

IPEX is a unique X-linked syndrome characterized by immune dysfunction, polyendocrinopathy, enteropathy, and a variety of autoimmune phenomena

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The rare syndrome known as IPEX (OMIM: 304930) is characterized by immune-dysfunction, polyendocrinopathy, enteropathy, and X-linked inheritance. The gene responsible for IPEX maps to Xp11.23-q13.3, a region of the X chromosome that also harbors the Wiskott-Aldrich syndrome gene (*WASP*). IPEX syndrome results from mutations of a unique DNA binding protein gene, *FOXP3*. Mutations invariably impair the seemingly essential forkhead domain of the protein, which is uniquely located in the carboxyl terminus, affecting protein function. In this review, we describe the identification of IPEX as a unique X-linked syndrome, the clinical features of IPEX, mutations of the immune-specific *FOXP3* DNA binding protein, and bone marrow transplantation as a potential cure for the syndrome, which is usually lethal within the first year of life in affected males. *Curr Opin Pediatr* 2001, 13:533–538 © 2001 Lippincott Williams & Wilkins, Inc.

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The lethal syndrome known as IPEX (immune dysfunction, polyendocrinopathy, enteropathy, X-linked; OMIM: 304930) was first described as a distinct entity by Powell *et al.* in 1982. Affected males typically present during the first few months of life with diabetes mellitus, intractable diarrhea, eczema, hemolytic anemia, thyroiditis, and serious infections. The syndrome subsequently was mapped to chromosome Xp11.23–Xq13.3 [1,2].

Scurfy syndrome in mice is a lethal X-linked disease characterized by progressive lymphocytic infiltration of lymph nodes, spleen, liver, and skin, resulting in splenomegaly, hepatomegaly, and greatly enlarged lymph nodes. These mice develop severe anemia, an exfoliated dermatitis, thickened malformed ears, and a wasting syndrome. The scurfy gene is tightly linked to the murine *Gata-1* [3] and *Wasp* [4] and recently has been mapped to Xp 11.23. The murine gene responsible for scurfy syndrome (*Foxp3*) and its human equivalent have been identified by positional cloning and subsequently sequenced [5••]. Based on the clinical similarities between scurfy syndrome in mice and IPEX, we decided to sequence the human *FOXP3* and found it to be mutated in affected patients.

An early observation that resembled the IPEX syndrome was reported by Meyer *et al.* [6], who described two brothers with absent islet cells, neonatal insulin-dependant diabetes mellitus (IDDM), diarrhea, and failure to thrive. One brother had numerous infections (including fungal infections, thigh abscess, and discharge from his ears) and died at 4 months; the other died at 32 days of infection. The mother had ten brothers who died of unknown causes in infancy, and a healthy sister, suggesting X-linked inheritance. The first report of the complete IPEX phenotype was published by Powell *et al.* [7], describing an X-linked syndrome in a large kindred in which eight males in three generations had various combinations of intractable diarrhea, eczema, hemolytic anemia, thrombocytopenia, diabetes mellitus, thyroid disease, and infection. Death in infancy or early childhood occurred in 11 additional males in the kindred. Satake *et al.* [8] described a Japanese family in which two brothers and their maternal uncle suffered autoimmune enteropathy with hemolytic anemia and polyendocrinopathy. Two of the boys died from severe diarrhea accompanied by total or subtotal intestinal villous atrophy.

The third affected male, who showed the same symptoms and had circulating IgG antibodies against enterocytes, improved dramatically after the introduction of Cyclosporin A (CSA). Kobayashi *et al.* [9] have treated an IPEX patient with a combination of FK506 and betamethasone.

The clinical phenotype of IPEX

The full extent of the clinical presentation of the syndrome, the laboratory abnormalities, and the response to treatment has been reported by a number of investigators [2,7–18]. Most IPEX patients described to date have developed symptoms shortly after birth or during the first three to four months of life. The most common findings have been diabetes mellitus, severe diarrhea, failure to thrive, eczema, and hemolytic anemia. Less common are thrombocytopenia caused by autoantibodies, autoimmune hypothyroidism, and lymphadenopathy associated with splenomegaly.

Characteristic histopathologic findings were observed in small bowel biopsies and consisted of severe villous atrophy and mucosal erosion with lymphocytic infiltrates of the submucosa or lamina propria. Lymphocytic infiltrates also have been observed in pancreas and thyroid. There are no pathognomonic laboratory abnormalities. Serum IgE is elevated in most patients and eosinophilia is common. Anti-islet cell antibodies and antithyroid antibodies are present in some and absent in other patients. The lymphocytic infiltrates observed in pancreas and thyroid glands suggest a T-cell mediated autoimmune mechanism. Systematic evaluation of immune competence has not been performed. T lymphocyte subsets are normal and *in vitro* lymphocyte proliferation to mitogens and specific antigens is preserved, although in some reports a slightly lower response was noticed. In contrast, Shigeoka *et al.* [19] observed an increased response to mitogens and overexpression of IL-2, and Chatilia *et al.* [17•] reported increased production of multiple lymphokines by peripheral blood mononuclear cells. These observations, together with increased expression on MHC class 2 antigens, [19] suggest a global activation of the immune system.

Hypogammaglobulinemia and poor responses to immunization with diphtheria and tetanus toxoid was observed in one patient and normal antibody responses to protein antigens but defective response to pneumococcal polysaccharides were observed in another. The fragmented analysis of the immune system is not surprising because these patients are usually seriously ill, often malnourished and infected, and in recent years treated immediately with immunosuppressive drugs including Cyclosporin A, FK506 and steroids.

IPEX, a distinct syndrome mapping to Xp11.23-q13.3

Two independent linkage studies of large pedigrees were used to map the gene for IPEX to chromosome Xp11.23-q13.3 [1,2]. As there was genetic overlap of this interval with that of the Wiskott-Aldrich syndrome (WAS)/X-linked thrombocytopenia (XLT) (Xp11.23-p11.22) (OMIM: 301000) and some clinical features were common to both syndromes, the possibility that the WAS gene (*WASP*) also may be responsible for the IPEX syndrome was considered. However, *WASP* was normal by sequence analysis in both IPEX families [1,2]. Recently a syndrome of X-linked congenital neutropenia (XLN) (OMIM: 300299) was shown to map to Xp11.23-p11.22. Interestingly, XLN results from a rare point mutation of the *cdc42* binding domain of *WASP* [20], showing that domain specific mutations of *WASP* can lead to highly variable clinical phenotypes (Table 1). The major bacterial infections observed in patients with XLN are caused by severe congenital neutropenia and monocytopenia. In contrast to WAS and XLT, platelets are not decreased in XLN, and there is no history of eczema in affected individuals. Bone marrow examination showed a maturation arrest at the promyelocyte/myelocyte stage, without gross abnormalities in megakaryopoiesis or erythropoiesis. The unique missense mutation cosegregating with XLN in this pedigree (843T[C]) results in a 270L[P] substitution in a conserved GTPase binding domain. *In vitro*, the mutant protein was shown to be activated constitutively through disruption of an autoinhibitory domain in the wildtype protein, indicating that

Table 1. Clinical features of X-linked immune syndromes

Clinical feature	IPEX	WAS	XLT	XLN	GATA-1
Anemia	+/-	+/-	+/-	no	+
Abnormal bleeding	yes	yes	yes	no	yes
Autoimmune manifestations	yes	yes		no	no
Diarrhea	yes	yes	yes	no	no
Eczema	yes	yes	+/-	no	no
Recurrent infections	yes	yes	+/-	yes*	no
Thrombocytopenia	+/-	yes	yes	no	yes
Platelets	normal	small	small	normal	large
T-cell activation	yes	no	no	no	no
Neutropenia	no	no	no	yes	no
Nonrandom X chromosome inactivation	no	yes	yes	yes	no

*Infections secondary to neutropenia.

loss of WASP autoinhibition is the key event in XLN [20].

Preferential inactivation of the X chromosome carrying the mutated WAS gene was found in both available carriers (peripheral white blood cells tested), indicating that selection operates against the L270P allele *in vivo*. Non-carrier females had random X inactivation. The same preferential inactivation of the X chromosome carrying a mutant allele is found in hematopoietic cells of WAS carriers [21,22]. This feature has not been observed in IPEX carrier females [19].

A third X-linked syndrome (OMIM: 305371) associated with thrombocytopenia recently has been described as mapping to this interval. Nichols *et al.* [23] described a woman with mild chronic thrombocytopenia who had two pregnancies complicated by severe fetal anemia, necessitating *in utero* red blood cell transfusions. The offspring were male half-siblings who were anemic and severely thrombocytopenic at birth and thereafter. Abnormalities were present in the erythrocyte and platelet lineages. Peripheral blood showed a paucity of platelets, poikilocytosis, and anisocytosis of erythrocytes. There were three asymptomatic female siblings. This pedigree showed complete cosegregation of a 613G→A nucleotide transition with the GATA-1 gene. The mutation predicts a 205V→M substitution of a highly conserved residue within the GATA-1 protein, an erythroid tissue-specific transcription factor known to interact with the gamma-globin promoter [24]. Further mutations of this gene have been reported by Raskind *et al.* [25] within a pedigree suffering from X-linked thrombocytopenia associated with thalassemia (XLTT). As shown in Table 1, IPEX can be readily distinguished from these other X-linked syndromes.

IPEX and mouse scurfy are caused by mutations of *FOXP3* and *Foxp3*, respectively

Mouse scurfy is an X-linked recessive disorder of immune regulation [26]. Affected males have scaly skin, apparent infections, diarrhea, progressive Coombs-positive anemia, thrombocytopenia, gastrointestinal bleeding, hypogonadism, leukocytosis, lymphadenopathy, and cachexia [5,27]. They die within four weeks after birth. The mutation found responsible for mouse scurfy is a 2-bp insertion within the *Foxp3* gene. This recently cloned gene encodes a highly conserved protein that is truncated in the scurfy mouse, eliminating a forkhead/winged-helix domain at the carboxy terminus [5••]. *FOXP3* is the human orthologue of murine *Foxp3*.

Mutations of the *FOXP3* gene recently were described in affected males of six unrelated families [28•,29•], validating the scurfy mouse as a useful model for the human syndrome. Chatila *et al.* [17•] report the identification of mutations of a JM2 gene showing complete cosegrega-

tion with two small pedigrees. The syndromes described, as X-linked autoimmunity-allergic dysregulation (XLAAD), are indistinguishable from that of IPEX. After corrections to the gene structure, it became clear that the JM2 gene was the human orthologue of murine *Foxp3*, now accepted as *FOXP3*.

Brunkow *et al.* [5••] surveyed a large number of mouse tissues for expression of *Foxp3*, using real-time RT-PCR, and found the highest levels in thymus and spleen. The *FOXP3* gene is one of multiple genes encoding transcription factors that are distinguished by a characteristic 100-amino acid motif that was originally identified in *Drosophila melanogaster* as forkhead. The forkhead domain or winged-helix of the human FOXP3 protein exists between amino acid residues 337 and 420 at the C terminus (see comparison with the murine Foxp3 protein in Figure 1) [5••]. This structure contains many of the sequence features thought to be important for mediating protein-DNA contacts. As in other Fox protein family members, the forkhead domain contains several basic residues at either end, which may serve to direct the protein to the nucleus [30,31]. A single C₂H₂ zinc-finger domain exists 116 amino acids upstream from the winged-helix domain; no other well-described functional motifs are present [5••]. *FOXP3* encodes a new member of the forkhead family of transcriptional regulators, which is required for normal T-cell function. To date, seven of eight *FOXP3* mutations reported within classic IPEX pedigrees seem to have a direct bearing on the essential forkhead DNA binding domain or total protein function (Fig. 2). The mutations include four missense mutations within the forkhead domain (371Phe→Cys; 384Ala→Thr [x2]; 397Arg→Trp) two microdeletions (2-bp and 20-bp) that remove the native stop codon and a splice site mutation that leads to a truncated protein lacking the forkhead domain. These molecular aberrations all have a direct bearing on the forkhead domain or in the case of the microdeletions, potentially leading to nonspecific mRNA degradation. The remaining mutation, identified in a classic IPEX patient is an inframe deletion of nucleotides 600–602, predicting the removal of a glutamic acid (Glu) residue upstream of the forkhead domain in the mature protein [17•]. The authors suggest that this Glu(201) residue lies in the second of the three heptad repeats that constitute the Zip motif of the gene. However, no significant homology of this region of the *FOXP3* protein can be demonstrated with other proteins. Phenotypically, the IPEX pedigree segregating this mutation was unremarkable in terms of recognizable symptoms. Obligate carrier females were unaffected, which has been the case with all IPEX families reported to date. There was, however, an unexpectedly high incidence of fatal hydrops fetalis. Pedigrees harboring mutations affecting other protein domains, yet leaving the forkhead domain functionally intact, may present with features atypical of IPEX that have yet to be identified.

Figure 1. Mouse and human scurfin proteins contain a highly conserved forkhead domain

m Fxp3	MPNPRPAKPMAPSLALGPSGLVPSWKTAPKGSSELLGTRGSGGPFQGRDL	50
h FOXP3	MPNPRPGKPSAPSLALGPSGASPSWRAAPKASDLLGARGPGGTFQGRDL	50
m Fxp3	RSGAH TSSSLNPLPPSQLQLPTVPLVMVAPSGARLGPSPHLQALLQDRP	99
h FOXP3	RGGAHASSSLNPMPPSQLQLPTLPLVMVAPSGARLGPLPHLQALLQDRP	100
m Fxp3	HFMHQLSTVDAHAQTPVLQVRPLDNPAMISLPPPSAATGVFSLKARPGLP	149
h FOXP3	HFMHQLSTVDAHARTPVLQVHPLESAMISLTPPTTATGVFSLKARPGLP	150
m Fxp3	PGINVASLEWVSREPALLCTFPRSGTPRKDSNLLAAPQGSYPLLANGVCK	199
h FOXP3	PGINVASLEWVSREPALLCTFPNPSAPRKDSTLSAVPQSSYPLLANGVCK	200
m Fxp3	WPGCEKVFEPEEFLKHCQADHLLDEKGKAQCLLQREVVQSLEQQLELEK	249
h FOXP3	WPGCEKVFEPEDFLKHCQADHLLDEKGRAQCLLQREVMQSLEQQLVLEK	250
m Fxp3	EKLGAMQAHLAGKMALAKAPSVASMDKSSCCIVATSTQGS VLPAWSAPRE	299
h FOXP3	EKLSAMQAHLAGKMALTKASSVASSDKGSCCIVAAGSQGPVPAWSGPRE	300
m Fxp3	APDGGFLFAVRRHLWGSHGNSSFPEFFHNMDYFKYHNMRPPFTYATLIRWA	349
h FOXP3	APD SLFAVRRHLWGSHGNSTFPEFLHNMDYFKFHNMRPPFTYATLIRWA	349
m Fxp3	ILEAPERORTLNEIYHWFRMFAPPRNHHPATWKNAIRHNLSLHKCFVRVE	399
h FOXP3	ILEAPERORTLNEIYHWFRMFAPPRNHHPATWKNAIRHNLSLHKCFVRVE	399
m Fxp3	SEKGA>VWTVDEFEFRKKRSORPNKCSNPPC	429
h FOXP3	SEKGA>VWTVDEFEFRKKRSORPSRCSNPTPGP	431

Needle-man-Wunsch algorithm was used to align the mouse and human sequences; the two proteins have an overall similarity index of 86%. The forkhead domain, with a similarity index of 94%, is shaded, the C₂H₂ zinc finger domain is boxed and potential nuclear localization signals are under-lined. Asterisk indicates position of 2-bp insertion in sf mutant. One difference between the hypothetical JM2 transcript and mouse sf cDNAs was an in-frame insertion of 180-bp in the forkhead domain of the human sequence (between coding exons 10 and 11). The arrow below the human FOXP3 sequence indicates the site of this insertion, which would encode an additional 60 aa (Taken from [5•]).

The IPEX pedigree originally described by Powell *et al.*, and later examined by linkage analysis [1] is the only pedigree for which a mutation of the FOXP3 gene was not shown [28•,29•]. The pedigree potentially represents a phenotype of greater survivability. One patient died at age 30 years, a second lived to age 8 years, and one patient survives at age 5 years. The DNA sequence of all 11 FOXP3 exons, including at least 50-bp of each intron/exon boundary, 531-bp of promoter sequence and 487-bp of 3'-untranslated region (UTR), was examined without detection of a polymorphism. The authors recently identified a rare polyadenylation signal mutation showing complete cosegregation with the IPEX syndrome in the pedigree originally described by Powell *et al.* [33].

Treatment of IPEX

The natural course of IPEX is devastating, with symptoms starting in early infancy and death occurring during the first or second year of life. The observation of MHC class 2 expression by activated T cells, increased lymphokine production, and the consistent lymphocyte infiltration of affected organs, *eg*, epidermis, pancreas, and thyroid suggest activation of the immune system. Auto-antibodies are frequently present and may play a role in autoimmune manifestations. Based on this observation, immunosuppressive therapy has been attempted with steroids, Cyclosporin A, and FK506. Most patients responded at least temporarily to immunosuppressive

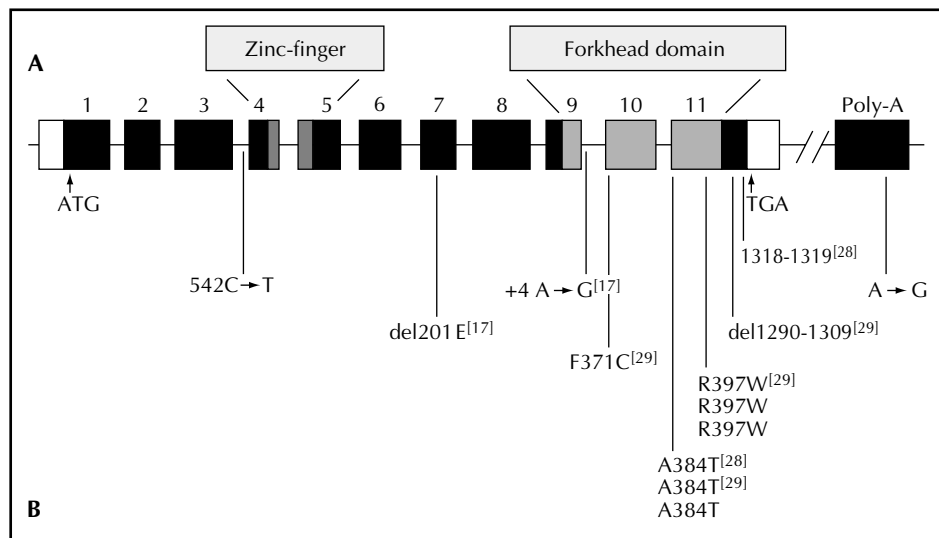
agents. However, only a few patients have survived early childhood. To date, bone marrow transplantation has been performed in two IPEX patients. One of the patients reported by Wildin *et al.* received a transplant from a matched sibling at the age of four months [32•]. Complete clinical, histologic, and biologic remission was achieved. Interestingly, the conditioning regimen, consisting of anti-T lymphocyte globulin, busulfan, and cyclophosphamide was in itself effective in controlling most of the clinical features. After transplantation, the insulin dependent diabetes reversed to normal. In spite of the extensive conditioning, only between 20 and 30% of the circulating lymphocytes were of donor origin. This chimeric state was stable and the patient remained asymptomatic. Unfortunately, 30 months after bone marrow transplantation, the patient developed a fatal hemol-phagocytic syndrome. A second patient receiving a matched marrow transplant is asymptomatic, with the exception of IDDM, approximately 12 months after transplantation (Howard Lederman, personal communication). Thus, stem cell transplantation seems to be the treatment of choice, although the development of a hemophagocytosis syndrome in one of the two patients treated with bone marrow transplantation is of concern.

Conclusions

IPEX is a rare X-linked syndrome characterized by neonatal IDDM, enteropathy, endocrinopathy, eczema, and severe infections with variable autoimmune phenomena.

Figure 2. *FoxP3* mutations reported within classic IPEX pedigrees

(A) Genomic organization of the *FOXP3* gene, including the location of a Zinc-finger domain spanning exon 4 and 5; and a forkhead DNA binding domain spanning exons 9, 10 and part of 11. (B) Location of mutations identified to date within the *FOXP3* gene, with the preponderance locating to the forkhead domain or the carboxyl terminal. Where mutations have been published the reference is given, all others are unpublished results of the authors.



Murine scurfy, an X-linked lethal disorder of immune regulation [26], is the equivalent of human IPEX and provides a model of the human disease [5••]. The mutation found responsible for mouse scurfy is a 2-bp insertion within the *Foxp3* gene. The cloning of the human orthologue of the mouse gene, *FOXP3*, led to its identification as the immune specific DNA binding protein gene responsible for IPEX. Point mutations and micro-deletions have been identified in all affected members of eight of nine families suffering from IPEX to date. A rare polyadenylation signal mutation of the *FOXP3* gene accounts for the remaining IPEX pedigree, suggesting no genetic heterogeneity exists within this syndrome. Treatment with Cyclosporin A or FK506 improves the clinical course, and HLA-identical bone marrow transplantation may be curative.

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Causal gene mutations within the *FOXP3* gene were identified in two families with rare X-linked immune syndromes that are now recognized as the IPEX syndrome. No mutations of the *FOXP3* gene were identified in a third family that was the archetypal IPEX pedigree originally reported by Powell *et al.* and used to define linkage of the IPEX syndrome to a 17 cM interval at Xp11.23-Xq13.3

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