Cincinnati Children's

Division of Human Genetics

# Lymphoproliferative Disorders (including EBV-Related)

## *SH2D1A, XIAP/BIRC4, ITK, MAGT1*


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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

Individuals with EBV-related illnesses who develop fulminant mononucleosis, hemophagocytic syndrome, hypogammaglobulinemia, or recurrent primary lymphomas may have an underlying genetic basis for their disease. To date, several genes have been implicated in these disorders.

Mutations in ***SH2D1A*** account for at least 60% of cases of X-linked lymphoproliferative disease (XLP1). Affected males who survive the initial EBV infection may develop a variable hypogammaglobulinemia and have a high risk of developing malignant lymphoma or other lymphoproliferative disease. Symptoms of XLP1 develop in some individuals without evidence of EBV infection. *SH2D1A* encodes a small protein known as SAP (SLAM associated protein) which is involved in lymphocyte activation signaling. Large deletions account for approximately 25% of identified mutations in *SH2D1A*. SAP protein expression by flow cytometry and T cell restimulation induced cell death (RICD) are typically abnormal in individuals with mutations in *SH2D1A*. iNKT cells are absent in patients with mutations in *SH2D1A*.

Mutations in ***BIRC4* (also known as *XIAP*)**, the gene responsible for XLP2, are identified in a minority of males with hemophagocytic syndromes. Splenomegaly has been noted in a majority of patients reported with mutations in *BIRC4*. Unlike patients with *SH2D1A* mutations, progression to lymphoma has not been reported to date in male patients with *BIRC4* mutations. *BIRC4* encodes the protein *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*.

Mutations in ***MAGT1***, the gene responsible for X-linked immunodeficiency with magnesium defect, EBV infection and neoplasia (XMEN) syndrome, have been identified in males presenting with chronic EBV infection, abnormal T cell receptor (TCR) function, and lymphoma. *MAGT1* functions as a magnesium transporter, and mutations in the gene lead to defective T-lymphocyte activation. Characterization of the incidence of this disease, the spectrum of *MAGT1* mutations, as well as the clinical variability of the disorder awaits further study.

***ITK deficiency*** was first described in female siblings who presented with EBV-associated lymphoproliferation, decreased iNKT cells and hemophagocytic lymphohistiocytosis. Mutations in *ITK* are also associated with lymphoma. In contrast to the X-linked disorders described above, *ITK* deficiency is inherited as an autosomal recessive disorder. *ITK* is an important component of the TCR signaling pathway. Characterization of the incidence of this disease, the spectrum of *ITK* mutations, and the clinical variability of the disorder awaits further study. ***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.** Currently, there is not an immunologic assay for *ITK* deficiency.

## INDICATIONS:

- Diagnosis in a symptomatic individual
- Presymptomatic diagnosis in an at-risk individual
- Carrier identification in females 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 5 mLs whole blood in a lavender top (EDTA) tube. Label tube with patient's name, birth date, and date of collection. Cytobrushes are required for analysis in patients who have undergone bone marrow transplantation and may facilitate DNA isolation in patients undergoing chemotherapy or in individuals with leukopenia. Please call for a free cytobrush collection kit.

## TESTING METHODOLOGY:

PCR-based sequencing of entire coding region and intron/exon boundaries of the *SH2D1A*, *BIRC4*, *ITK* and *MAGT1* genes. Testing may be ordered sequentially or tandemly. SAP and *XIAP* protein expression by flow cytometry may be helpful in determining the most cost-effective order of tests. Please contact the Diagnostic Immunology Laboratory at 513-636-4769 for more information about SAP and *XIAP* testing.

## 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. Large exonic deletions, large insertions and genetic recombinational events will not be identified in females using this test methodology. Large deletions account for at least 25% of mutations in *SH2D1A* and *BIRC4* and are not detected by this test methodology in female carriers. Rare primer site mutations may lead to erroneous results.

## TURN-AROUND TIME:

30 days

## COST:

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

## CPT CODES:

***SH2D1A*** *81404*
***BIRC4*** *81479*
***ITK*** *81479*
***MAGT1*** *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 10/15