Heterogeneity in IPEX syndrome: A Foxp3 mutation causing type 1 diabetes without enteropathy

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Introduction

IPEX syndrome (immunodysregulation, polyendocrinopathy, enteropathy, X-linked) is a rare disease of early onset multisystem autoimmunity caused by mutations in Foxp3, a transcription factor in regulatory T cell development. The traditional hallmarks of IPEX syndrome are infantile onset type 1 diabetes, severe enteropathy, and dermatitis. IPEX was historically thought to be lethal within the first 2 years of life, however, there are now reports of individuals with milder manifestations and survival into adulthood[1-3]. Here, we report three additional members of a family with published Foxp3 missense mutation (c694A>C; p.C232G)[4,5] who have demonstrated milder manifestations than the "classic" IPEX triad.

Case History

Initial Presentation: A 6 month old boy (Patient A; IV-2 in Fig. 1) with history of mild eczema presented to the emergency department with diabetic ketoacidosis and hemoglobin A1c of 7.5%. Subsequent testing identified two positive type 1 diabetes-associated autoantibodies.

Family History: Our proband's family history included a 5 year old first cousin (Patient B; IV-4) with antibody-negative diabetes diagnosed at age 5 months. This cousin had tested negative on a genetic panel for congenital diabetes (which did not include the Foxp3 gene) and had normal Treg cell counts on a quantitative panel. Interestingly, Patient B's mother (III-7) had a history of insulinoma which was removed surgically.

Our patients had three cousins (III-1, III-2, III-3) related through their maternal grandfather who were diagnosed with IPEX syndrome when the youngest was 2 years old, with a missense mutation in Foxp3 (c.694A>C; p.C232G). Their cases were originally published by Okou *et al.*[4] and were marked by enteropathy, dermatitis, and recurrent infections (Table 1). *In vitro* analysis of samples from these patients indicated a qualitative defect in Treg function with normal Treg numbers.[4] Their mother (II-2) also had several autoimmune diagnoses. Another set of distant cousins (III-9, III-10) was diagnosed with the same mutation after developing enteropathy and type 1 diabetes.

The grandfather (II-2) through which patients A and B were related was never diagnosed with IPEX syndrome, although his medical history is suggestive, including diagnoses of psoriasis, Crohn's disease, aplastic anemia, and steroid-induced diabetes. For aplastic anemia he received a bone marrow transplant from his sister (II-1), who at the time was not aware of her status as an IPEX carrier, and he later developed graft versus host disease. His death in his 50s was attributed to pancreatic cancer.

Laboratory Evaluation: Genetic testing of Patients A and B confirmed the same Foxp3 mutation as their cousins. His subsequent course to the age of 18 months has also been notable for severely elevated IgE levels (2316.6 IU/mL, upper reference limit 83 IU/mL), food allergies with anaphylaxis, subclinical autoimmune hypothyroidism, frequent skin infections at insulin pump sites, and arthritis. Patient B had an elevated IgE (728 IU/mL); at the age of 5 years old his other manifestations are limited to positive thyroid peroxidase antibody with normal thyroid function, eczema, and a history of transient urticaria. Genetic screening of the remaining family members identified the mutation in one asymptomatic female carrier (IV-5) and in Patient A's 3 year old brother (Patient C; IV-1), whose only symptom is mild eczema. Screening labs of Patient C identified severely elevated IgE (3862.4 IU/mL) and two positive type 1 diabetes with normal hemoglobin A1c (4.9%).

Subsequent Course: With the goal of preventing progression pending consideration of definitive therapy (bone marrow transplant versus gene therapy), Patients A and C have started rapamycin, which restores T_{reg} cell function and increases T_{reg} cell stability via a Foxp3-independent mechanism[6]. As Patient B's only overt clinical manifestation is diabetes, his family has elected to observe conservatively for now.

Figures and Tables

Fig. 1. Family pedigree

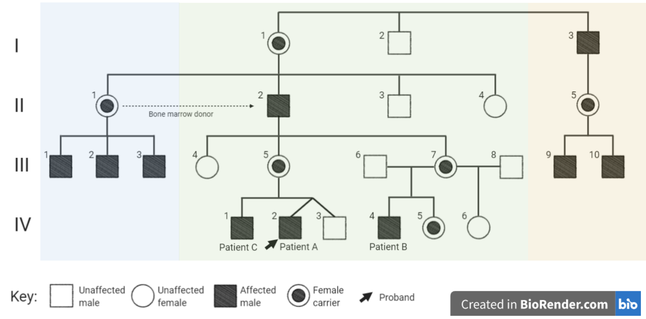
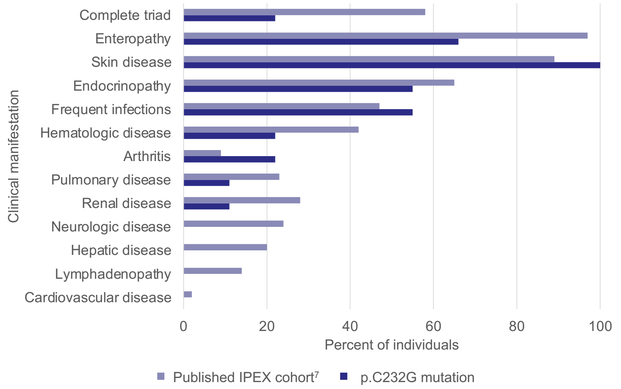


Fig. 2. Clinical phenotypes in this family compared to the IPEX literature



Percent of individuals in the family reported here with each type of IPEX manifestation, compared to data from a large cohort of IPEX patients published by Gambineri *et al*[7]. "Complete triad" refers to individuals with all three classic manifestations: skin disease, enteropathy, and type 1 diabetes.

Table 1. Clinical phenotypes of individual family members

II-1.	III-2.	III-3.
Ulcerative colitis	Eczema	Severe eczema
Psoriasis	Enteropathy	Enteropathy
Nephropathy	Type 1 diabetes	Candidiasis
	Candidiasis	Skin infections
III-1.	Sinopulmonary infections	Sinopulmonary infections
Eczema	Arthritis	Sepsis
Enteropathy	Low stimulated IgG	Recurrent DVT
Candidiasis	Normal IgE	Onychomycosis
Sinopulmonary infections		Unilateral hearing loss
Allergic rhinitis		Normal immunoglobulins
Chronic lung disease		
Low IgG		
Normal IgE		

This group of individuals were the first to be reported in the literature with this Foxp3 c.694A>C (p.C232G) mutation. *In vitro* studies of samples from these patients demonstrated diminished T_{reg} function[4].

II-2.	**IV-2. Patient A**	III-9.
Psoriasis	Eczema	Eczema
Crohn's disease	Type 1 diabetes	Enteropathy
Aplastic anemia	Hashimoto's thyroiditis	Type 1 diabetes
Graft vs host disease	Skin infections	Sinopulmonary infections
Secondary diabetes	Arthritis	Nephropathy
Pancreatic cancer	Elevated IgE	
		III-10.
IV-1. Patient C	III-7.	Eczema
Eczema	Insulinoma	Enteropathy
Type 1 diabetes antibodies		Anemia
Elevated IgE	**IV-4. Patient B**	
	Eczema	
	Type 1 diabetes	
	Elevated IgE	
	Urticaria	

This group of individuals is first reported here. All have confirmed Foxp3 c.694T>G (p.C232G) mutation except for II-2, who died in his sixth decade without genetic testing.

This group of individuals was recently diagnosed elsewhere; their information is per verbal history from the family.

Discussion

This family demonstrates the heterogeneity of phenotypes that can occur in IPEX syndrome, even among individuals with the same mutation. It is notable that while IPEX is usually referred to in textbooks as lethal by age 2 years[8], only one of the individuals in this extended family with a Foxp3 missense mutation was diagnosed prior to age 2. Indeed, missense mutations do result in milder IPEX phenotypes than more severe disruptions.[7] This particular point mutation (c.694A>C; p.C232G) is located in a linker region between two functional domains (the zinc finger and leucine zipper domains), making it more likely to have a subtle effect on protein structure and function.[7]

Comparing the pattern of phenotypes of our patients' family branch (green in Fig. 1 and Table 1) with that of their published cousins (blue in Fig. 1 and Table 1) highlights the potential for variability in different genetic or environmental contexts. While the cousins had courses marked by enteropathy, hypogammaglobulinemia, and frequent infections, our patients have had elevated IgE and autoimmune endocrinopathies predominate instead. While most female carriers of IPEX are asymptomatic, one mother in this extended family (II-1) had multiple autoimmune disease. This raises the possibility of unidentified modifying genetic factors affecting the IPEX phenotype. It should also be noted that two members of this family (II-2 and III-7) had pancreatic tumors, although there is so far no evidence to implicate a role for Foxp3 in this disease process.

While enteropathy is the most commonly reported manifestation of IPEX syndrome, at 97% in one review of the literature[7], none of the three patients newly reported here have developed gastrointestinal symptoms by ages 5, 3, and 1.5 years. Studies screening patients with neonatal diabetes have reported a few similar individuals in the literature, including patients who have lived into their 30s with type 1 diabetes as their only major manifestation[2]. This raises the possibility that IPEX syndrome may be underdiagnosed in the absence of enteropathy and could be a more common cause of early onset type 1 diabetes than is currently appreciated. Further research is needed to delineate the frequency of Foxp3 mutation in isolated early onset type 1 diabetes and to better predict the severity of disease course in individuals with mild IPEX phenotypes. For patients presenting with infantile onset diabetes, with or without positive autoantibodies, genetic testing for IPEX syndrome should be considered.

Conclusions

- We report 3 additional members of a family with a previously published Foxp3 missense mutation (c.694A>C; p.C232G) who have eczema and type 1 diabetes but not enteropathy.
- This family highlights the heterogeneity of IPEX syndrome phenotypes even among individuals with the same mutation, as well as the possibility of mild disease courses.
- IPEX syndrome could be a more common cause of early onset type 1 diabetes than is currently understood.

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