

Variable Phenotype in IPEX with a novel mutation

Lisa Kobrynski, M.D., M.P.H.*, Troy R. Torgerson, M.D., Ph.D.†, Hans Ochs, M.D.†
*Department of Pediatrics, Emory University, Atlanta, GA, †Department of Pediatrics,
University of Washington, Seattle, WA

IPEX is disorder characterized by immune dysfunction, polyendocrinopathy, enteropathy and X-linked inheritance. The region on the X chromosome, containing the *FOXP3* gene, encodes a member of the forkhead family of transcriptional regulators. Mutations in affected patients have been identified in 6 of 11 exons, in the polyadenylation region and in an intron/exon splice junction. However, a significant proportion of patients with the IPEX phenotype do not have identifiable mutations in *FOXP3*. We report the identification of a new mutation in exon 6 of *FOXP3* in 2 male siblings with a milder IPEX phenotype.

Patient 1 developed an eczematous dermatitis, chronic thrush, recurrent otitis media and pneumonia in infancy. He developed T1DM at 3 years of age. He also developed a pauciarticular arthritis and had intermittent diarrhea, which was attributed to food allergies. At 13 years of age, he was found to have poor specific antibody responses and did not produce IgG to ϕ X174, despite normal total IgG levels. Serum IgE was normal. His arthritis and recurrent infections improved on monthly gamma globulin therapy. Incidentally he was found to be 47XYY.

Patient 2 developed severe eczematous dermatitis in infancy with recurrent bacterial skin infections. He had intermittent diarrhea and poor weight gain, which was attributed to food allergy. He had bacterial sepsis at age 2 years and has had recurrent thrush, onychomycosis and recurrent pneumonia. He also developed bilateral DVT's at age 2 and had a recurrence of a right DVT at age 5 years. He has not developed any endocrinopathies or autoimmune disease. Serum IgG, IgM, and IgA were normal. Serum IgE was elevated.

A third male sibling has eczema and hypogammaglobulinemia with chronic lung disease and cutaneous candidiasis. The patients' mother has psoriasis and had a partial colectomy for ulcerative colitis. Her brother also has psoriasis and inflammatory bowel disease and required a bone marrow transplant for aplastic anemia.

Sequencing of the *FOXP3* gene revealed a novel mutation (T694G) in Exon 6, resulting in an amino acid substitution (C232G) in both patients. This mutation lies in the short linker region between the zinc finger and leucine zipper and results in a change from a sulfhydryl-containing cysteine to a hydrophobic glycine. Since these patients appear to have a milder phenotype, this mutation may result in production of an unstable message or nonfunctional protein, rather than an absence of *FOXP3*. Measurement of *FOXP3* expression and genotyping of other family members is in progress.