

Familial Hemophagocytic Lymphohistiocytosis (FHL) Panel Test #215

Brief Description of Clinical Features: Hemophagocytic Lymphohistiocytosis (HLH) (OMIM 267700) is a rapidly progressing, hyperinflammatory syndrome in which activated T cells and macrophages infiltrate numerous organs. Clinical manifestations include fever, hepatosplenomegaly, pancytopenia, hemophagocytosis, and severely attenuated or absent NK cell function (Henter et al. *Pediatr Blood Cancer* 48:124-131, 2007). Familial (primary) 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 a genetically heterogeneous, autosomal recessive disorder. Mutations in the *PRF1*, *UNC13D/MUNC13-4*, *STX11*, and *STXBP2* genes cause FHL Types 2 (OMIM 603553), 3 (OMIM 608898), 4 (OMIM 603552) and 5 (OMIM 613101), respectively. Griscelli Syndrome-Type 2 (GS2, OMIM 607624), caused by mutations in *RAB27A*, has a phenotype that overlaps that of FHL. Products of these genes facilitate cellular cytotoxicity mediated by CTL and NK cells. Types of FHL vary among ethnic groups.

Description of This Particular Test: This test involves bidirectional DNA sequencing of the *PRF1*, *UNC13D/MUNC13-4*, *STX11*, and *STXBP2*, and *RAB27A* genes plus ~50 bp of flanking non-coding DNA on either side of each exon. The following genes will be tested sequentially in the order specified by the client. Tests for the individual genes are also available.

Reference Sequences:

Gene:	FHL type:	Genomic: NC_	mRNA: NM_	Exons	Protein: NP_	CCDS:
<i>PRF1</i>	2	000010.10	001083116.1	3	001076585	7305.1
<i>UNC13D/MUNC13-4</i>	3	000017.10	199242.2	32	954712.1	11730.1
<i>STX11</i>	4	000006.11	003764.3	2	003755.2	5205.1
<i>STXBP2</i>	5	000019.9	006949.2	19	008880.2	12181.1
<i>RAB27A</i>	GS2	000015.9	004580.3	6	004571.2	10153.1

Indications for Test: Patients with clinical features or family history of FHL or FHL-related disorders including Chediak-Higashi Syndrome (*CHS/LYST*) and Hermansky Pudlak Syndrome (*HPS2/AP3B1*).

Sensitivity of Test: Mutations in the five FHL genes account for >80% of FHL cases worldwide (*PRF1*, 20-50%; *UNC13D/MUNC13-4* ~19%; *STX11* ~10% predominantly found in Turkish and Kurdish families; *STXBP2* ~16%, and *RAB27A* ~10%) (Zur Stadt et al. *Hum Mutat* 27:62-68, 2006; Lee et al. *J Pediatr* 149:134-137, 2006; Horne et al. *Br J Haematol* 143:75-83, 2008; Zur Stadt et al. *Am J Hum Genet* 85:482-492, 2009).

Turnaround Time: Maximum of 60 calendar days.

Specimen Requirements: See page 4 of Requisition Form.

Price: Sequencing of *PRF1*, *UNC13D/MUNC13-4*, *STX11*, *STXBP2*, and *RAB27A*:

CPT Codes:	<i>PRF1</i>	<i>UNC13D</i> (Tier 1)	<i>UNC13D</i> (Tier 2)	<i>STX11</i>	<i>STXBP2</i>	<i>RAB27A</i>	Panel
83890	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)
83891	\$ 40 (x1)	\$ 40 (x1)	\$ 40 (x1)	\$ 40 (x1)	\$ 40 (x1)	\$ 40 (x1)	\$ 40 (x1)
83898	\$140(x7)	\$230 (x16)	\$250 (x17)	\$110(x4)	\$320(x20)	\$120(x5)	\$1230 (x69)
83904	\$210(x7)	\$340 (x16)	\$380 (x17)	\$160(x4)	\$470(x20)	\$190(x5)	\$1840 (x69)
83894	\$ 40 (x1)	\$ 80 (x1)	\$ 80 (x1)	\$ 30 (x1)	\$ 80 (x1)	\$ 30 (x1)	\$ 210 (x1)
83912	\$ 80 (x1)	\$120 (x1)	\$110 (x1)	\$ 70 (x1)	\$120 (x1)	\$ 80 (x1)	\$ 270 (x1)
Totals:	\$540*	\$840*	\$890*	\$440*	\$1060*	\$490*	\$3620

* When three or more of the genes are tested, a 15% discount will apply to the sum of the prices of the individual tests.

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

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