

Familial Hemophagocytic Lymphohistiocytosis-Type 2 (FHL2) via Sequencing of the *PRF1* Gene (Test #216)

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. Causative mutations in *PRF1*, including both missense and premature termination mutations, have been identified throughout the coding region (exons 2 and 3) (Stepp et al. *Science* 286:1957-1959, 1999; Clementi et al. *J Med Genet* 38:643-646, 2001; Göransdotter et al. *Am J Hum Genet* 68:590-597, 2001; Lee et al. *J Pediatr* 149:134-137, 2006). No single predominant *PRF1* mutation has been identified, but some appear more commonly in certain patient populations. For example, *PRF1* mutations account for ~50% of FHL patients of African American ancestry, and all of these patients have the c.50delT mutation (Lee et al. *J Pediatr* 149:134-137, 2006; Molleran Lee et al. *J Med Genet* 1:137-144, 2004). Similarly, a p.W374X mutation appears at a high frequency in Turkish patients (Stadt et al. *Hum Mutat* 27:62-68, 2006). *PRF1* encodes Perforin, a component of lytic granules important for the release of granzyme B from CTLs to target cells where it induces apoptosis.

Description of This Particular Test: This test involves bidirectional DNA sequencing of all coding exons (exons 2 and 3) of the *PRF1* 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_000010.10 mRNA: NM_001083116.1 Protein: NP_001076585.1 (CCDS 7305.1)

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 *UNC13D*, *STX11*, and *STXBP2*. In addition, Griscelli Syndrome (GS2) (*RAB27A*), Chediak-Higashi Syndrome (CHS) (*LYST/CHSI*) 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: FHL2 accounts for 20-50% of all 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 *PRF1* Gene \$540

CPT Codes							
Test	83890 x1	83891 x1	83898 x7	83904 x7	83894 x1	83912 x1	Total
<i>PRF1</i>	\$30	\$40	\$140	\$210	\$40	\$80	\$540

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

Contact: Michael Chicka, PhD, michael.chicka@preventiongenetics.com, www.preventiongenetics.com