety of mutations also lead to increased susceptibility to infections due to particular organisms. These patterns of infections due to specific organisms are important keys in properly identifying the part of the immune system which is affected in these patients. This review will discuss recent genetic discoveries that enhance our understanding of these complex diseases.

Keywords Primary immunodeficiencies · Genetics · Mutations · Immune system

The recent decades have elucidated the genetic etiology for many primary immunodeficiency diseases (PIDD). PIDD can be defined by the part of the immune system which is affected, thus leading to a deficiency in the immune system which frequently results in an increased risk of and frequency of infections. The classification of PIDD has continued to

evolve, with increased numbers of PIDD described in the recent past [1].

T lymphocyte Disorders

Severe combined immunodeficiency (SCID) is defined based on the absence of T lymphocytes, and presence or absence of B and NK lymphocytes. Recent description of patients with a variety of genetic mutations have improved our understanding of the presentation of many patients with previously undiagnosed primary immunodeficiency (Table 1) [1, 2]. The improved understanding aids clinicians in making the appropriate diagnosis, along with instituting a treatment plan appropriate for the disease.

T–B+NK+SCID

CD3

Mutations resulting in impaired signaling through the pre-T cell receptor (TCR) have been described. Defects in different components of CD3 have been described in the recent past [3–8]. These autosomal recessive disorders are seen in defects of the subunits of CD3, including CD3 δ , CD3 ϵ , CD3 γ , and CD3 ζ . Without these subunits, signal transduction that is necessary for T cell production as well as activation of mature T lymphocytes does not occur [2]. Patients with CD3 δ deficiency have complete blocks in T cell development [3–5]. Families with history of consanguinity and defects in CD3 δ have been described. The patients presented early in life with low T cell numbers, as well as low serum immunoglobulins [3, 4]. A family of Mennonite descent with infants who presented with respiratory distress and viral infections has also been described [4]. CD3+ T lymphocytes were low, whereas CD4+ and CD8+ T lymphocytes were not detectable. The mitogen response to phytohemagglutinin was also very depressed.

CD3 δ chain is incorporated into both TCR $\alpha\beta$, as well as TCR $\gamma\delta$. Two unrelated patients with Ecuadorian ancestry were described with a mutation in CD3 δ [5]. These patients presented with clinical histories of diarrhea, low expression of

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Table 1 Recently described defects resulting in SCID phenotype

Phenotype (OMIM)			
T-B+NK+	T-B-NK+	T-B-NK-	T+B+NK+
CD3δ	DNA-PKcs	Reticular dysgenesis	ZAP70
186790	600899	267500	176947
CD3ε	DNA-ligaseIV		MHC II
186830	601837		209920
CD3γ	Cernunnos		
186740	611290		
CD3ζ			
610163			
CD45			
151460			
Coronin-1A			
60500			
P56lck			
153390			
WHN/Nude SCID			
600838			

CD3, low T cell mitogen proliferation, and low T cell-dependent B cell functions. Both patients had the same mutation in CD3δ. These patients had very low numbers of αβ T cells, whereas γδ T cell numbers were normal. This is a novel “leaky mutation” which results in a phenotype of SCID that reveals the importance of measuring both TCR αβ, as well as TCR γδ levels, when one suspects deficiency in CD3 [5].

Patients with defects in CDε with severe T cell deficiency have also been described [3]. These patients also presented early in life with low immunoglobulin levels. Patients with CDγ have reduced TCR expression, but normal numbers of circulating T cells [1, 6]. Other patients with defects in the zeta chain and SCID phenotype have also been described [7, 8]. A 4-month-old male with diarrhea, pulmonary abscesses, and recurrent HSV viral infections was described. He had low proliferative responses to mitogens and lack of response to vaccines [7]. Another 4-month-old female with failure to thrive, pneumonia, and *Salmonella* gastroenteritis was separately described. She had low T cell numbers, along with lack of T cell mitogen responses [8]. These patients had both partial and complete deficiencies in CD3ζ that resulted in SCID.

CD45

Patients with defects in transmembrane proteins important for lymphocyte transduction, such as CD45, a protein tyrosine phosphatase have also been described [9–12]. This is another form of autosomal recessive SCID. A 2-month-old female with pancytopenia, rash, hepatosplenomegaly, and failure to thrive was diagnosed with CD45 deficiency.

CMV infection was present. Her T lymphocyte numbers and serum immunoglobulins were decreased [10]. A 2-month-old male with decreased T lymphocytes, low mitogen proliferation, and decreasing immunoglobulins over time was also diagnosed with CD45 deficiency [11]. Recently, a 10-year-old child with CD45 deficiency was described secondary to disomy of a mutant gene from the child’s maternal chromosome 1 [12]. This child also had low T cell numbers, low mitogen proliferation, and decreased immunoglobulins.

Coronin-1A

Coronins are actin regulators that are expressed in T lymphocytes, and defects result in impaired movement of lymphocytes secondary to intracellular membrane transport [2, 13]. At 13 months of age, a patient with Coronin-1A deficiency developed a severe post-vaccination varicella infection. She was diagnosed with an autosomal recessive form of T-B+NK+SCID.

LCK

Another autosomal recessive form of SCID that has been described recently includes deficiency of LCK, which is lymphocyte specific protein tyrosine kinase, important in TCR signaling. LCK is essential in the phosphorylation of immunoreceptor tyrosine-based activation motifs (ITAMs), which is the first signaling once TCR engagement occurs [14–16]. Different degrees of immunodeficiency have been described, including children with combined immunodeficiency [14, 15].

A female child with LCK deficiency that resulted in SCID phenotype has been described [15]. From 15 months of age, she suffered from failure to thrive secondary to protracted diarrhea. The child also had pneumonia with pneumatocele, along with panniculitis of the hypodermis. By 29 months, she developed thrombocytopenia with autoantibodies to platelets. The patient’s T cells had decreased expression of CD4 and CD8 lymphocytes, along with lack of response to pHA. Interesting was presence of elevated IgM with normal IgG, IgA, and IgE. Decreased specific antibodies to vaccine titers were seen. In adults with idiopathic CD4+ lymphocytopenia, defective activity of LCK has also been described [16].

WHN/Nude SCID

Winged helix naked (WHN) deficiency has been described in patients with another form of autosomal recessive SCID, secondary to defect in thymus embryogenesis. WHN encodes Forkhead box N1 (FOXP1) expressed in thymic epithelia and skin. Patients have been described with absent thymus, alopecia, and decreased T cell numbers [17–19]. Sisters from an Italian village were first described [17, 18]. Patients also have decreased serum immunoglobulins and markedly decreased lymphocyte responses to mitogens. A patient with

anencephaly and spina bifida has also been described, indicating the importance of FOXP1 in embryogenesis [19].

T–B–NK+

DNA-PKcs

DNA-dependent protein kinase catalytic subunit (DNA-PKcs) is part of DNA hairpin-opening complex with Artemis. This form of SCID results from defective VDJ recombination and defect of DNA-PKcs recombinase repair protein [20–22]. A daughter of Turkish consanguineous parents was the first human described. She had an aphthous ulcer. The patient had decreased T and B lymphocyte numbers that improved post-hematopoietic cell transplant. Patients with this form of autosomal recessive SCID have radiosensitivity.

DNA Ligase IV Defect

DNA ligase IV is important in the DNA repair process. DNA double-strand breaks are repaired by nonhomologous rejoining. Patients with DNA ligase IV deficiency, an autosomal recessive disease, and varying degrees of immunodeficiency have been described. Patients have been described with dysmorphic facies, psychomotor delay, growth retardation, microcephaly, and pancytopenia in this autosomal recessive form of SCID [22–24]. Some of the patients presented with delayed clinical onset. The patients also have radiosensitivity, whereas other patients without the syndromic features have been described [23]. A female Turkish patient presented with chronic diarrhea, diaper candidiasis, and severe respiratory infections in the second year of life. She subsequently developed failure to thrive. The patient had decreased numbers of both CD3+ T lymphocytes and CD19+ B lymphocytes, along with decreased lymphocyte proliferation. Patients without immunodeficiency but with radiosensitivity and leukemia have also been described [22].

Cernunnos-XLF Deficiency

Similar to patients with Ligase IV deficiency, patients with Cernunnos deficiency have impaired nonhomologous end joining. Patients present with microcephaly, growth retardation, dysmorphic facies, and radiosensitivity [25, 26]. Patients characteristically had recurrent infections, while some patients had autoimmune cytopenia or bone marrow failure. Another female patient, born to consanguineous parents from Turkey, presented at 6 months of age with failure to thrive [26]. She also had pulmonary infections requiring hospitalization. She later developed microcephaly and clubbing. The patient also suffered from recurrent otitis media and generalized molluscum. The patient had decreased T and B lymphocyte numbers with normal IgM and decreased IgG and IgA.

T–B–NK–

Reticular Dysgenesis

Reticular Dysgenesis is another form of SCID due to increased lymphocyte apoptosis. Patients have mutations in a gene that encodes adenylate kinase 2, a mitochondrial enzyme. This autosomal recessive disorder is seen in patients who also suffer from markedly decreased leukocyte numbers, congenital neutropenia, and sensorineural deafness [2, 27]. The patients have hypoplasia of lymphoid organs and thymus. T lymphocytes are markedly decreased, and infants are at risk of death due to sepsis very early in life.

Other Forms of SCID

T+B+NK+

ZAP70

Patients with ZAP70 deficiency have lymphocytosis, unlike patients with other forms of SCID. The clinical presentation can also vary with patients, making the diagnosis more challenging [28]. While patients usually present before 2 years of age, the patients may have different signs and symptoms that bring them to medical attention. Some patients may present with failure to thrive, whereas others present with skin lesions similar to eczema associated with eosinophilia. Another patient presented with wheezing as an infant. Patients have abnormal development of the thymus. CD8+ cells are absent in these patients with defective TCR signaling.

MHC II Deficiency

Deficiency of MHC II results from mutations in several genes. This leads to CD4+ lymphopenia [29]. Patients present with respiratory and gastrointestinal infections, diarrhea and failure to thrive. Patients present with hypogammaglobulinemia and low antibody titers to protein antigens. The lymphocyte proliferative responses to antigens are low in these patients.

ORA1 Defect and STIM Defect

For T lymphocytes to function properly, several steps are required that are dependent on proper calcium influx. ORA-1 is a calcium channel component that forms pores in calcium release-activated calcium channels [1, 2, 30]. STIM-1 is a stromal interaction molecule and sensor of Calcium levels. The defect is impaired lymphocyte calcium influx, and patients present with non-progressive myopathy presenting in infancy, autoimmunity and anhydrotic ectodermal dysplasia. T cell numbers are normal, but have deficient activation and proliferation to

mitogens. Patients with STIM-1 also have CD4⁺ lymphocyte deficiency. Patients have deficient specific antibody responses. Patients also have autoimmune hemolytic anemia and thrombocytopenia [30].

Atypical Presentation Of Previously Reported SCID

Some well-described forms of SCID can present with a myriad of presentations. Mutations in RAG, for example, can present with different phenotypes. A report of three female patients with heterozygous mutations in RAG described the clinical presentation of granulomas and EBV associated lymphoma [31]. The patients were unrelated offspring of nonconsanguineous parents. Two patients did not have infections in infancy. Two patients did have severe varicella and recurrent bronchopneumonia. All patients presented with granulomas by 24 months. The leading symptom in two patients were skin lesions, whereas the third patient had splenomegaly as the main symptom. The girls had B cell lymphoma associated with EBV. The patients also had varying degrees of hypogammaglobulinemia, and T and B cell lymphopenia.

Cellular PIDDs Presenting Concomitantly

A report of two infants with deletion 22q11.2 discussed the difficulties in making the diagnosis in patients with PIDDs. The patients had T–B–NK+immunodeficiency. Both infants had deletion of 22q11.2 and Artemis deficiency [32]. The infants were initially diagnosed with complete DiGeorge due to the deletion of 22q11.2. One patient received thymus transplantation without development of naïve T lymphocytes. The patients were treated with bone marrow transplant. This report is a reminder of the complexities and difficulties of patients with PIDDs.

PIDDs affecting T lymphocytes with increased susceptibility to particular organisms

IL-2 Inducible T cell Kinase Deficiency (ITK Deficiency)

ITK is a tec kinase, an important mediator of antigen receptor signaling. ITK is particularly important in T lymphocytes, and patients with ITK deficiency have decreased T cells. ITK deficiency has been reported in patients with EBV lymphoproliferation [33, 34]. Unlike X-linked lymphoproliferative disease, which presents in male patients, ITK deficiency presents with similar. A report of three patients diagnosed as Hodgkins lymphoma who presented with fever and lymphadenopathy [33] was described. Some patients have hypogammaglobulinemia and hemophagocytic lymphohistiocytosis. EBV was present in

all three patients. Another report of Turkish sisters, born to consanguineous parents, with fatal EBV lymphoproliferation was described [34]. The presentation was also fever, hepatosplenomegaly, and lymphadenopathy. NK lymphocytes in one sister were absent.

Magnesium Transporter Gene Deficiency

Magnesium is a necessary cofactor for ATP and enhances lymphocyte activation. Mutations have been described in magnesium transporter gene (MAGTI) [35]. This X-linked disease results in immunodeficiency, and is also called XMEN, or X-linked immunodeficiency with magnesium defect and EBV infection and neoplasia [35]. Two brothers with recurrent viral infections were described. The patients had low CD4 lymphocyte counts, along with susceptibility to EBV. The CD4 to CD8 ratio was inverted. Immunoglobulin and vaccine responses were intermittently defective. MAGTI deficiency delays phospholipase C γ 1 in TCR signaling, and T cell function was impaired. Patients are at risk of neoplasia, and a third patient with EBV lymphoma was also described.

New Modalities in the Diagnosis of PIDD—Newborn Screening

Recent advances in the diagnosis of patients with SCID have occurred through the use of newborn screening [36–39]. The use of T cell receptor excision circles (TRECs) from newborn dried blood spots has been shown to be an effective screening tool to diagnose patients early in life [36, 38]. The TREC assay used in Wisconsin over a 3-year period identified five infants with severe T cell lymphopenia and, most importantly, did not miss the diagnosis in any patient [37]. These screening tests are essential in identifying patients and beginning treatment as soon as possible to avoid infections that could be life threatening. There are some patients with combined immunodeficiency disorders, such as CD40L, FOXP3, or IL10 receptor deficiency, who will have normal TREC levels, however, and thus would benefit from another laboratory assay to diagnose their immunodeficiency [39].

PIDD Associated with Syndromes

CHARGE Syndrome

Patients with (CHARGE) syndrome have coloboma, heart defects, choanal atresia, retarded growth, genital hypoplasia, and ear abnormalities (Table 2) [40, 41]. Similar to patients with deletion 22q11, patients with CHARGE syndrome may have an associated immunodeficiency [40, 41]. These patients would benefit from an immune evaluation. More than half of the

Table 2 Recently described mutations in PIDD associated with syndromes

Disease name	OMIM number	Gene
CHARGE	608892	CDH7
Hyper IgE syndrome AD	102582	STAT3
Hyper IgE syndrome AR	611432	DOCK8
	611521/176941	Tyk2
WHIM	162643	CXCR4
Mono Mac	614172/137295	GATA 2
Chronic mucocutaneous candidiasis	600555	STAT 1
	603149	IL-17RA
	606496	IL-17F
	607212	CARD9

patients had lymphopenia. Patients may present with varying degrees of T lymphopenia, while others may present with a more severe clinical picture that is similar to SCID. In the cohort described, two patients died from infections, sepsis and viral pneumonia, while two others with SCID phenotype died from respiratory complications. Some patients also had varying degrees of hypogammaglobulinemia, while others had IgA deficiency. Studying these patients early in life would be beneficial.

Hyper IgE Syndrome

Autosomal Dominant Hyper IgE Syndrome

Recently, the genetic mutation responsible for the autosomal dominant form of Hyper IgE has been described [42–45]. Signal transducer and activator of transcription (STAT)3 gene mutations result in Hyper IgE syndrome. Patients with STAT3-associated Hyper IgE syndrome have features of coarse facies, eczema, and bony abnormalities including fractures, hyperextensible joints, and retained primary teeth [41]. On laboratory evaluation, the patients have eosinophilia and elevated IgE levels. A feature seen in many of the patients includes infections, such as abscesses, pneumonia with pneumatoceles, and candidiasis of mucosal surfaces and nails. In particular, patients have problems with infections secondary to *Staphylococcus aureus* and *Candida albicans*. *Aspergillus* is also a problem for these patients, particularly in the lungs. In these patients, naïve T lymphocytes are unable to differentiate into Th 17 cells. Production of Interleukin 17 is absent in these patients [45, 46].

Autosomal Recessive Hyper IgE Syndrome

The genetic mutations described to be associated with autosomal recessive forms of Hyper IgE, include DOCK8 deficiency and tyrosine kinase 2 (Tyk) deficiency [47–61]. DOCK stands for dedicator of cytokinesis proteins, which

are important for cell migration and growth. The phenotype of patients with autosomal recessive forms of Hyper IgE include problems with frequent lung infections, most with recurrent pneumonia, secondary to a variety of bacteria and fungal organisms [47–49]. Unlike patients with AD Hyper IgE, these patients do not have pneumatoceles or skeletal problems. Some patients had gastrointestinal infections. All patients had atopic dermatitis. Almost half had food allergies, some with anaphylaxis, and others have asthma [47–49]. Some patients also had bronchiectasis. The majority also have skin infections, including abscesses, particularly *S. aureus*, and recurrent viral infections, like molluscum or herpes simplex virus. Candidiasis was also frequently seen, but not as often as in STAT3-deficient patients [48, 49]. Meningitis and CNS vasculitis were seen in few patients, along with malignancies that present early in life. The immune evaluation of these patients revealed eosinophilia and elevated IgE (median 20,225 IU/mL). CD4+ and CD8+ T lymphocytes were decreased in many of the patients, with decreased lymphocyte proliferation [47–49]. More than three fourths had decreased IgM, although the majority had normal IgG levels.

Tyk2 is a tyrosine kinase, member of the janus kinase family, that is important in the cytokine signaling [48–50]. Patients suffer from recurrent sinopulmonary infections and viral infections. Patients also have problems with intracellular bacterial infections, infections with mycobacteria, along with herpes viral infections [48–50]. No dental or skeletal abnormalities are seen in these patients. Laboratory evaluation revealed decreased response to several interleukins including IL-6, IL-10, IL-12, and IL-23 [50].

PIDD Associated with DNA Repair/NK Deficiency

MCM4/PRKDC are genes involved in DNA repair. A cohort of patients from Ireland, born to consanguineous parents, has been described [51]. Mutation in the genes results in a syndrome that is a triad. The patients have familial glucocorticoid deficiency and DNA repair that is impaired. The mutation also results in NK lymphocyte deficiency, which results in viral infections and failure to thrive. The authors remind us that this is a diagnosis to consider in patients with pigmentation and failure to thrive.

PIDD Associated with Increased Susceptibility to Infections to Particular Organisms

Some PIDD have been identified due to their predilection for infections from specific microorganisms (Table 3). When clinically feasible, isolation of the causative organism can aid in diagnosis and treatment. These PIDD range in

Table 3 Recently described PID with increased susceptibility to infections to particular organisms

Name of disease	OMIM number	Organism increased susceptibility to
ITK deficiency	613011/186973	EBV
MAGTI	300853	EBV
CD27 deficiency	615122/186711	EBV
WHIM	193670	HPV
GATA 2/Mono Mac	614172/137295	Mycobacteria/HPV/histoplasmosis
IRF 8	607948/601565	Mycobacteria
STAT1	600555	<i>Candida</i>
IL-17RA	603149	<i>Candida</i>
IL-17F	606496	<i>Candida</i>
CARD 9	607212	<i>Candida</i>
TLR 3	603029/613002	HSV/CMV/ <i>Candida</i>
UNC93 B1	608204/610551	HSV
TRAF3	601896/614849	HSV
IRAK-4	606883	<i>Streptococcus pneumoniae</i> / <i>Staphylococcus</i> / <i>Pseudomonas</i>
MyD88	612260	<i>Streptococcus pneumoniae</i> / <i>Staphylococcus</i> / <i>Pseudomonas</i>

susceptibility to viral infections, like EBV, HPV, and HSV, to bacterial infections such as *Streptococcus pneumoniae* or mycobacteria, and fungal infections, like *Candida*. Once the particular microorganism is identified, this can help guide clinicians to properly identify the PID.

CD27 Deficiency

CD27 is an important molecule for lymphocytes T, B, and NK differentiation [52]. Patients with deficiency in CD27 have a phenotype consisting of combined immunodeficiency and persistent EBV viremia [52]. Two brothers have been identified with persistent symptomatic EBV viremia. Hypogammaglobulinemia was seen later. One brother succumbed to aplastic anemia. Laboratory evaluation revealed absent CD27⁺ T cells, although naïve CD45RA⁺ T cells were present at normal percentage levels. Impaired specific antibody production to protein antigens, T cell-dependent B cell response, was seen. This diagnosis should be considered in patients with recurrent and symptomatic EBV infection.

Warts, Hypogammaglobulinemia, Infections, and Myelokathexis

Warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome, an autosomal dominant disorder, has been described in patients who present with recurrent HPV, hypogammaglobulinemia, and leukopenia due to myelokathexis or retention of neutrophils in the bone marrow [53]. Gain of function mutations in the chemokine receptor, CXCR4, is present in patients. All patients had neutropenia and leukopenia. In a recent report, warts were present in the majority of patients; however, the presence of hypogammaglobulinemia varied [54].

In this report, patients with WHIM were treated with granulocyte colony-stimulating factor for the neutropenia. Infections ranged from recurrent respiratory infections and pneumonia to otitis media, meningitis and enteritis [54]. Malignancies have been reported in patients with WHIM. While symptom onset varied from infancy to 9 years, patients were diagnosed much later. The authors recommended consideration of mutation analysis of CXCR4 gene in patients with neutropenia and myelokathexis alone, even in the absence of the other features of WHIM.

GATA 2 Deficiency/Mono Mac Syndrome

A syndrome has been described affecting young adults with Monocytopenia with *Mycobacterium avium* complex, or Mono Mac syndrome [54]. Because there is loss of dendritic cells, monocytes, and B and NK lymphocytes, the disease is also called DCML deficiency. GATA 2 is important in the survival of stem cells. When the defect in GATA 2 in this autosomal-dominant disease occurs, patients have bone marrow failure that may appear later. Patients have megakaryocyte dysplasia, along with other cytopenias. The disease progresses to myelodysplasia and leukemia. The patients also have pulmonary alveolar proteinosis [55]. Other features of the disease include autoimmune disease, solid tumors, warts/HPV, and carcinoma in situ. Laboratory evaluation reveals normal immunoglobulins but decreased peripheral T regulatory cells. These patients require treatment, or they will die from malignancy or progressive lung disease.

IRF8 Deficiency

IRF8 is the interferon regulatory factor 8, which is important in phagocyte development, particularly monocytes and dendritic

cells. Patients with IRF8 deficiency present with susceptibility to mycobacterium, including BCG [56]. A report of patients with this disease included an infant with disseminated BCG after vaccination and oral candidiasis, another patient with recurrent episodes of lymphadenopathy biopsy positive for acid-fast bacilli, and a third patient with recurrent lymphadenopathy biopsy positive for *Mycobacterium bovis* [56]. The first infant had an autosomal recessive form of the disease with complete loss of monocytes and dendritic cells and opportunistic infections. The other patients with the autosomal dominant form of the disease had susceptibility to mycobacterial infections. This diagnosis should be considered in patients with disseminated BCG or mycobacterial infection.

Chronic Mucocutaneous Candidiasis

Signal Transducer and Activator of Transcription 1 Gain of Function

Patients with chronic mucocutaneous candidiasis form a spectrum of diseases that result in increased susceptibility to candida infections of the nails, skin and mucous membranes [57, 58]. Patients with some forms of chronic mucocutaneous candidiasis (CMC) may have defects due to STAT 1 gain of function [58]. Prior studies have described STAT1 loss of function results in susceptibility to mycobacterial disease. The defects result in increased susceptibility to candida and fungal infections. Twelve patients with autosomal dominant forms of CMC were found to have mutations in STAT1 that led to impaired IL-17 immunity by enhancing responses to STAT1-dependent repressors [58].

IL-17 RA and IL-17F

Other causes of mucocutaneous candidiasis have also been described. IL-17 is a cytokine produced by T and NK lymphocytes [59, 60]. One form was described in a patient with Candida dermatitis as a newborn. The patient was found to have a mutation in IL17RA, which constitutes an autosomal recessive form of CMC. A family from Argentina with autosomal dominant form of CMC was described to have a mutation in IL-17F. Other reports have described the presence of autoantibodies to IL-17A and IL-17F in patients with autoimmune polyendocrine syndrome type I [60]. These patients have susceptibility to candida and CMC as well, as part of their disease. They do not have increased risk of infections from other micro-organisms.

CARD9

CARD9 is caspase recruitment domain family, member 9, that is part of the signaling cascade important for fungal recognition [61]. Patients with deficiency in CARD9 have problems with isolated chronic mucocutaneous candidiasis. This is an autosomal recessive form of disease. Laboratory

evaluation reveals decreased T cells expressing IL-17 and very diminished Th17 response. While patients with defects in IL17RA, and possibly some patients with deficiency of Dectin-1, have isolated forms of CMC, it is likely other genetic causes of chronic mucocutaneous candidiasis will be described in the future [61].

TLR3

TLR3 is important in suppressing autoimmune disorders [62]. Patients with TLR3 deficiency have increased susceptibility to HSE encephalitis. Patients with the L412F variant of TLR 3 present with distinctive features of oral and skin candidiasis. These patients also have pneumonia, and half with bronchiectasis. CMV infection was seen in almost half of patients in a recent report. Patients also have enteritis, autoimmune cytopenias and endocrine abnormalities. Patients have decreased response to protein antigens. Laboratory evaluation also reveals decreased proliferation to antigens, including *Candida* [62]. TLR3 should be considered in patients presenting with HSE encephalitis or cutaneous candidiasis with CMV infections.

UNC93 B1/TRAF3

Susceptibility to HSV Encephalitis has also been reported in patients with deficiencies in UNC93B1 and TRAF3. UNC93B1 is an endoplasmic reticulum protein involved in TLR activation. TRAF3 is TNF receptor associated factor 3 that is important in the cascade involved in interferon production. These affect CNS cells and fibroblasts. The defect in these patients includes defective interferon induction [1, 62–64]. A report from two children in France with UNC93B1 deficiency showed susceptibility to HSE due to decreased interferon production [63]. A report of another patient in France with HSE susceptibility had a mutation in TRAF3 [64].

IL-1R-Associated Kinase/MyD88

IL-1R-associated kinase (IRAK4) and MyD88 are part of the TLR and IL1 receptor pathways [64]. MyD88 is an adaptor protein essential for the Toll-IL-1R pathway [64]. IRAK4 is a cytosolic kinase recruited by adaptors in TLR pathways. Patients with deficiencies in either IRAK4 or MyD88 have recurrent invasive infections, often meningitis or sepsis, with pyogenic bacteria. Invasive disease is most often caused by *S. pneumoniae*, *S. aureus*, and *P. aeruginosa*, although other gram-positive and gram-negative infections are seen. Non-invasive infections, often in the skin, also occur, most often due to *S. aureus* [64]. These are autosomal recessive diseases that affect lymphocytes and monocytes in patients. Impaired pneumococcal antibody responses along with impaired ability to mount a febrile response early in an infection are seen.

The immunodeficiency in these patients does improve with age, although some patients die from their infections.

Conclusions

This review demonstrates the recent gain in understanding about the genetic basis of PIDD. As laboratory techniques continue to improve and research of patients with no identifiable genetic cause of their PIDD grows, the undoubtedly identification of other genetic causes for PIDD will increase.

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