Cincinnati Children's

Division of Human Genetics

ITK DEFICIENCY (EBV-ASSOCIATED LYMPHOPROLIFERATIVE DISEASE)

Gene tested: *ITK*

Molecular Genetics Laboratory
CLIA#: 36D0656333
Phone: (513) 636-4474
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Email: moleculargenetics@cchmc.org

Additional information and test requisitions are available at:
www.cincinnatichildrens.org/molecular-genetics

Helping you fit the pieces together

Shipping Instructions

Please enclose test requisition with sample. All information must be completed before sample can be processed.

Place samples in Styrofoam mailer and ship at room temperature by overnight Federal Express to arrive Monday through Friday

Ship to:
Cytogenetics and Molecular Genetics Laboratories
3333 Burnet Avenue NRB 1042
Cincinnati, OH 45229
513-636-4474

ITK **deficiency** is characterized by lymphoproliferation and severe immune dysregulation following EBV infection and is inherited as an autosomal recessive disorder. *ITK* maps to 5q31-5q32, consists of 17 exons and encodes a 620 residue protein. Currently, there is not an immunologic assay for ITK deficiency. ITK is an important component of the TCR signaling pathway and also plays a role in regulating T-helper-cell differentiation. ITK deficiency was recently identified in female siblings who presented with EBV associated lymphoproliferation, absence of NKT cells and hemophagocytic lymphohistiocytosis. ***ITK* testing should be considered in any female with uncontrolled EBV-associated lymphoproliferative disease and in any male with uncontrolled EBV-associated lymphoproliferative disease and normal *SH2D1A* and *BIRC4* mutation analyses.** Characterization of the incidence of this disease, the spectrum of ITK mutations as well as the clinical variability of the disorder awaits further study.

Mutations in *SH2D1A* and *BIRC4* are common genetic causes of EBV-associated lymphoproliferative disease in males. Mutations in ***SH2D1A*** account for at least 60% of cases of X-linked lymphoproliferative disease (XLP1). Affected males who survive the initial EBV infection develop a variable hypogammaglobulinemia and have a high risk of developing malignant lymphoma or other lymphoproliferative disease. Symptoms of XLP develop in some individuals without evidence of EBV infection. *SH2D1A* maps to Xq24-26 and encodes a 128 amino acid protein known as SAP (SLAM associated protein) which is involved in lymphocyte activation signaling. The gene consists of four exons and three introns. Mutations involving all four exons have been identified. Large deletions account for approximately 25% of identified mutations in *SH2D1A*. NK cell function and SAP protein expression by flow cytometry are typically abnormal in individuals with mutations in *SH2D1A*.

BIRC4, the gene responsible for XLP2, maps to Xq25, and is identified in a minority of males with XLP. More commonly, we have identified *BIRC4* mutations in young males with hemophagocytic syndrome. *BIRC4*, consisting of six exons and five introns, encodes a 497amino acid protein known as XIAP (X-linked inhibitor of apoptosis). Large deletions account for about one-third of mutations in *BIRC4*. XIAP protein expression by flow cytometry is typically abnormal in individuals with mutations in *BIRC4*. Splenomegaly was noted in the few patients reported to date with mutations in *BIRC4* while splenomegaly is not a typical feature of XLP secondary to mutations in *SH2D1A*. Unlike patients with *SH2D1A* mutations, progression to lymphoma has not been reported to date in male patients with *BIRC4* mutations.

Other cause of lymphoproliferation and/or hemophagocytic lymphohistiocytosis, both genetic and non-genetic, should also be considered in patients presenting with apparent EBV-associated lymphoproliferative disease.

INDICATIONS

- Diagnosis in a symptomatic individual
- Presymptomatic diagnosis in an at-risk individual
- Carrier identification in individuals with a family history
- Prenatal diagnosis of an at-risk fetus, after identification of a mutation in a proband (by prior arrangement only)

SPECIMEN:

At least 3 mLs whole blood in a lavender top (EDTA) tube for each test ordered. Label tube with patient's name, birth date, and date of collection. Buccal swabs (cytobrushes) are required for analysis in patients who have undergone transplantation and may facilitate DNA isolation in patients undergoing chemotherapy or in individuals with leukopenia.

Please call for a free cytobrush collection kit.

METHODOLOGY:

PCR-based sequencing of entire coding region and intron/exon boundaries of the *ITK* gene.

SENSITIVITY:

The sensitivity of PCR-based sequence analysis is over 99% for the detection of nucleotide base changes, small deletions, and insertions in the regions analyzed. Mutations in regulatory regions or other untranslated regions are not detected by this test. Multiple exon deletions, large insertions and genetic recombinational events will not be identified in patients with *ITK* deficiency using this test methodology. Large deletions account for an unknown percentage of mutations in *ITK*.

TURN-AROUND TIME:

1 month

COST:

Please call 1-866-450-4198 for current pricing or with any billing questions.

CPT CODES:

- *ITK* 81479
- *Family specific study* 81403

RESULTS:

Results will be reported to the referring physician or health care provider as specified on the requisition form.

Updated 08/2012