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IPEX Syndrome

Synonym: Immunodeficiency, Polyendocrinopathy, and Enteropathy X-Linked Syndrome

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Summary

Clinical characteristics

IPEX (*i*mmune dysregulation, *p*olyendocrinopathy, *e*nteropathy, *X*-linked) syndrome is characterized by systemic autoimmunity, typically beginning in the first year of life, which includes the triad of enteropathy (manifesting as malabsorption and watery diarrhea), endocrinopathy (most commonly type 1 insulin-dependent diabetes mellitus), and eczematous dermatitis. In addition to these manifestations, many children have other autoimmune phenomena including cytopenias, autoimmune hepatitis, nephropathy, lymphadenopathy, splenomegaly, alopecia, arthritis, and interstitial lung disease related to immune dysregulation. Fetal presentation of IPEX syndrome includes hydrops, echogenic bowel, skin desquamation, intrauterine growth deficiency, and fetal akinesia. Without aggressive immunosuppression or hematopoietic stem cell transplantation (HSCT), the majority of affected males will die within the first one to two years of life from metabolic derangements, severe malabsorption, or sepsis. Individuals with a milder phenotype have survived into the second or third decade of life, but this is uncommon.

Diagnosis/testing

The diagnosis is established in a male proband with typical clinical findings, absent regulatory T cells (Treg) in blood or tissues, decreased numbers of FOXP3-expressing T cells in peripheral blood determined by flow cytometry (although FOXP3 levels in Treg can be normal in some individuals), and a hemizygous pathogenic variant in *FOXP3* identified by molecular genetic testing. Heterozygous females have not been reported to have clinical findings typical of IPEX syndrome.

Management

Targeted therapies: HSCT offers the only potential cure for IPEX syndrome. T cell-directed immune suppression can include either an mTOR inhibitor (sirolimus) or calcineurin inhibitor (cyclosporin A or tacrolimus), alone or in combination with corticosteroids.

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Supportive care: Total parenteral nutrition (TPN) with fluids and electrolyte support is needed until intestinal function can be established with immune suppression. Treatment of type 1 insulin-dependent diabetes mellitus with insulin and carbohydrate management is standard, as is management of autoimmune thyroid disease. Skin conditions are managed with topical therapies, which can include steroids, tacrolimus, and emollients. Autoimmune neutropenia has been successfully treated with granulocyte colony-stimulating factor; pemphigus nodularis has been treated with rituximab (anti-CD20), and rituximab has been used for other autoantibody-mediated disease. Prophylactic antibiotic therapy may be required for autoimmune neutropenia or recurrent infections with central venous access and TPN. Aggressive management of dermatitis with topical steroids and anti-inflammatory agents as needed to prevent cutaneous infections.

Surveillance: Monitor growth, nutritional intake, and stooling patterns at each visit; glucose tolerance test, hemoglobin A1c, and thyroid function tests every three to six months; skin exam at each visit; complete blood count, blood urea nitrogen, creatinine, urinalysis, and serum aspartate transaminase and alanine transaminase every three to six months.

Agents/circumstances to avoid: Withhold immunizations until after HSCT, if possible.

Evaluation of relatives at risk: It is appropriate to clarify the genetic status of at-risk males either prenatally or immediately after birth to enable early diagnosis and HSCT and/or immune suppression treatment in affected males before significant organ damage occurs.

Genetic counseling

IPEX syndrome is inherited in an X-linked manner. The risk to sibs of the proband depends on the genetic status of the mother. If the mother of the proband has a *FOXP3* pathogenic variant, the chance of transmitting the pathogenic variant in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be heterozygous (to date, IPEX syndrome has not been reported in females who are heterozygous for a *FOXP3* pathogenic variant). Affected males transmit the pathogenic variant to all of their daughters and none of their sons. Once the *FOXP3* pathogenic variant has been identified in an affected family member, identification of female heterozygotes and prenatal/preimplantation genetic testing are possible.

Diagnosis

The term "IPEX" is an acronym for *i*mmune dysregulation, *p*olyendocrinopathy, *e*nteropathy, *X*-linked.

Suggestive Findings

IPEX syndrome **should be suspected** in males with the following clinical triad, family history, and suggestive laboratory findings.

Clinical triad

- **Enteropathy** that manifests as chronic watery diarrhea. Onset is typically in the first months of life; villous atrophy with a mononuclear cell infiltrate (activated T cells) in the lamina propria is the most common finding in intestinal biopsy.
- **Endocrinopathy,** most commonly type 1 insulin-dependent diabetes mellitus with onset in the first months or years of life. Autoimmune thyroid disease leading to hypothyroidism or hyperthyroidism has also been observed [Wildin et al 2002, Gambineri et al 2003].
- **Dermatitis,** most commonly eczematous presenting within the first months of life, although prenatal skin desquamation has been reported (see Figure 1) [Louie et al 2017]. Erythroderma, exfoliative dermatitis,

psoriasis-like lesions, and pemphigus nodularis have also been observed (see Figure 2) [Nieves et al 2004, McGinness et al 2006].

Family history is consistent with X-linked inheritance (e.g., no male-to-male transmission). Absence of a known family history does not preclude the diagnosis.

Suggestive laboratory findings. No laboratory findings specifically identify affected individuals. Evidence of **immune dysregulation** manifesting as the following is suggestive of IPEX syndrome:

- Elevated serum concentration of immunoglobulin E (IgE), and in some individuals elevated serum concentration of IgA
- Eosinophilia
- Autoimmune anemia, thrombocytopenia, and/or neutropenia
- Autoantibodies to pancreatic islet antigens, thyroid antigens, small bowel mucosa, and other autoantigens
- Decreased numbers of FOXP3-expressing T cells in peripheral blood determined by flow cytometry – although FOXP3 levels in regulatory T cells (Treg) can be normal in some individuals

Note: Standard lymphocyte enumeration of T cells, B cells, and NK cells as well as T cell function measured by mitogen proliferation is generally normal and not helpful for diagnosis.

Establishing the Diagnosis

Male proband. The diagnosis of IPEX syndrome **is established** in a male proband with suggestive findings and a hemizygous pathogenic (or likely pathogenic) variant in *FOXP3* identified by molecular genetic testing (see Table 1).

Female proband. Affected females have not been reported. Carrier status is determined by identification of a heterozygous pathogenic (or likely pathogenic) variant in *FOXP3* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of a hemizygous *FOXP3* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *FOXP3* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

Note: Pathogenic variants have been reported in the 5' UTR (c.-7G>T) and the 3' UTR (c.*876A>G). Since the 3' UTR variants are not typically included in sequencing assays, the assay design may need to be modified to include these variants.

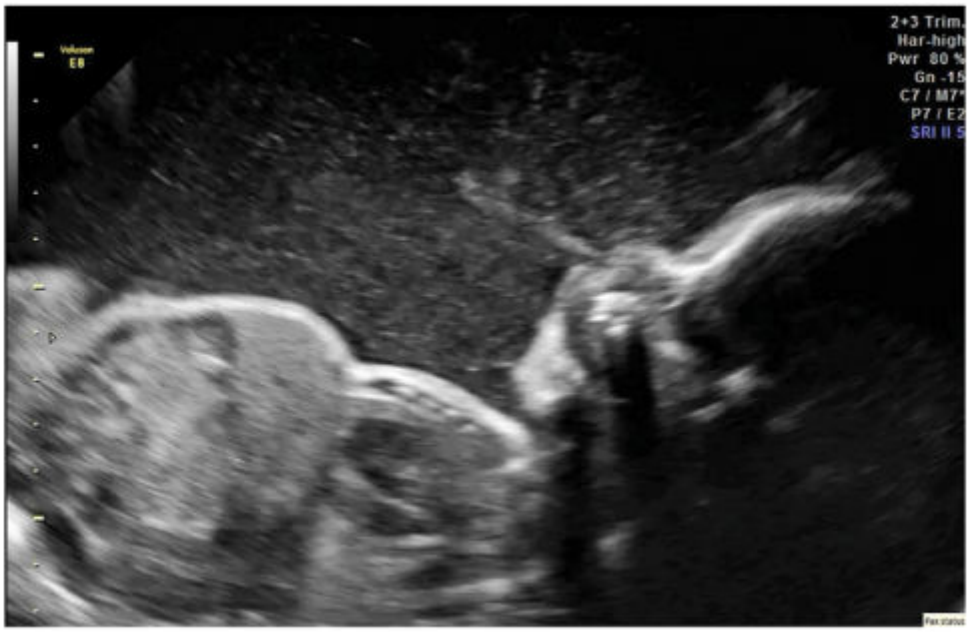

Figure 1. Intrauterine ultrasound at 32 weeks' gestation of fetus with IPEX syndrome showing desquamation with dense, echogenic amniotic fluid with particulate appearance and sediment layering, as well as echogenic debris in the stomach.

Reprinted with permission from Louie et al [2017]

A multigene panel that includes *FOXP3* and other genes of interest (see Differential Diagnosis) may be considered to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

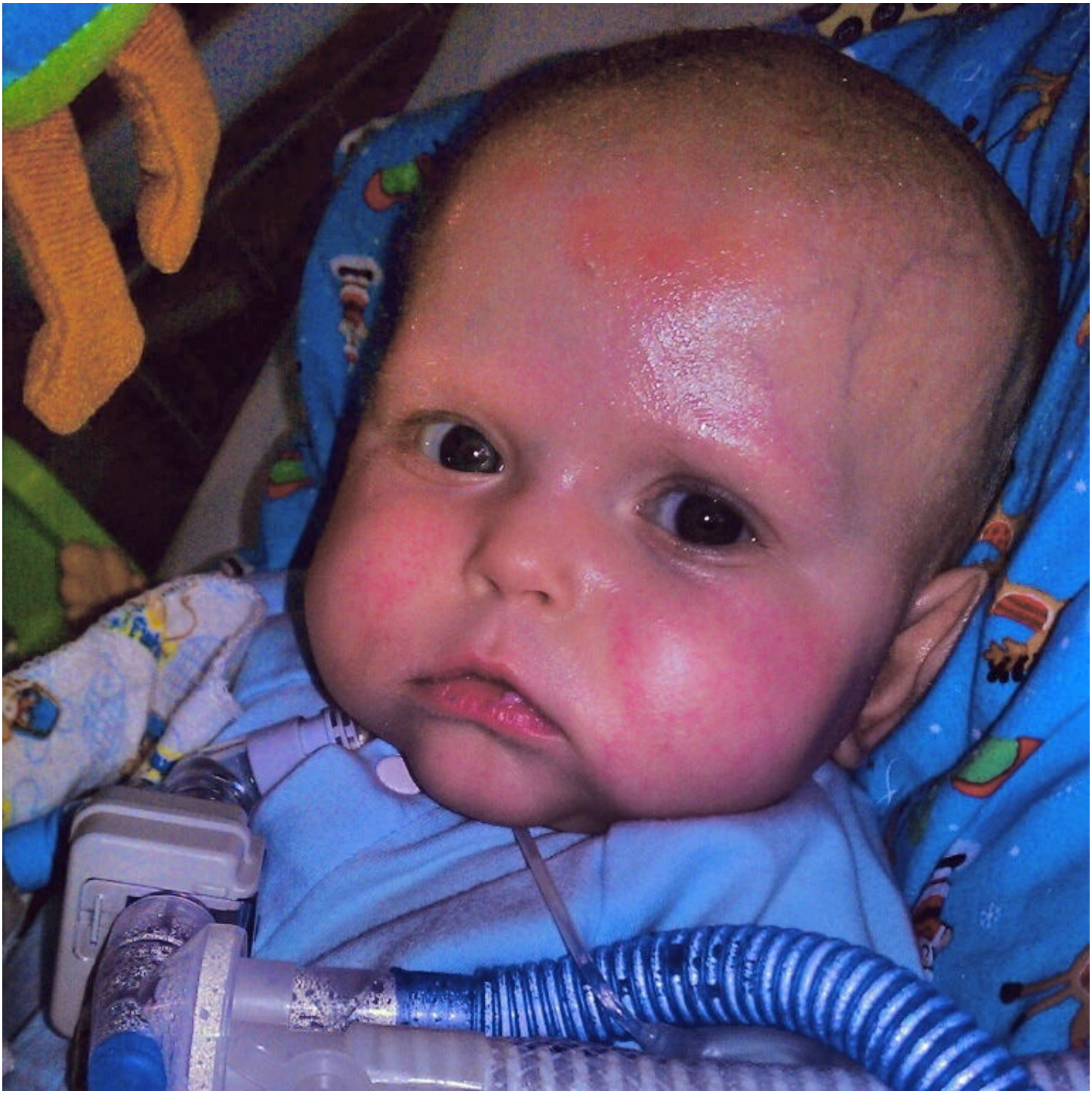

Figure 2. Typical erythematous rash seen in individuals with IPEX syndrome.

Table 1. Molecular Genetic Testing Used in IPEX Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
FOXP3	Sequence analysis [3]	~99%
	Gene-targeted deletion/duplication analysis [4]	1 reported [5]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
5. A deletion of the noncoding exon 1 has been reported [Torgerson et al 2007]; however, no systematic data on detection rate of gene-targeted deletion/duplication analysis are available.

Clinical Characteristics

Clinical Description

Males

IPEX syndrome is generally considered to be a syndrome of neonatal enteropathy [Ruemmele et al 2004] and neonatal polyendocrinopathy [Dotta & Vendrame 2002] found in males. In a large natural history study, 95% of individuals with IPEX syndrome had disease onset in the first year of life, with 50% by age one month [Barzaghi et al 2012]. However, atypical clinical presentation has been reported with onset later in childhood [Consonni et al 2021].

Presentation. The most common presentation of IPEX syndrome is malabsorption with severe watery diarrhea, type 1 insulin-dependent diabetes mellitus, thyroiditis, and dermatitis in males younger than age one year. This disorder is frequently accompanied by other autoimmune phenomena. Males with a somewhat milder/atypical disease phenotype can present at older ages [Ge et al 2017, Hwang et al 2018]. Fetal presentation of IPEX syndrome includes hydrops, echogenic bowel, skin desquamation, intrauterine growth deficiency, and fetal akinesia. There may be a family history of pregnancy loss [Rae et al 2015, Vasiljevic et al 2015, Xavier-da-Silva et al 2015, Reichert et al 2016, Louie et al 2017, Shehab et al 2017].

Enteropathy. The enteropathy of IPEX syndrome, often the initial symptom, is present in virtually all affected individuals. Even in those with milder disease, the diarrhea typically begins in the first six to 12 months of life. Autoimmune enteropathy results in loss of intestinal villi architecture with malabsorption and watery diarrhea, which may contain mucus and blood. Malabsorption ultimately leads to growth failure and cachexia [Bacchetta et al 2018]. Small bowel biopsy is helpful in evaluating the extent of enteropathy. Histologic findings in most individuals have shown graft-vs-host-like changes with lymphocytic infiltrates with depletion of goblet cells and anti-enterocyte antibody deposition [Patey-Mariaud de Serre et al 2009]. Exocrine pancreatic insufficiency has been observed in some individuals [Gambineri et al 2008, Scaillon et al 2009], which may worsen the diarrhea. Other gastrointestinal manifestations include colitis [Lucas et al 2007] and gastritis [Gambineri et al 2008, Scaillon et al 2009]. Food allergies and intolerance are common, which can be diagnosed based on results of immunoglobulin E (IgE) testing to specific food antigens or skin prick testing [Torgerson et al 2007].

Endocrinopathy is present in the majority of affected individuals. Type 1 insulin-dependent diabetes mellitus, often with onset in the first months of life, is the most common endocrine manifestation [Gambineri et al 2008,

Rubio-Cabezas et al 2009]. Thyroid disease (thyroiditis with either hypothyroidism [more common] or hyperthyroidism) is also frequently present [Wildin et al 2002, Gambineri et al 2003, Gambineri et al 2008, Rubio-Cabezas et al 2009].

Dermatitis. The dermatitis is most frequently eczematous, but psoriasiform and ichthyosiform dermatitis have been reported as well. Other dermatologic manifestations include painful chelitis and skin lesions related to food allergies. Rare cutaneous symptoms include pemphigoid nodularis and epidermolysis bullosa acquisita [Nieves et al 2004, McGinness et al 2006, Halabi-Tawil et al 2009, Bis et al 2015].

Autoimmune disorder. Most affected individuals have other autoimmune phenomena including cytopenias (autoimmune hemolytic anemia, immune thrombocytopenia, autoimmune neutropenia [Barzaghi et al 2018]), autoimmune hepatitis [López et al 2011], and nephropathy (membranous nephropathy, interstitial nephritis, and – rarely – minimal change nephrotic syndrome) [Park et al 2015, Sheikine et al 2015]. Lymphadenopathy and splenomegaly as a result of lymphoproliferation have been reported [Ochs &Torgerson 2007, Nademi et al 2014, Bacchetta et al 2018, Barzaghi et al 2018]. Alopecia and arthritis have also been observed [Barzaghi et al 2018], as well as interstitial lung disease related to immune dysregulation [Baris et al 2014].

Infectious complications. Infections of the gastrointestinal tract, skin, and airways occur in individuals with IPEX syndrome [Bacchetta et al 2018], and severe or invasive infections including sepsis, meningitis, pneumonia, and osteomyelitis affect a significant number of subjects [Gambineri et al 2008, Barzaghi et al 2012, Barzaghi et al 2018]. Common pathogens identified were *Staphylococcus*, *Enterococcus*, cytomegalovirus, and *Candida* [Halabi-Tawil et al 2009, Barzaghi et al 2012]. Some infections may be secondary to immunosuppressive therapy, malnutrition, and central venous access; however, many occur prior to the initiation of treatment. Serious infections in individuals with IPEX syndrome are not thought to be due to an intrinsic immune defect but instead are typically related to poor barrier function of the small intestines and skin [Bacchetta et al 2018].

Survival. The outcome of IPEX syndrome is universally poor. Many children die within the first or second year of life from metabolic derangements, severe malabsorption, or sepsis. Although improvements in immunosuppressive regimens have prolonged survival, long-term immunosuppression does not appear to prevent morbidity due to disease progression and side effects or complications in the majority of individuals [Barzaghi et al 2018].

Early hematopoietic stem cell transplantation (HSCT) can cure IPEX syndrome; some survivors are now more than ten years post transplant and doing well. If individuals develop diabetes or thyroiditis prior to HSCT, these aspects of the disorder usually persist, but the other signs of IPEX syndrome resolve. Survival and long-term outcomes are improved if HSCT occurs at an earlier age, prior to the individual developing irreversible organ damage related to the extensive, systemic autoimmunity present in virtually all individuals with IPEX syndrome [Rao et al 2007, Burroughs et al 2010, Kucuk et al 2016].

Heterozygous Females

Heterozygous females have not been reported to have IPEX syndrome.

Note: Recurrent miscarriage of male fetuses, including fetal hydrops and abnormal findings on fetal ultrasound, have been reported and are associated with fetal rather than maternal factors [Rae et al 2015, Vasiljevic et al 2015, Xavier-da-Silva et al 2015, Reichert et al 2016, Louie et al 2017, Shehab et al 2017, Carneiro-Sampaio et al 2022].

Genotype-Phenotype Correlations

There are currently no genotype-phenotype correlations. The same genotype can present with variable severity in different individuals, even within the same family [Seidel et al 2016, Bacchetta et al 2018]. Furthermore, it is

difficult to correlate the type of pathogenic variant and outcome. Loss-of-function variants (frameshift) predicted to be missing the forkhead domain have been described in fetal-onset and nonviable infants, but also in individuals who survive into adolescence [Louie et al 2017, Ben-Skowronek 2021]. Within the cohort of affected individuals with extremely early onset of symptoms (<24 hours of life), the types of variants and their position within the gene vary [Reichert et al 2016].

FOXP3 missense variants can result in FOXP3 expression resulting in normal regulatory T cell (Treg) enumeration by flow cytometry but abnormal Treg function [Seghezzo et al 2017, Lin et al 2018].

Nomenclature

IPEX syndrome may also be referred to as X-linked autoimmunity-allergic dysregulation (XLAAD) syndrome or X-linked syndrome of polyendocrinopathy, immune dysfunction, and diarrhea (XPID).

Prevalence

IPEX syndrome is rare: fewer than 300 affected individuals have been identified worldwide. No accurate estimates of prevalence have been published.

Genetically Related (Allelic) Disorders

No other phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *FOXP3*.

Differential Diagnosis

IPEX syndrome is classified by the International Union of Immunological Societies (IUIS) as an inborn error of immunity that results in immune dysregulation due to absent or defective regulatory T cells (Treg) [Bousfiha et al 2022]. Autoimmunity is the primary clinical manifestation. Among the ten unique disorders with Treg dysfunction, LRBA deficiency, CTLA4 haploinsufficiency, CD25 deficiency, FERMT1 deficiency, BACH2 deficiency, IKAROS GOF (gain of function), and CD122 deficiency have the most clinical overlap with IPEX syndrome [Tangye et al 2022]. Other inborn errors of immunity without Treg dysfunction, including immune dysregulation with colitis, can also mimic IPEX syndrome [Cepika et al 2018, Tangye et al 2022].

In addition to immune dysregulation disorders, monogenic forms of neonatal diabetes that are clinically evident soon after birth can present similarly to IPEX syndrome. These conditions are most commonly associated with pancreatic defects and lack autoimmune manifestations [Rubio-Cabezas et al 2011]. Similarly, intrinsic defects of the intestinal microvilli have clinical presentations consistent with enteropathy with malabsorption and diarrhea but are not immune mediated [Cai et al 2020].

See Table 2 for these and other considerations in the differential diagnosis.

Table 2. Syndromes of Known Genetic Cause to Consider in the Differential Diagnosis of IPEX Syndrome

Gene(s) / Genetic Mechanism	Disorder	MOI	Additional Key Features
Syndromes with immunodeficiency with reduced Treg markers [1]			
BACH2	BACH2-related immunodeficiency & autoimmunity [2]	AD	Enteropathy, chronic variable immunodeficiency
CTLA4	CTLA4 haploinsufficiency (autoimmune lymphoproliferative syndrome, type V) (OMIM 616100)	AD	Enteropathy, autoimmune cytopenias, autoimmune thyroiditis

Table 2. continued from previous page.

Gene(s) / Genetic Mechanism	Disorder	MOI	Additional Key Features
FERMT1	FERMT1 deficiency	AR	Gingivitis, periodontitis, mucosal inflammation
IKZF1	IKAROS GOF (OMIM 616873)	AD	• Low Treg numbers, immune deficiency, & autoimmune disease • Distinguished from IPEX syndrome by low B cell numbers [3]
IL2RA	CD25 deficiency (OMIM 606367)	AR	• Identified in 3 persons w/IPEX syndrome-like clinical phenotype. In addition to autoimmunity, however, these persons had features of severe cellular immunodeficiency w/ susceptibility to severe cytomegalovirus infections. • Distinguished from IPEX syndrome by normal IgE & absence of CD25 expression on T cells
IL2RB	CD122 (IL-2 receptor beta) [4]	AR	Enteropathy, autoimmune hemolytic anemia, ↑ IgG & IgE, dermatitis; endocrinopathy is uncommon [4]
LRBA	LRBA deficiency (OMIM 614700)	AR	Autoimmune enteropathy, type 1 diabetes mellitus, autoimmune hypothyroidism, autoimmune hemolytic anemia
MALT1	MALT1 deficiency [5]	AR	Enteropathy, dermatitis
STAT3	STAT3 GOF (OMIM 615952)	AD	• Enteropathy, type 1 diabetes mellitus, autoimmune cytopenias • Distinguished from IPEX syndrome by short stature [6]
STAT5B	STAT5b deficiency (OMIM 245590) [7]	AR	• Low T & NK cell numbers • Distinguished from IPEX syndrome by dwarfism & GH resistance [8]
Syndromes with immunodeficiency typically without reduced Treg markers [9]			
AIRE	Autoimmune polyendocrinopathy w/candidiasis & ectodermal dystrophy (APECED) (OMIM 240300)	AD AR	• Endocrinopathy, enteropathy • Distinguished from IPEX syndrome by chronic mucocutaneous candidiasis & ectodermal dysplasia (dental enamel hypoplasia, keratopathy)
CASP10 *FAS* *FASLG*	Autoimmune lymphoproliferative syndrome	AD AR [10]	Hemolytic anemia, thrombocytopenia, splenomegaly, chronic adenopathy, type 1 diabetes mellitus, thyroid disease
DCLRE1C *RAG1* *RAG2*	Omenn syndrome [11] (OMIM 603554)	AR	Eosinophilia
DOCK8	DOCK8 deficiency (hyper-IgE recurrent infection syndrome) (OMIM 243700)	AR	Atopic dermatitis

Table 2. continued from previous page.

Gene(s) / Genetic Mechanism	Disorder	MOI	Additional Key Features
ITCH	ITCH deficiency (autoimmune disease, multisystem, w/facial dysmorphism) (OMIM 613385)	AR	• Type I diabetes mellitus, thyroiditis, enteropathy • Distinguished from IPEX syndrome by facial dysmorphisms
TTC7A	Immunodeficiency w/multiple intestinal atresias (OMIM 243150)	AR	• Enteropathy • Distinguished from IPEX syndrome by intestinal atresias (variably present) [12]
WAS	Wiskott-Aldrich syndrome (See *WAS*-Related Disorders.)	XL	Thrombocytopenia, eczema, combined immune deficiency
Syndromes with neonatal diabetes mellitus			
ABCC8 *GCK* *INS* *KCNJ11* *PDX1*	Permanent neonatal diabetes mellitus [13]	AR AD [14]	Non-immune-mediated neonatal diabetes mellitus assoc w/pancreatic agenesis
GATA6	Heart defects, congenital, & other congenital anomalies (OMIM 600001) [15]	AD	Neonatal diabetes mellitus, pancreatic aplasia, complex congenital heart disease, GH deficiency
PDX1 *PTF1A*	Pancreatic agenesis (OMIM PS260370)	AR	Pancreatic hypoplasia
Overexpression of imprinted genes at 6q24 (*PLAGL1* & *HYMAI*) [16]	Transient neonatal diabetes mellitus, 6q24-related	See footnote 16.	Transient neonatal diabetes mellitus w/ nonsuppurative submandibular sialadenitis [17]
Syndromes with protracted diarrhea in infancy			
EPCAM	Tufting enteropathy (OMIM 613217) [18]	AR	Enteropathy w/abnormal intestinal villi
IL10RA *IL10RB*	IL-10 receptor deficiency (OMIM 613148, 612567) [19]	AR	Distinguished from IPEX syndrome by severe, early-onset, fistulating enterocolitis in IL-10 receptor deficiency
MYO5B	Microvillus inclusion disease (OMIM 251850)	AR	Enteropathy w/abnormal intestinal villi

Table 2. continued from previous page.

Gene(s) / Genetic Mechanism	Disorder	MOI	Additional Key Features
SKIV2L *TTC37*	Trichohepatoenteric syndrome	AR	

AD = autosomal dominant; AR = autosomal recessive; GH = growth hormone; GOF = gain of function; Ig = immunoglobulin; IL = Interleukin; MOI = mode of inheritance; Treg = regulatory T cell(s); XL = X-linked

1. Cepika et al [2018], Bousfiha et al [2022], Tangye et al [2022]

2. Afzali et al [2017]

3. Boutboul et al [2018]

4. Zhang et al [2019]

5. Charbit-Henrion et al [2017]

6. Flanagan et al [2014]

7. Hwa [2021]

8. Individuals with STAT5B deficiency also have a form of dwarfism related to the fact that growth hormone mediates its effects through STAT5.

9. Ren et al [2021]

10. Inheritance of autoimmune lymphoproliferative syndrome (ALPS)-CASP10, most instances of ALPS-FAS, and some instances of ALPS-FASLG is autosomal dominant. ALPS-FAS can also be the result of somatic mosaicism. Somatic pathogenic variants have not been reported in ALPS-FASLG or ALPS-CASP10 to date.

11. Omenn syndrome is also known as familial reticuloendotheliosis with eosinophilia or severe combined immunodeficiency (SCID) with hypereosinophilia.

12. Avitzur et al [2014]

13. Rubio-Cabezas et al [2011]

14. The mode of inheritance of permanent neonatal diabetes mellitus (PNDM) is autosomal dominant for *KCNJ11*-related PNDM, autosomal dominant or autosomal recessive for *ABCC8*- and *INS*-related PNDM, and autosomal recessive for *GCK*- and *PDX1*-related PNDM.

15. Du et al [2019]

16. See Diabetes Mellitus, 6q24-Related Transient Neonatal.

17. Rubio-Cabezas et al [2011], Mustafa et al [2021]

18. Cai et al [2020]

19. Engelhardt & Grimbacher [2014]

Syndromes of unknown genetic cause to consider in the differential diagnosis of IPEX syndrome include the following:

- Pancreatic beta cell agenesis with neonatal diabetes mellitus (OMIM 600089), a presumed recessive disorder or imprinting defect causing an islet cell developmental defect
- Autoimmune polyendocrine syndrome, type II (OMIM 269200)

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with IPEX syndrome, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. IPEX Syndrome: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Gastrointestinal	Nutrition assessment incl serum electrolyte levels, calcium, magnesium, zinc, serum albumin, & pre-albumin	The majority of persons will require discontinuation of enteral feeding & initiation of TPN.
	Hepatic assessment	Incl serum AST, ALT, GGT, total bilirubin, & assessment of hepatic autoantibodies
	Small bowel biopsy incl specific staining for Treg	To assess response to treatment
Endocrine	• Glucose tolerance test • Hemoglobin A1c • Thyroid function tests • Autoantibodies to pancreatic islet antigens & thyroid antigens	
Dermatologic	Eval of any skin lesions	Should incl biopsy for histology
Immunologic	• Serum IgG, IgM, IgA, & IgE concentrations • Lymphocyte enumeration by flow cytometry • Lymphocyte response to mitogens	Serum immunoglobulins, lymphocyte enumeration, & mitogen proliferation to assess cellular immune reconstitution following HSCT
Hematologic	• Complete blood count & differential • Coombs test • Eval of autoimmune hypercoagulability (anti-phospholipid antibodies, lupus anticoagulant)	
Renal	• BUN, creatinine • Urinalysis	
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of IPEX syndrome to facilitate medical & personal decision making
Family support & resources	By clinicians, wider care team, & family support organizations	Assessment of family & social structure to determine need for: • Community or online resources such as Parent to Parent • Social work involvement for parental support • Home nursing referral

ALT = alanine transferase; AST = aspartate transferase; BUN = blood urea nitrogen; GGT = gamma-glutamyl transferase; HSCT = hematopoietic stem cell transplantation; Ig = immunoglobulin; MOI = mode of inheritance; TPN = total parenteral nutrition; Treg = regulatory T cell(s)

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Targeted Therapies

In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure. —ED

Hematopoietic stem cell transplantation (HSCT) currently offers the only potential cure for IPEX syndrome. Myeloablative conditioning regimens showed a high degree of transplant-related mortality and other

complications, so most centers have used non-myeloablative conditioning regimens, resulting in better overall survival [Baud et al 2001, Burroughs et al 2007, Lucas et al 2007, Rao et al 2007]. Overall, 15-year survival is 77.5% following HSCT. Survival is similar among individuals with IPEX syndrome who receive transplants from matched related, matched unrelated, cord blood, or haploidentical donors. Individuals with more severe disease at the time of transplant have poorer outcomes. If HSCT is performed in early infancy there is evidence that early-onset diabetes and thyroiditis is reversible [Yamauchi et al 2019]. Taken together, HSCT results in better outcomes and lower overall morbidity compared with non-transplanted individuals receiving chronic immunosuppressive therapy [Barzaghi et al 2018].

Immunosuppression therapy. The most recent multicenter study examining long-term outcomes in individuals with IPEX syndrome treated with different therapeutic modalities showed that calcineurin inhibitors such as tacrolimus or mTOR inhibitors such as rapamycin were the backbone of immune suppression strategies with azathioprine, mycophenolic acid, and methotrexate used in addition to these agents [Barzaghi et al 2018]. More recently, rapamycin, dosed to achieve levels of 8-12 ng/mL, has been shown to restore regulatory T cell (Treg) function, and when used early in the course of disease it has the potential to reverse endocrinopathy [Passerini et al 2020]. Immune suppression treatment requires closing monitoring for nephrotoxicity and drug levels, and close observation for opportunistic infection. Cutaneous manifestations can be treated with topical corticosteroids and topical tacrolimus. There have been reports that improved dermatitis and diabetes is associated with the use of dupilumab [Maher et al 2021, Caruso et al 2023].

Supportive Care

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 4).

Table 4. IPEX Syndrome: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Enteropathy	Monitor fluid intake & provide fluids as needed to assure adequate intravascular volume to adjust for insensible losses due to skin breakdown.	Aggressive mgmt of hyperglycemia is essential.
	Nutritional support incl TPN or elemental or low-carbohydrate-containing formula is necessary in almost all persons.	
	• T cell-directed immune suppression (i.e., sirolimus, cyclosporin A, or tacrolimus), either alone or in combination w/steroids • Sirolimus (rapamycin) as monotherapy or in combination w/other drugs [1] is considered 1st-line treatment; calcineurin inhibitors (e.g., tacrolimus) are an alternative. [2]	• Toxicity, tachyphylaxis, & ↑ susceptibility to infection related to chronic use of these agents reduce their potential for long-term amelioration of symptoms in most persons. • Sirolimus & tacrolimus are nephrotoxic & require close renal monitoring & plasma drug levels. • Sirolimus has been used successfully in persons for whom tacrolimus was either ineffective or toxic. [3] • The ability of sirolimus to suppress effector T cell function while allowing Treg cells to continue to develop & function offers some theoretic advantages for its use. [4]
Endocrinopathy	• Standard treatment of type 1 insulin-dependent diabetes mellitus w/insulin & carbohydrate mgmt • Standard treatment of autoimmune thyroid disease	

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Dermatitis	• Systemic T cell-directed immune suppression • Topical therapies (e.g., steroids, tacrolimus, emollients) can also be beneficial.	For severe dermatitis, persons have had good response to topical corticosteroids, tacrolimus, & dupilumab w/input from wound care specialist.[5]
Immune dysregulation	• For autoimmune neutropenia: G-CSF can improve neutrophil counts. • For pemphigus nodularis & other autoantibody-mediated disease: rituximab has been effective. .	May be beneficial
Infections	• Persons w/autoimmune neutropenia or recurrent infections due to severe eczema may benefit from prophylactic antibiotic therapy to ↓ risk of severe infectious complications. • Aggressive mgmt of dermatitis w/topical steroids & anti-inflammatory agents can help prevent infections from pathogens that enter as a result of the poor barrier function of the skin. • Standard antimicrobial therapy when indicated	

G-CSF = granulocyte colony-stimulating factor; TPN = total parenteral nutrition; Treg = regulatory T cell(s)
1. Bacchetta et al [2018]
2. Barzaghi et al [2018]
3. Bindl et al [2005], Yong et al [2008]
4. Strauss et al [2007]
5. Maher et al [2021], Caruso et al [2023]
6. McGinness et al [2006]

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 5 are recommended.

Table 5. IPEX Syndrome: Recommended Surveillance

System/Concern	Evaluation	Frequency
Enteropathy	Monitor growth, nutritional intake, & stooling patterns.	At each visit
Endocrinopathy	• Glucose tolerance test • Hemoglobin A1c • Thyroid function tests	Every 3-6 mos
Dermatitis	Skin exam	At each visit
Immune dysregulation	• Complete blood count • BUN, creatinine • Urinalysis • Serum AST, ALT	Every 3-6 mos

ALT = alanine transferase; AST = aspartate transferase; BUN = blood urea nitrogen

Agents/Circumstances to Avoid

Immune activation (e.g., by immunizations or severe infections) has been reported to cause worsening or exacerbation of disease symptoms [Powell et al 1982]. It is generally best practice to withhold immunizations until after HSCT, if possible.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of at-risk males either prenatally or immediately after birth to enable early diagnosis and HSCT and/or steroid treatment in affected males before significant organ damage occurs.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

HSCT carries the risk of significant morbidity and mortality, and suitable donors are not always available. For these and other reasons, IPEX syndrome is an excellent candidate for treatment with gene therapy. However, one major hurdle is the need to regulate the expression of *FOXP3* on mature T cells; thus, hematopoietic stem cells are not the ideal target for gene delivery. An alternative approach has been to convert $CD4^+$ T cells from individuals with IPEX syndrome using lentivirus vectors that carry normal *FOXP3*. Lentiviral delivery of exogenous *FOXP3* cDNA is accomplished under the constitutive promoter to achieve conversion of *FOXP3* mutated cells to normal functioning regulatory T cells (Treg) in vivo. A potential limitation to this approach is determining how long the converted Treg will survive. A human clinical trial is now ongoing using this strategy [Borna et al 2022] (see NCT05241444).

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

IPEX syndrome is inherited in an X-linked manner.

Risk to Family Members

Parents of a male proband

- The father of an affected male will not have the disorder, nor will he be hemizygous for the *FOXP3* pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote (carrier). Note: If a woman has more than one affected child and no other affected relatives and if the *FOXP3* pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism. Maternal somatic and germline mosaicism has been reported in IPEX syndrome [Lin et al 2018].
- If a male is the only affected family member (i.e., a simplex case), the mother may be a heterozygote (carrier), the affected male may have a *de novo FOXP3* pathogenic variant (in which case the mother is not a carrier), or the mother may have somatic/germline mosaicism. The percentage of affected males who have no family history of IPEX syndrome is not known.
- Molecular genetic testing of the mother is recommended to evaluate her genetic status and inform recurrence risk assessment.

Sibs of a male proband. The risk to sibs depends on the genetic status of the mother:

- If the mother of the proband has a *FOXP3* pathogenic variant, the chance of transmitting it in each pregnancy is 50%.
  - Males who inherit the pathogenic variant will be affected. Male sibs with the same *FOXP3* pathogenic variant can present with variable severity (see Genotype-Phenotype Correlations).
  - Females who inherit the pathogenic variant will be heterozygous (carriers). To date, IPEX syndrome has not been reported in females who are heterozygous for a *FOXP3* pathogenic variant.
- If the proband represents a simplex case and if the *FOXP3* pathogenic variant cannot be detected in the leukocyte DNA of the proband's mother, the recurrence risk to sibs is presumed to be low but slightly greater than that of the general population because of the possibility of maternal germline mosaicism [Lin et al 2018].

Offspring of a male proband. Affected males transmit the *FOXP3* pathogenic variant to all of their daughters, who will be heterozygotes (carriers), and none of their sons.

Other family members. The proband's maternal aunts and their offspring may be at risk of being heterozygotes (carriers) for the pathogenic variant, and the aunts' offspring, depending on their sex, may be at risk of being heterozygotes for the pathogenic variant or of being affected.

Carrier Detection

Identification of female heterozygotes requires prior identification of the *FOXP3* pathogenic variant in the family.

X-chromosome inactivation is skewed only in regulatory T cells [Di Nunzio et al 2009] and is random in all other lymphocyte populations [Tommasini et al 2002]; therefore, X-chromosome inactivation studies are of limited use in carrier detection.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

Once the *FOXP3* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **American Diabetes Association**
  Phone: 800-DIABETES (800-342-2383)
  Email: AskADA@diabetes.org
  diabetes.org
- **Diabetes UK**
  United Kingdom
  Phone: 0345 123 2399
  Email: helpline@diabetes.org.uk
  diabetes.org.uk
- **International Patient Organization for Primary Immunodeficiencies (IPOPI)**
  United Kingdom
  Phone: +44 01503 250 668
  Fax: +44 01503 250 668
  Email: info@ipopi.org
  ipopi.org
- **Jeffrey Modell Foundation/National Primary Immunodeficiency Resource Center**
  Email: info@jmfworld.org
  info4pi.org
- **European Society for Immunodeficiencies (ESID) Registry**
  Email: esid-registry@uniklinik-freiburg.de
  ESID Registry
- **Latin American Society for Immunodeficiency (LASID) Registry**
  Email: lagid.adm@gmail.com
  www.lasid.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. IPEX Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
FOXP3	Xp11.23	Forkhead box protein P3	FOXP3 @ LOVD CCHMC - Human Genetics Mutation Database (FOXP3)	FOXP3	FOXP3

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for IPEX Syndrome (View All in OMIM)

300292	FORKHEAD BOX P3; FOXP3
304790	IMMUNODYSREGULATION, POLYENDOCRINOPATHY, AND ENTEROPATHY, X-LINKED; IPEX

Molecular Pathogenesis

FOXP3 encodes forkhead box protein P3 (FOXP3), a forkhead DNA-binding protein that is expressed primarily in $CD4^+CD25^+$ regulatory T cells. The protein has important functional domains including:

- An N-terminal proline-rich domain, which is essential for the gene-suppressive function of FOXP3 and for interaction with other key transcription factors including RORα and RORγt [Du et al 2008, Zhou et al 2008];
- A C2H2 zinc finger and leucine zipper (both conserved structural motifs involved in protein-protein interactions) in the central portion;
- A forkhead DNA-binding domain at the C terminus, from which it derives its name (forkhead box) [Ochs et al 2005, Lopes et al 2006]. A putative nuclear localization signal is located at the C-terminal portion of the forkhead domain [Lopes et al 2006].

Proteins bearing forkhead DNA-binding motifs comprise a large family of related DNA-binding proteins that play diverse roles in enhancing or suppressing transcription from specific binding sites. Several members of this protein family are involved in patterning and development [Gajiwala & Burley 2000]. FOXP3 is expressed primarily in lymphoid tissues (thymus, spleen, and lymph nodes), particularly in $CD4^+CD25^+$ regulatory T-cell lymphocytes. In mice, it is required for the development and suppressive function of this important regulatory T cell population [Fontenot et al 2003, Hori et al 2003, Khattri et al 2003, Sakaguchi 2003]. In humans, it is not expressed at baseline in $CD4^+CD25^-$ or $CD8^+$ T cells but is expressed upon T-cell activation [Gavin et al 2006, Allan et al 2007]. The significance of this inducible expression in effector T cells is unknown.

The majority of pathogenic variants in *FOXP3* are either missense variants or small in-frame amino acid deletions. Loss-of-function variants have been described both in individuals with a neonatal presentation and others with a childhood presentation; thus, haploinsufficiency of *FOXP3* does not appear to be lethal. The highest concentration of variants cluster within the C-terminal forkhead DNA-binding domain. Some pathogenic variants also affect the leucine zipper and an amino-terminal proline-rich domain that is involved in interactions with other key protein partners. Clustering of variants within these key functional regions of the protein demonstrates the essential role for these domains in FOXP3 function [Chatila et al 2000, Lopes et al 2006]. Pathogenic alterations can affect mRNA stability, protein function, and intracellular localization. The FOXP3 protein is a transcription factor that regulates the expression of hundreds of targets and is necessary for proper development of Treg, a population of cells responsible for tolerance of self-antigens.

Mechanism of disease causation. Loss of function

***FOXP3*-specific laboratory technical considerations.** *FOXP3* pathogenic variants have been reported in the 5' UTR (c.-7G>T) and the 3' UTR (c.*876A>G). Since the 3' UTR variants are not typically included in sequencing assays, the assay design may need to be modified to include these variants.

Table 6. *FOXP3* Pathogenic Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_014009.4	c.-7G>T	--	Examples of reported pathogenic variants outside the coding region.
	c.*876A>G	--	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

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