

Familial Hemophagocytic Lymphohistiocytosis-Type 5 (FHL5) via Sequencing of the *STXBP2* Gene (Test #214)

Brief Description of Clinical Features: Hemophagocytic Lymphohistiocytosis (HLH) (OMIM 267700) is a rapidly progressing, hyperinflammatory syndrome in which activated T cells and macrophages infiltrate the liver, spleen, bone marrow, and central nervous system. Clinical manifestations include fever, hepatosplenomegaly, pancytopenia, hemophagocytosis, high triglyceride and ferritin levels, hypofibrinogenemia, severely attenuated or absent NK cell function, and high soluble CD25 (Henter et al. *Pediatr Blood Cancer* 48:124-131, 2007). Familial HLH (FHL) and sporadic (secondary) HLH are clinically indistinguishable and may be triggered by viral infections, rheumatic disorders and malignancies (Fisman, *Emerging Infect. Dis* 6:601-608, 2000). The incidence of FHL is approximately 1 in 50,000 live births with 70-80% of patients showing clinical symptoms during infancy (Aricò et al. *Leukemia* 10:197-203, 1996; Janka, *Eur J Pediatr* 140:221-230, 1983). Late-onset FHL cases (*i.e.* teens or twenties) have also been reported (Allen et al. *Haematologica* 86:499-503, 2001).

Genetics: FHL is an autosomal recessive disorder. Mutations in the *PRF1*, *UNC13D*, *STX11*, and *STXBP2* genes cause FHL Types 2 (OMIM 603553), 3 (OMIM 608898), 4 (OMIM 603552) and 5 (OMIM 613101), respectively. Though genetically heterogeneous, FHL is clinically homogeneous. To date, about 20 different causative mutations along the length of *STXBP2* have been identified comprising missense, nonsense, splice-site, and in-frame or frameshift deletions (zur Stadt et al. *Am J Hum Genet* 85:482-492, 2009; Côte et al. *J Clin Invest* 119:3765-3773, 2009; Meeths et al. *Blood* 2010). *STXBP2* encodes Munc18-2, a regulatory protein involved in SNARE-mediated granule secretion in NK cells and CTLs. In patients with FHL5, missense mutations in *STXBP2* disrupt the ability of Munc18-2 to interact with syntaxin 11, a SNARE protein mutated in FHL4. Mutations in FHL3, 4, and 5 genes result in defective NK cell and CTL degranulation whereas mutations in the FHL2 gene directly affect lytic granule constituents.

Description of This Particular Test: This test involves bidirectional DNA sequencing of all 19 coding exons of the *STXBP2*, gene plus ~50 bp of flanking non-coding DNA on either side of each exon. As indicated, we will also sequence any single exon (Test #100) or two exons (Test #200) in family members of patients with known mutations, or to confirm research results (\$190-340). We also offer a Panel test (Test #215) for all four FHL genes.

Reference Sequences: Genomic: NC_000019.9 mRNA: NM_006949.2 Protein: NP_008880.2 (CCDS 12181.1)

Indications for Test: Patients with clinical features of FHL or FHL-related disorders, individuals with a family history of FHL, and FHL patients who test negative for mutations in *PRF1*, *UNC13D*, and *STX11*. In addition, Griscelli Syndrome (GS2) (*RAB27A*), Chediak-Higashi Syndrome (CHS) (*LYST/CHS1*) and Hermansky Pudlak Syndrome (HPS2) (*AP3B1*) patients who test negative for those genes may be candidates for *PRF1* and additional FHL gene testing. Conversely, FHL patients who test negative for *PRF1*, *UNC13D*, *STX11*, and *STXBP2* may be candidates for GS2, CHS, and HPS2 DNA testing.

Sensitivity of Test: FHL5 accounts for ~16% of FHL cases.

Turnaround Time: Maximum of 40 calendar days, although many tests are completed in 3-4 weeks.

Specimen Requirements: See page 4 of the Requisition Form.

Price: Sequencing of *STXBP2* Gene \$1060

CPT Codes							
Test	83890 x1	83891 x1	83898 x20	83904 x20	83894 x1	83912 x1	Total
<i>STXBP2</i>	\$30	\$40	\$320	\$470	\$80	\$120	\$1060

Accreditation Info: CLIA ID #: 52D1027685 (expires 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12)

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