



IPEX Syndrome: Mutation Analysis of *FOXP3*

Clinical Features

IPEX syndrome [Immune dysregulation, polyendocrinopathy, enteropathy, X-linked, OMIM#304790] is characterized by the onset in infancy due to enteropathy, type 1 diabetes mellitus, and dermatitis. Other autoimmune phenomena including Coombs-positive anemia, autoimmune thrombocytopenia, autoimmune neutropenia and tubular nephropathy are also commonly described (1). Without aggressive treatment (immunosuppression or hematopoietic stem cell transplantation) the majority of affected individuals die within the first two year so life.

Molecular Genetics

Mutations in the *FOXP3* [OMIM#300292] gene cause IPEX syndrome (2). *FOXP3* plays an important role in the development and function of naturally occurring CD4-positive/CD25-positive T regulatory cells, which are involved in active suppression of inappropriate immune responses. Individuals with truncating mutations (nonsense, frameshift, splicing mutations) typically have severe-early onset IPEX syndrome. A number of affected individuals have been identified with missense mutations, some of which appear to be functionally hypomorphic, and are associated with a milder phenotype (1).

Inheritance

IPEX syndrome is a rare X-linked condition, with fewer than 150 affected individuals identified worldwide (1). Recurrence risk for a carrier female is 50%. In general, female carriers are healthy.

Test methods:

Comprehensive sequence coverage of the coding regions and splice junctions of the *FOXP3* gene is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All pathogenic and likely pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20 bp. Our CNV detection algorithm was developed and its performance determined for the sole purpose of identifying deletions and duplications within the coding region of the gene(s) tested. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Regions of high homology and repetitive regions may not be analyzed. This methodology will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of our deletion/duplication assay may be reduced when DNA extracted by an outside laboratory is provided.

FOXP3 sequencing and deletion/duplication analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	\$1000
CPT codes:	81405, 81406
Turn-around time:	4 weeks

Results:

Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

References:

1. Hannibal M, Torgerson T. IPEX Syndrome. In: Pagon R, Bird T, Dolan C, eds. GeneReviews [Internet]. Seattle: University of Washington, 2004.
2. Wildin RS, Ramsdell F, Peake J et al. X-linked neonatal diabetes mellitus, enteropathy and endocrinopathy syndrome is the human equivalent of mouse scurvy. Nat Genet 2001; 27: 18-20.

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