



Category: Clinical Genomics

# Retrospective analysis of 60 patients with Hemophagocytic Lymphohistiocytosis (HLH): focus on genetic variants associated with secondary/late onset disease

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## Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a rare disorder of uncontrolled cytotoxic T-lymphocyte and macrophage activation associated with extreme inflammation, which if left untreated is invariably fatal. HLH can be classified either as primary (familial) or secondary (acquired). Genetic mutations underlie primary HLH which typically occurs in young children, while secondary HLH is associated with infections, metabolic disease, and malignancies and manifests later in life. Both categories of HLH affect the function of T-lymphocytes and natural killer (NK) cells. Homozygous null mutations in several genes including *PRF1*, *UNC13D* (*MUNC13-4*), *STX11*, and *STXBP2* (*MUNC18-2*) have been described in cases of primary HLH, where consanguinity has been shown to play a role. These mutations contribute to an uncontrolled inflammatory response, over production of interferon gamma ( $IFN\gamma$ ) and pro-inflammatory cytokines leading to macrophage activation and eventually to tissue and organ damage. While no known genetic mutations have been described in patients with acquired HLH, an underlying genetic predisposition has been suggested.

In an effort to better understand the genetic and clinical correlates of this disease, we performed retrospective analyses of 60 suspected HLH cases that were submitted by physicians for genomic analysis to our diagnostic laboratory. High throughput exome sequencing of the 60 HLH samples was carried out on an Illumina HiSeq 2500 platform, followed by bioinformatics analysis.

Our data showed that 1) 34% of the patients had homozygous mutations in known HLH-associated genes, the majority of which were in the Perforin1 (*PRF1*) gene (70%) followed by mutations in the *UNC13D* (20%) and *STXBP2* (10%) genes. Most patients with homozygous *PRF1* mutations were products of consanguineous marriages. The parents of these patients while being carriers, however, remained unaffected. 2) 18% of our patients had mutations in other congenital immune deficiency syndromes that are known to lead to HLH. 3) The remaining 48% of the patients lacked any known HLH-associated mutation. Our data suggest that heterozygous mutations in novel genes may contribute to predisposing patients to secondary HLH, particularly since most of these genes are associated with T-lymphocyte activation, which plays a vital role in the etiology of this devastating disease.

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