Hemophagocytic Lymphohistiocytosis Panel: Sequencing and CNV Analysis

Test Code: MM640
Turnaround time: 6 weeks
CPT Codes: 81404 x1, 81479 x1

**Condition Description**

Hemophagocytic lymphohistiocytosis (HLH) is a rare autosomal recessive disorder, in which the immune system produces too many activated immune cells (histiocytes and T cells). Main clinical findings may include hepatosplenomegaly, cytopenia, prolonged fever, low or absent natural killer (NK)-cell activity, and neurological abnormalities such as hypotonia or hypertonia, ataxia, coma, blindness, increased intracranial pressure, and neck stiffness. Liver dysfunction and bone marrow hemophagocytosis may also be present. The progression of disease and infection usually account for the majority of deaths in untreated individuals. The estimated prevalence of familial HLH is 1 in 50,000 births.

There are five subtypes of HLH. Types 2-5 are each caused by a mutation in a different gene: Type 2 (PRF1), Type 3 (UNC13D), Type 4 (STX11), and Type 5 (STXB2). The genetic mechanism for type 1 has not been identified. Approximately, 40 to 60 percent of cases of familial HLH are caused in mutations in the PRF1 or UNC13D genes. The pathogenic variant p.Leu17ArgfsTer34 in PRF1 has been observed at a high frequency in individuals with familial HLH in the African American population.

This panel also includes genes that cause specific types of Hermansky-Pudlak, Chediak-Higashi, and lymphoproliferative syndromes due to overlapping of symptoms seen in individuals with these disorders and hemophagocytic lymphocytic syndrome.

**References:**

3. OMIM.

**Genes**

AP3B1, BLOC1S6, CD27, GATA2, ITK, LYST, MAGT1, NLRC4, PRF1, RAB27A, SH2D1A, SLC7A7, STX11, STXB2, UNC13D, XIAP

**Indications**

This test is indicated for:

- Individuals with a clinical or suspected diagnosis of hemophagocytic lymphohistiocytosis.

**Methodology**

**Next Generation Sequencing:** In-solution hybridization of all coding exons is performed on the patient's genomic DNA. Although some deep intronic regions may also be analyzed, this assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications. Direct sequencing of the captured regions is performed using next generation sequencing. The patient's gene sequences are then compared to a standard reference sequence. Potentially causative variants and areas of low coverage are Sanger-sequenced. Sequence variations are classified as pathogenic, likely pathogenic, benign, likely benign, or variants of unknown significance. Variants of unknown significance may require further studies of the patient and/or family members.

**Copy Number Analysis:** Comparative analysis of the NGS read depth (coverage) of the targeted regions of genes on this panel was performed to detect copy number variants (CNV). The accuracy of the detected variants is highly dependent on the size of the event, the sequence context and the coverage obtained for the targeted region. Due to these variables and limitations a minimum validated CNV size cannot be determined; however, single exon deletions and duplications are expected to be below the detection limit of this analysis.

**Detection**

**Next Generation Sequencing:** Clinical Sensitivity: Unknown. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's clinical/biochemical phenotype.

Analytical sensitivity for sequence variant detection is ~99%.

**Copy Number Analysis:** The sensitivity and specificity of this method for CNV detection is highly dependent on the size of the event, sequence context and depth of coverage for the region involved. The assay is highly sensitive for CNVs of 500 base pairs or larger and those containing at least 3 exons. Smaller (< 500 base pairs) CNVs and those that involving only 1 or 2 exons may or may not be detected depending on the sequence context, size of exon(s) involved and depth of coverage.

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Specimen Requirements