

Division of Human Genetics

FAMILIAL HEMOPHAGOCYtic LYMPHOHISTIOCYTOSIS (FHL)

Genes Tested:

PRF1, *MUNC13-4 (UNC13D)*, *STXBP2*, *STX11*, *RAB27A* (Griscelli syndrome)

Molecular Genetics Laboratory

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

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

Hemophagocytic lymphohistiocytosis (HLH) is a disorder of widespread accumulation of lymphocytes and mature macrophages, sometimes with hemophagocytosis, primarily involving the spleen, lymph nodes, bone marrow, liver, and cerebral spinal fluid. HLH can either occur sporadically (secondary HLH), or can be inherited as the autosomal recessive condition known as familial hemophagocytic lymphohistiocytosis (FHL). The incidence of FHL is about 1-in-50,000 live births. The age of onset of FHL is typically in infancy or young childhood, although initial presentation in adulthood has been observed. FHL is generally fatal unless treated with hematopoietic stem cell transplantation. Both familial and secondary HLH can be triggered by infections and are clinically indistinguishable.

The diagnostic criteria for HLH, based on the recommendations of the Histiocyte Society include at least five of the eight following findings:

- Fever
- Splenomegaly
- Cytopenias affecting at least two of three cell lineages in peripheral blood
- Hypertriglyceridemia and/or hypofibrinogenemia
- Hemophagocytosis in bone marrow, spleen or lymph nodes
- Low or absent natural killer (NK) cell function activity
- Hyperferritinemia
- High levels of soluble IL-2r

Biallelic mutations in any of the above listed genes also confirm the diagnosis of FHL.

Genetics: FHL is inherited as an autosomal recessive condition. Biallelic mutations are identified in approximately 50% of North American patients with FHL. FHL is genetically heterogeneous and, to date, mutations in five genes have been identified in FHL patients: *PRF1*, *MUNC13-4*, *STXBP2*, *RAB27A* and *STX11*. Mutations in *BIRC4* (XIAP) and *SH2D1A*, the genes causing X-linked lymphoproliferative disease (XLP), should also be considered in males presenting with hemophagocytic lymphohistiocytosis not attributable to mutations in one of the FHL-causing genes listed above.

Gene	Chromosome	Disease	Mutation frequency in FHL patients
<i>PRF1</i>	10q21-q22	FHL2	20% Caucasians; >50% African -Americans
<i>MUNC13-4</i>	17q25	FHL3	30% Caucasians; rare in African-Americans
<i>STX11</i>	6q24	FHL4	1% in ethnically diverse HLH population
<i>RAB27A</i>	15q21	Griscelli syndrome*	10% in ethnically diverse cohort
<i>STXBP2</i>	19p13.3-13.2	FHL5	16% in Central Europeans, Turks and Saudis**

* Patients studies had FHL but did not have pigmentary changes typically described in GS2.

** ZurStadt et al 2009. AJHG (85) 482-492.

INDICATIONS:

- Confirmation of diagnosis in a symptomatic individual
- Presymptomatic testing of at-risk siblings
- Carrier identification in individuals with a family history of FHL
- Prenatal diagnosis of an at-risk fetus, after confirmation of biallelic mutations in the parents (by prior arrangement only)

SPECIMEN:

Each test requires 3 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. If inadequate DNA is present, we will prioritize testing according to the FHL testing algorithm unless you indicate a different order of prioritization on the test requisition.

METHODOLOGY:

Testing is performed by PCR-based sequencing of the entire coding regions and intron/exon boundaries of the *PRF1*, *MUNC13-4*, *STX11*, *RAB27A*, and *STXBP2* genes. Testing may be ordered sequentially or tandemly.

ANCILLARY TESTING:

NK function, perforin and Granzyme B expressions by flow cytometry, and CD107a mobilization assay may be helpful in determining the most cost-effective testing sequence. A testing algorithm is available on our website. Please contact the Diagnostic Immunology Laboratory at 513-636-4769 for more information about these tests.

SENSITIVITY:

The sensitivity of DNA sequencing is over 99% for the detection of nucleotide base changes, small deletions, and insertions in the regions analyzed. Multiple exon deletions, large insertions and genetic recombinational events may not be identified using these methods. Large deletions have been reported in *STX11* and *RAB27A* may be present in other FHL causing genes.

TURN-AROUND TIME:

- 1 month for *PRF1*, *STX11*, *RAB27A*, and *STXBP2*
- 6 weeks for *MUNC13-4*

COSTS:

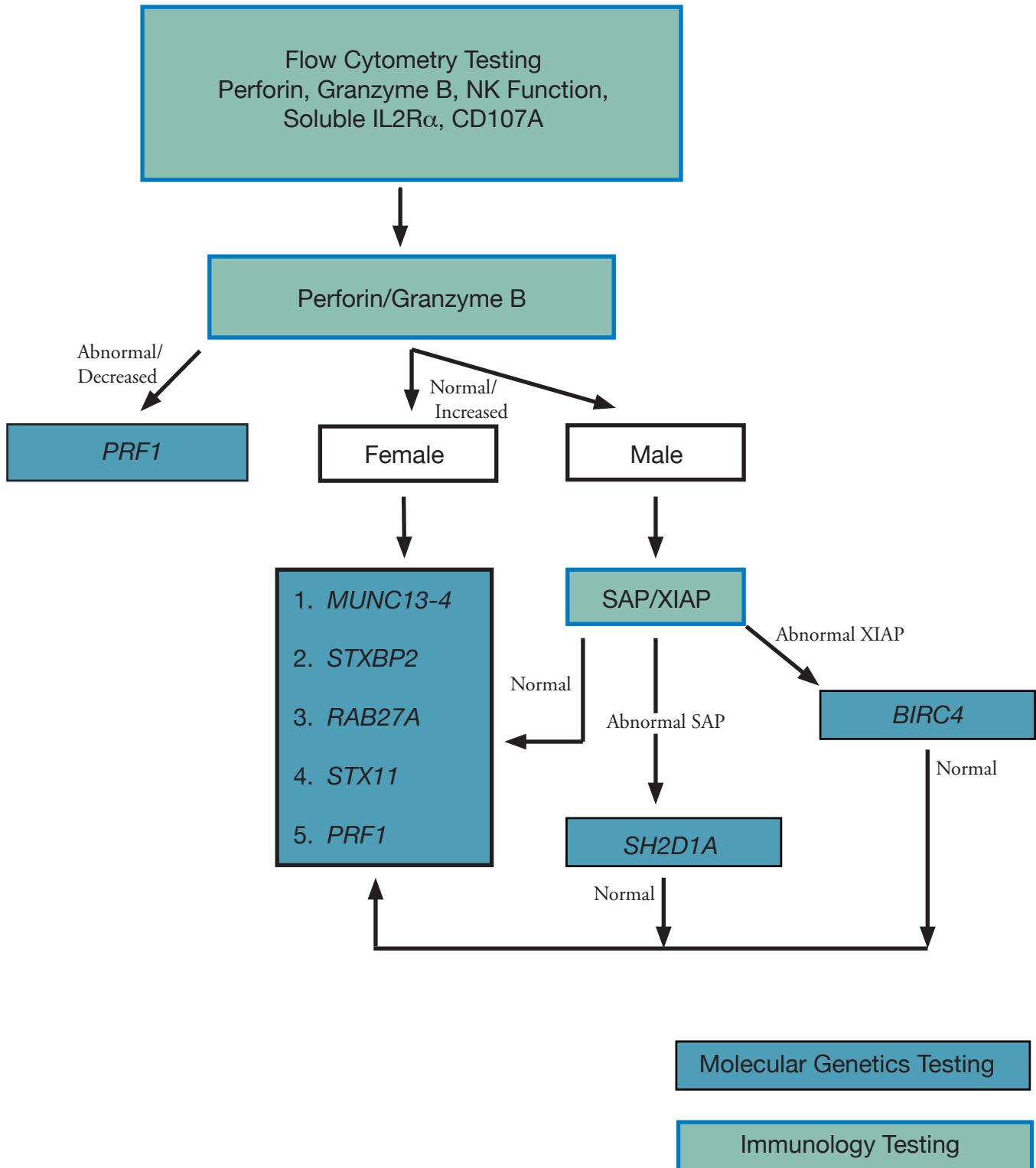
Please call 1-866-450-4198 for current pricing or with any billing questions

CPT CODES:

- *PRF1* 83890, 83898(x3), 83894(x3), 83891(x2), 83904(x12), 83912
- *MUNC13-4* 83890, 83898(x22), 83894(x5), 83891(x22), 83904(x44), 83912
- *STX 11* 83890, 83898, 83894, 83891, 83904(x6), 83912
- *RAB27A* 83890, 83898(x5), 83894(x7), 83891(x5), 83904(x12), 83909(x12), 83912
- *STXBP2* 83890, 83898(x12), 83894(x14), 83891(x12), 83904(x24), 83909(x24), 83912
- Family Specific Mutation analysis 83890, 83898, 83894, 83891, 83904, 83912

RESULTS:

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



- If WBC <500 K/mL and absolute lymphocyte count <200 K/mL, proceed to sequencing in lieu of flow cytometry testing.
- Cytobrushes are preferred method of sample collection in patients with low WBCs.
- Genetic testing may be ordered sequentially or in tandem, depending on clinical urgency.