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**NLM Citation:** Zhang K, Astigarraga I, Bryceson Y, et al. Familial Hemophagocytic Lymphohistiocytosis. 2006 Mar 22 [Updated 2021 Sep 30]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
**Bookshelf URL:** https://www.ncbi.nlm.nih.gov/books/


# Familial Hemophagocytic Lymphohistiocytosis

Synonyms: Familial Erythrophagocytic Lymphohistiocytosis, Primary Hemophagocytic Lymphohistiocytosis

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Created: March 22, 2006; Updated: September 30, 2021.

## Summary

### Clinical characteristics

Familial hemophagocytic lymphohistiocytosis (fHLH), defined as the presence of biallelic pathogenic variants in one of four genes (*PRF1*, *STX11*, *STXBP2*, or *UNC13D*), is an immune deficiency characterized by the overactivation and excessive proliferation of T lymphocytes and macrophages, leading to infiltration and damage of organs including the bone marrow, liver, spleen, and brain. Familial HLH usually presents as an acute illness with prolonged and high fever, cytopenias, and hepatosplenomegaly. Rash and lymphadenopathy are less common. Individuals with fHLH may also exhibit liver dysfunction and neurologic abnormalities. Although manifestations of fHLH are usually evident within the first months or years of life and may develop in utero, symptomatic presentation can occur throughout childhood and into adulthood. Median survival in untreated infants with fHLH who develop active disease is less than two months after onset of manifestations; progressive manifestations of fHLH, organ dysfunction, invasive infection, and bleeding account for the majority of deaths. Use of etoposide-containing regimens such as the HLH-94 and HLH-2004 protocols followed by allogeneic hematopoietic stem cell transplantation (HSCT) has improved survival.

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## Diagnosis/testing

The diagnosis of fHLH is established in a proband with suggestive findings by identification of either biallelic pathogenic variants in one of four genes (*PRF1*, *STX11*, *STXBP2*, or *UNC13D*) or (rarely) a gain-of-function heterozygous variant in *STXBP2*.

## Management

*Treatment of manifestations:* Management should be coordinated by or in consultation with a multidisciplinary team with expertise in fHLH, including specialists in hematology/oncology, bone marrow and stem cell transplantation, immunology, rheumatology, infectious diseases, critical care, neurology, nephrology, pathology, and medical genetics. Treatment regimens focus on use of chemoimmunotherapy to treat active disease followed by allogeneic HSCT, the only curative therapy. Supportive care that should accompany treatment with chemoimmunotherapy and allogenic HSCT includes antibiotics or antiviral agents to treat or prevent infections, and antipyretics, intravenous fluids, electrolyte replacement, transfusion of packed red blood cells and platelets, infusions of immunoglobulin, fresh frozen plasma, and/or cryoprecipitate.

*Surveillance:* Individuals responding to treatment and HSCT are technically not at risk for other organ system involvement; thus, surveillance focuses on potential complications of fHLH while fHLH is active, such as bleeding, hypotension, respiratory distress, neurologic complications, malnutrition, infection, liver, or other organ failure.

*Agents/circumstances to avoid:* Live vaccines; exposure to infections; acetaminophen in persons with liver failure; nonsteroidal anti-inflammatory drugs in persons with thrombocytopenia; areas of construction or soil manipulation (which increase the risk for fungal infection in individuals with neutropenia); transfusion of non-irradiated blood products in individuals undergoing chemoimmunotherapy and/or allogeneic HSCT.

*Evaluation of relatives at risk:* It is appropriate to identify – before symptoms occur –those at-risk sibs who have the family-specific pathogenic variants so that they can be monitored and preemptive HSCT considered (particularly during febrile episodes) for development of manifestations of active disease. Any manifestations of possible active disease should prompt more detailed evaluation and referral to a clinician with expertise in fHLH.

## Genetic counseling

Familial HLH is inherited in an autosomal recessive manner. (Autosomal dominant inheritance of *STXBP2*-fHLH is suggested by rare reports of symptomatic individuals with heterozygous gain-of-function variants. Autosomal dominant inheritance will not be discussed further in this section.)

If both parents are known to be heterozygous for an fHLH-causing pathogenic variant, each sib of an affected individual has a 25% chance of inheriting biallelic pathogenic variants, a 50% chance of inheriting one pathogenic variant and being an asymptomatic carrier, and a 25% chance of inheriting neither of the familial fHLH-causing pathogenic variants. Once the fHLH-causing pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives and prenatal and preimplantation genetic testing are possible.

## *GeneReview* Scope

Hemophagocytic lymphohistiocytosis (HLH) is a phenotype characterized by critical illness caused by toxic activation of immune cells from different underlying mechanisms. The signs and symptoms of HLH (recurring episodes of hyperinflammation) result from infiltration of organs (e.g., bone marrow, liver, spleen, and brain) by

hyperactivated T lymphocytes and macrophages that secrete high levels of proinflammatory cytokines [Janka & Lehmberg 2014].

HLH may occur as an acquired condition (see Differential Diagnosis) or as a hereditary condition resulting from pathogenic variants in genes involved in lymphocyte granule-dependent cytotoxicity, inflammasome activation, or other immune functions. The hereditary forms of HLH are also often referred to as "primary" or "genetic" HLH. The term "familial HLH" (see following table) is used to designate the subset of genetic HLH disorders due to biallelic pathogenic variants in one of the following four genes that regulate granule-dependent cytotoxicity: *PRF1*, *UNC13D*, *STX11*, and *STXBP2*. Familial HLH is the subject of this *GeneReview*.

| Familial Hemophagocytic Lymphohistiocytosis (fHLH) Types |
| --- |
| • *PRF1*-related familial HLH (*PRF1*-fHLH; perforin deficiency)<br>• *STX11*-related familial HLH (*STX11*-fHLH; syntaxin-11 deficiency)<br>• *STXBP2*-related familial HLH (*STXBP2*-fHLH; Munc18-2 deficiency)<br>• *UNC13D*-related familial HLH (*UNC13D*-fHLH; Munc13-4 deficiency) |

# Diagnosis

The diagnosis of familial hemophagocytic lymphohistiocytosis (fHLH) is based on suggestive clinical and laboratory findings and is established by identification of biallelic pathogenic variants in one of four genes: *PRF1*, *STX11*, *STXBP2*, and *UNC13D*.

## Suggestive Findings

Familial HLH (fHLH) should be suspected in young children with the following clinical findings, supportive laboratory findings, and suggestive family history.

### Clinical Findings

**Common**

- Prolonged fever
- Hepatosplenomegaly
- Skin rash
- Lymphadenopathy
- Neurologic abnormalities [Horne et al 2008b] including:
  - Increased intracranial pressure, irritability, coma
  - Neck stiffness
  - Hypotonia, hypertonia
  - Seizures
  - Cranial nerve palsies
  - Ataxia
  - Hemiplegia/quadriplegia
  - Blindness

**Less common**

- **Isolated central nervous system (CNS) involvement** without other signs or symptoms of fHLH [Shinoda et al 2005, Chong et al 2012, Blincoe et al 2020]. Onset may be insidious and occur at any age, but most often develops in children age >1 year.
- **Acute liver failure** [Kumar et al 2018, Najib et al 2020] in the presence of other signs of fHLH, such as fever, splenomegaly, and peripheral blood cytopenias

## Supportive Laboratory Findings

**Laboratory findings highly suggestive of fHLH**

- **Decreased expression of perforin** (a pore-forming protein expressed by cytotoxic lymphocytes such as natural killer [NK] cells and CD8+ T-cells). More than 90% of individuals with *PRF1*-related fHLH (*PRF1*-fHLH) have absent or markedly decreased perforin expression based on intracellular staining and flow cytometric analysis [Abdalgani et al 2015, Rubin et al 2017].
- **Decreased NK cell degranulation (the CD107a assay**) has 96% sensitivity and 88% specificity for detecting *UNC13D*-fHLH, *STX11*-fHLH, or *STXBP2*-fHLH. Cytotoxic lymphocytes mediate their function by releasing perforin-containing granules near the site of target cells. CD107a (also known as lysosomal-associated membrane protein-1 or LAMP1), which lines the membrane of perforin-containing granules, can be identified by flow cytometric analysis on the surface of CTLs following in vitro activation [Bryceson et al 2012].

**Laboratory findings that may be suggestive of fHLH**

- **Elevated serum level of ferritin.** Elevated serum levels of ferritin, which is secreted by activated macrophages, are a sensitive indicator of HLH [Allen et al 2008]. A cutoff serum ferritin value of 500 ng/mL (used in the HLH-2004 diagnostic criteria; see Table 1) has an 84% sensitivity for detecting HLH, but its specificity is not known [Henter et al 2007]. A serum ferritin threshold >2,000 ng/mL resulted in 70% sensitivity and 68% specificity in a cohort of 113 individuals with HLH [Lehmberg et al 2014].
- **Elevated soluble interleukin (IL)-2 receptor.** The IL-2 receptor (also known as CD25) is upregulated on activated T cells, where its increasing density causes it to be shed from the cell surface [Damoiseaux 2020]. The soluble form of the receptor (sIL-2r) is a useful marker for T-cell activation. Serum levels of sIL-2r >2,400 U/mL have a sensitivity of 88% to 93% in identifying children with fHLH and nonfamilial HLH [Lin et al 2017]. However, an elevated sIL-2r alone is not specific for HLH, as sIL-2r can be elevated in any condition in which T-cell activation is present. Because normal values are age dependent [Sack et al 1998], age-based laboratory reference ranges should be used when interpreting results in children.
- **Increased granzyme B expression.** Along with perforin, granzyme B is an essential component of cytotoxic granules needed by cytotoxic lymphocytes to kill target cells. Increased expression of granzyme B in NK and/or CD8+ T cells serves as a marker of immune activation in fHLH, irrespective of genetic type, and may be a useful measure of immune activation in other related conditions [Mellor-Heineke et al 2013].
- **Increased T cell HLA-DR expression.** Upregulation of HLA-DR, an MHC class II cell surface receptor encoded by the human leukocyte antigen complex, is observed on activated T cells. HLA-DR expression by 14.4% of CD8+ T cells and 4.8% of CD4+ T cells has >80% sensitivity and 90% specificity for detecting active HLH (both fHLH and nonfamilial HLH were examined in this study) [Ammann et al 2017]. Presence of >7% peripheral blood CD38high/HLADR+ cells among CD8+ T cells has strong positive and negative predictive value for distinguishing active HLH (either fHLH or nonfamilial HLH) from early sepsis or healthy controls [Chaturvedi et al 2021].
- **Elevated serum cytokine levels.** Elevated serum levels of pro-inflammatory cytokines such as the following have been observed in individuals with active HLH (either fHLH or nonfamilial HLH) [Henter et al 1991, Takada et al 2003, Meyer et al 2020, Krei et al 2021]: interferon-gamma (IFN-g); tumor necrosis factor (TNF); interleukin (IL)-6; IL-18; interferon-induced protein 10 (IP-10, also known as C-X-C motif chemokine ligand 10 [CXCL10]); and monokine-induced by gamma interferon (MIG, also known as chemokine C-X-C motif chemokine ligand 9 [CXCL9]).
- **Hemophagocytosis.** Phagocytosis of erythrocytes, lymphocytes, or other hematopoietic cells by activated macrophages may be seen in biopsied tissues including bone marrow, lymph nodes, and spinal fluid, but occasionally may not be apparent early in the disease course.

### Supportive Imaging Findings

For individuals with suspected CNS involvement, brain MRI most commonly shows diffuse or focal white matter changes in the cerebrum and cerebellum [Blincoe et al 2020]. Bleeding, nodular lesions, masses, generalized atrophy, and brain edema may also be observed [Horne et al 2008b].

A normal brain MRI does not eliminate the possibility of CNS involvement, especially in individuals with elevated cerebrospinal fluid protein levels and increased numbers of mononuclear cells (with or without evidence of hemophagocytosis).

### Core HLH Diagnostic Criteria

Prompt recognition and treatment of fHLH are essential to an optimal outcome. To facilitate the identification of HLH, a core set of diagnostic criteria were developed in 1994 and revised in 2004 (Table 1). However, due to the high mortality associated with active disease in the absence of appropriate treatment, HLH-directed therapy is generally not delayed if an individual does not meet all of the criteria listed in Table 1.

**Table 1.** HLH-2004 Diagnostic Criteria

The diagnosis of HLH can be established if either A or B is fulfilled:

A. A molecular diagnosis consistent with HLH
B. Any 5 of the 8 following clinical and laboratory criteria for HLH:
    1. Fever >38.5° C
    2. Splenomegaly
    3. Cytopenia (affecting ≥2 of 3 lineages in peripheral blood):
        - Hemoglobin <9 g/dL (in infants <4 weeks: Hb <100 g/L)
        - Platelets $<100\times10^9$/L
        - Neutrophils $<1.0\times10^9$/L
    4. Hypertriglyceridemia and/or hypofibrinogenemia: fasting triglycerides >3.0 mmol/L (>265 mg/dL) or fibrinogen ≤1.5 g/L
    5. Hemophagocytosis in bone marrow, spleen, liver, lymph nodes, or other tissues
    6. Low or absent natural killer (NK) cell activity
    7. Serum ferritin concentration ≥500 µg/L
    8. Soluble CD25 (soluble IL-2 receptor) ≥2400 U/mL

From Henter et al [2007], Table 1

### Family History

Typically, family history is consistent with **autosomal recessive inheritance** (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

## Establishing the Diagnosis

The diagnosis of fHLH is established in a proband with Suggestive Findings by identification of either biallelic pathogenic (or likely pathogenic) variants in one of the following genes: *PRF1*, *STX11*, *STXBP2*, *UNC13D* (see Table 2), or (rarely) a gain-of-function heterozygous variant in *STXBP2* (see Molecular Genetics).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include any likely pathogenic variants. (2) Identification of biallelic variants of uncertain significance (VUS) in one of the four genes in Table 2 (or identification of one pathogenic variant and one VUS in the same gene) itself does not establish or rule out the diagnosis. Correlation with clinical and functional data is needed to support the genetic diagnosis.

The options for molecular genetic testing include use of a multigene panel or genomic testing.

- **A multigene panel** that includes *PRF1*, *STX11*, *STXBP2*, *UNC13D*, and other genes of interest as outlined in Differential Diagnosis can be used. Note: (1) Use of a multigene panel limits identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (2) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (3) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (4) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

- **Genomic testing** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

  For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

**Table 2.** Molecular Genetic Testing Used in Familial Hemophagocytic Lymphohistiocytosis

| Gene [1, 2] | Proportion of fHLH Attributed to Pathogenic Variants in Gene | Proportion of Pathogenic Variants [3] Detectable by Method | |
|---|---|---|---|
| | | Sequence analysis [4] | Gene-targeted deletion/duplication analysis [5] |
| *PRF1* | 30%-40% | >99% | No splice site variants or complex rearrangements reported as of 2020. [6] 1 gross deletion has been described. [7] |
| *STX11* | 5%-25% | >92% | At least 2 whole-gene deletions reported [8] |
| *STXBP2* | 5%-25% | >98% | 3 gross deletions reported [9] |
| *UNC13D* | 20%-40% | >99% | Several deep intronic variants & 1 large gene inversion reported [10] |

*1.* Genes are listed in alphabetic order.
*2.* See Table A. Genes and Databases for chromosome locus and protein.
*3.* See Molecular Genetics for information on variants detected in this gene.
*4.* Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
*5.* Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
*6.* Zur Stadt et al [2006], Tesi et al [2015], Gadoury-Levesque et al [2020]
*7.* Tong et al [2011]
*8.* zur Stadt et al [2005], Tesi et al [2015], Gadoury-Levesque et al [2020]
*9.* Zur Stadt et al [2006], Cetica et al [2010], Gadoury-Levesque et al [2020]
*10.* Zur Stadt et al [2006], Meeths et al [2011], Cichocki et al [2014], Tesi et al [2015], Gadoury-Levesque et al [2020]

# Clinical Characteristics

## Clinical Description

Familial hemophagocytic lymphohistiocytosis (fHLH) is an immune deficiency characterized by the overactivation and excessive proliferation of T lymphocytes and macrophages, leading to infiltration and damage of organs including bone marrow, liver, spleen, and brain [Zhang et al 2011]. Familial HLH usually presents as an acute illness with prolonged and high fever, cytopenias, and hepatosplenomegaly. Rash and lymphadenopathy are less common. Affected individuals may also exhibit liver dysfunction and neurologic abnormalities.

Often fHLH-associated inflammation is triggered by infection, especially with herpes viruses, but it can manifest after infection with many other pathogens, or it can occur in the absence of any detectable infection [Canna & Marsh 2020].

Although manifestations of fHLH are usually evident within the first months or years of life and may develop in utero [Malloy et al 2004], symptomatic presentation throughout childhood and into adulthood has been observed [Zhang et al 2011, Sieni et al 2012].

Except for individuals with *STXBP2*-fHLH, the manifestations and general treatment options do not differ by the associated fHLH gene (see Genotype-Phenotype Correlations).

Familial HLH has not been well studied in adults. The disease may present with acute onset of full-blown HLH manifestations or as a more insidious illness with recurrent bouts of nonspecific features. HLH in adults is often triggered by infection or malignancy [Birndt et al 2020]. The course of disease and life expectancy are not well studied in adults with fHLH. A systematic review of mortality in critically ill adults with HLH (not genetically verified as fHLH) reported an overall mortality of 57.8% [Knaak et al 2020].

## Common Signs and Symptoms

**Fever** may be high and protracted. In a few children, it may develop later in the disease course.

**Splenomegaly** and **hepatomegaly** are usually pronounced and progressive. It is difficult to know if splenomegaly affects splenic function, as low platelet counts could also result from bone marrow involvement from the disease process itself.

**Liver involvement.** Affected individuals often present with elevated transaminases (AST, ALT, and GGT), lactate dehydrogenase, and bilirubin with or without hepatomegaly. Hepatic dysfunction may manifest with abnormal markers of coagulation, such as elevated PT/PTT and D-dimers. Liver involvement can range in severity from mild involvement to acute liver failure.

**Skin rash** may be seen, often in association with high fever. It is often nonspecific and takes the form of pruritic morbilliform eruptions, although erythroderma has also been described [Morrell et al 2002, Griffin et al 2020].

**Lymph node enlargement** may be seen in some individuals.

**Neurologic abnormalities** may be an initial manifestation or – in many instances – may develop later in the disease course. The presentation may include irritability, bulging fontanel in infants, neck stiffness, hypotonia, hypertonia, and convulsions. Cranial nerve VI and/or VII palsy, ataxia, hemiplegia, quadriplegia, blindness, and coma may occur, as well as nonspecific signs of increased intracranial pressure [Horne et al 2008b].

**Other organ system involvement.** In severe cases, affected individuals may present with or progress to multisystem organ failure manifesting with hypotension, pulmonary dysfunction often requiring intubation, and renal dysfunction leading to fluid overload.

Individuals with *STXBP2*-fHLH may present with colitis, which can manifest as abdominal pain, vomiting, chronic diarrhea, failure to thrive, and inflammation of the lips and oral mucosa [Meeths et al 2010].

**Life expectancy.** Median survival in untreated infants with fHLH who develop active disease is less than two months after onset of manifestations. In these infants, progressive manifestations of fHLH, organ dysfunction, invasive infection, and bleeding account for the majority of deaths.

Use of etoposide-containing regimens such as the HLH-94 and HLH-2004 protocols followed by allogeneic hematopoietic stem cell transplantation (HSCT) has improved survival (see Management). Bergsten et al [2017] reported a 59% five-year probability of survival of children with fHLH who were treated with the HLH-2004 protocol and HSCT.

## Phenotype Correlations by Gene

***PRF1.*** Individuals with *PRF1*-fHLH appear to have an earlier age of onset than individuals with *UNC13D*-fHLH [Sieni et al 2011].

***STX11.*** Individuals with *STX11*-fHLH appear to have a later onset of manifestations and a milder disease course than those with *PRF1*-fHLH and *UNC13D*-fHLH [Horne et al 2008a, Kram et al 2019].

***STXBP2.*** Approximately one third of individuals have additional clinical findings including colitis, bleeding disorders, and hypogammaglobulinemia [Meeths et al 2010].

Although the age of onset in individuals with *STXBP2*-fHLH tends to be later than in individuals with *PRF1*-fHLH or *UNC13D*-fHLH, age of onset is variable even within the same family [Meeths et al 2010].

***UNC13D.*** CNS involvement may be more common in individuals with *UNC13D*-fHLH than those with *PRF1*-fHLH [Sieni et al 2011].

## Genotype-Phenotype Correlations

Hypomorphic pathogenic variants in *PRF1*, *MUNC13-4*, and *STXBP2* have been associated with mild and late-onset (i.e., adult) fHLH [Zhang et al 2011].

***PRF1.*** The *PRF1* c.272C>T (p.Ala91Var) variant has been reported in individuals with late-onset adult fHLH [Carvelli et al 2020, Miller et al 2020].

Nonsense variants are associated with younger age at onset than missense variants [Trizzino et al 2008].

***UNC13D.*** Biallelic truncating variants are associated with younger age at onset than missense variants [Sieni et al 2011].

## Nomenclature

Prior to discovery of the genes associated with fHLH, a locus-based naming system was used to identify the distinct genetic causes of this disorder (Table 3). Following discovery of the associated genes, a gene-based naming system was adopted.

**Table 3.** Familial Hemophagocytic Lymphohistiocytosis: Gene-Based Names vs Locus-Based Names

| Gene-Based Name | Locus-Based Name |
|---|---|
| *PRF1*-fHLH | FHL2 |
| *STX11*-fHLH | FHL4 |
| *STXBP2*-fHLH | FHL5 |

*Table 3. continued from previous page.*

| Gene-Based Name | Locus-Based Name |
|---|---|
| *UNC13D*-fHLH | FHL3 |

## Prevalence

The estimated prevalence of familial HLH (fHLH) is 1.8 per 100,000 births in Sweden with equal male/female distribution [Meeths et al 2015].

The estimated prevalence of the HLH phenotype in Texas has been calculated as 1:100,000 children younger than age 18 years [Niece et al 2010].

Ethnic groups with gene-specific pathogenic variants include the following:

- ***PRF1.*** The following pathogenic variants have been reported in particular ethnic groups:
  - c.50delT (p.Leu17ArgfsTer34) has been observed at a high frequency in individuals with fHLH in the African American population. There appears to be a founder effect for this variant: extent of haplotype sharing and variability of microsatellite alleles in chromosomes with this variant suggest that the variant arose approximately 1,000 to 4,000 years ago and is mostly restricted to individuals of African descent due to a founder effect [Lee et al 2006].
  - c.1090-1091delCT (p.Leu364fsTer) has been identified only in individuals of Japanese descent [Trizzino et al 2008].
  - c.1122G>A (p.Trp374Ter) has a high prevalence in Turkish individuals [Zur Stadt et al 2006].
- ***STX11.*** Initially, most individuals with *STX11* variants were from Middle Eastern regions and of Turkish, Kurdish, or Pakistani descent. Since these initial reports, individuals from other regions and ethnicities have been reported [Marsh et al 2010].
- ***UNC13D.*** The following pathogenic variants have been reported in particular ethnic groups:
  - c.118-308C>T, the most frequent cause of disease in Koreans, is also common in affected individuals of northern European descent [Meeths et al 2011, Seo et al 2013, Qian et al 2014].
  - c.754-1G>C is predominantly found in Korean individuals [Seo et al 2013].
  - c.1596+1G>C is described as the most common *UNC13D* variant in Japan [Yamamoto et al 2004].
  - A 253-kb inversion with a high prevalence in Scandinavia is also commonly found in North America [Meeths et al 2011, Qian et al 2014].

*STXBP2* pathogenic variants do not appear to be restricted to a specific geographic region.

# Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *PRF1*, *STX11*, *STXBP2*, or *UNC13D*.

The following reported associations observed with fHLH-causative genes remain an area of investigation.

- Biallelic and monoallelic pathogenic germline *PRF1* variants were reported in some persons with Hodgkin and non-Hodgkin lymphoma [Clementi et al 2005, Cannella et al 2007]. Similar findings were observed in a Chinese cohort [Chen et al 2017].
- Sidore et al [2021] reported an association between the *PRF1* c.272C>T (p.Ala91Val) variant and multiple sclerosis, replicating findings from the International Multiple Sclerosis Consortium [International Multiple Sclerosis Genetics Consortium 2018].
- Of 12 adults with chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS), three had biallelic *PRF1* pathogenic variants with reduced perforin expression,

and one had biallelic *UNC13D* pathogenic variants with cytotoxic lymphocyte-impaired degranulation [Taieb et al 2021].

## Differential Diagnosis

Several inherited inborn errors of immunity include the hemophagocytic lymphohistiocytosis (HLH) phenotype (resembling familial HLH) as a predominant feature due to defects in lymphocyte cytotoxicity or regulation of the inflammasome, a multi-protein complex that is essential for activation of inflammatory responses (see Table 4a). Hyperinflammation in these conditions is often triggered by infection. Children with the HLH phenotype may require investigation for these errors of immunity, particularly if they have a history of prior, recurrent, chronic, and/or severe infections.

**Table 4a.** Inherited Immune Disorders to Consider in the Differential Diagnosis of Familial Hemophagocytic Lymphohistiocytosis

| Gene | Disorder | MOI | Immune Defects Relevant to HLH | Selected Distinguishing Clinical Features |
|---|---|---|---|---|
| *AP3B1* | Hermansky-Pudlak syndrome 2 | AR | Defective granule-mediated cytotoxicity | Abnl pigment; neutropenia; susceptibility to infections, abnl bleeding |
| *CD27* | Lymphoproliferative syndrome 2 (OMIM 615122) | AR | CD27 expressed on T cells participates in co-stimulatory signaling – interacts w/CD70; required for nl T cell proliferation & triggering of cytotoxicity against EBV-infected B cells; ↓ iNKT cells | Chronic EBV infection; hypogammaglobulinemia; lymphoma [1] |
| *CDC42* | Neonatal onset of pancytopenia, autoinflammation, rash, & episodes of HLH (NOCARH) | AD | Defective formation of actin-based structures; defective proliferation, migration, & cytotoxicity; ↑ IL-1beta & Il-18 production | Neonatal cytopenias; hepatosplenomegaly; transaminitis; recurrent fevers; urticaria-like rash; failure to thrive; facial dysmorphisms [2] |
| *ITK* | Lymphoproliferative syndrome 1 (OMIM 613011) | AR | Defective tyrosine kinase function; defective cytotoxic T cell expansion & cytolytic capacity; ↓ iNKT cells | Chronic EBV infection; lymphoma [3] |
| *LYST* | Chediak-Higashi syndrome | AR | Defective granule-mediated cytotoxicity | Abnormal pigment; nystagmus; neurologic manifestations; giant granules & other granule abnormalities in leukocytes & precursors |
| *MAGT1* | Immunodeficiency, XL, w/ magnesium defect, EBV infection & neoplasia (OMIM 300853) | XL | Defective Mg++ transporter; low NKG2D, defective cytotoxicity | Chronic EBV infection rather than full-scale HLH; viral infections; lymphoma [4] |
| *NCKAP1L* | *NCKAP1L*-assoc hyperinflammatory disorder [5] | AR | Impaired actin reorganization → defects in early T-cell activation & neutrophil migration | Cellular immunodeficiency, lymphoproliferation, & inflammation |
| *NLRC4* | Autoinflammation w/infantile enterocolitis (OMIM 616050) | AD | Constitutively active NLRC4 inflammasome | Enterocolitis; extremely ↑ levels of IL-18 |
| *RAB27A* | Griscelli syndrome type 2 (OMIM 607624) | AR | Defective granule-mediated cytotoxicity | Abnl pigment in most but not all affected persons [6] |
| *RC3H1* | *RC3H1*-assoc hyperinflammatory disorder [7] | AR | Loss of post-transcriptional control due to impaired mRNA degradation, → dysregulated cytokine production | Chronic hepatitis, dyslipidemia, dysmorphic phenotype (short stature, webbed neck), & mild ID |

*Table 4a. continued from previous page.*

| Gene | Disorder | MOI | Immune Defects Relevant to HLH | Selected Distinguishing Clinical Features |
|---|---|---|---|---|
| *RHOG* | *RHOG*-assoc hyperinflammatory disorder [8] | AR | Defective granule-mediated cytotoxicity | Radiographs of long bones reveals a radiolucent bone lesion, ↑ sclerosis, & cupping on distal metaphyses. |
| *SH2D1A* | X-linked lymphoproliferative disease 1 | XL | Defective 2B4-mediated cytotoxicity; abnl T cell restimulation-induced cell death; absent iNKT cells | HLH virtually always triggered by EBV; lymphoma; hypo/dysgammaglobulinemia |
| *XIAP* | X-linked lymphoproliferative disease 2 | XL | TNF-receptor signaling & NLRP3 inflammasome dysregulation;↑ cell susceptibility to cell death | Inflammatory bowel disease; arthritis; uveitis; recurrent fevers; other inflammatory complications; hypogammaglobulinemia; susceptibility to infections |

abnl = abnormal; AD = autosomal dominant; AR = autosomal recessive; EBV = Epstein-Barr virus; GI = gastrointestinal; HLH = hemophagocytic lymphohistiocytosis; ID = intellectual disability; iNKT = invariant natural killer T (cells); MOI = mode of inheritance; nl = normal; XL = X-linked

*1.* Ghosh et al [2020]
*2.* Lam et al [2019]
*3.* Ghosh et al [2014]
*4.* Ravell et al [2020]
*5.* Castro et al [2020]
*6.* Cetica et al [2015]
*7.* Tavernier et al [2019]
*8.* Kalinichenko et al [2021]

In addition to the inherited immune disorders summarized in Table 4a, the differential diagnosis of fHLH should include inborn errors of metabolism and immunodeficiencies (see Table 4b).

**Inborn errors of metabolism** can present with a clinical picture consistent with the HLH phenotype [Sepulveda & de Saint Basile 2017]. Metabolic conditions usually appear during the first year of life and as early as the newborn period [McLean et al 2019] and in preterm newborns [Schüller et al 2016]. In these conditions, the accumulation of toxic metabolic compounds triggers an abnormal immune response resembling HLH. The initial manifestations may include nausea and vomiting, failure to thrive, jaundice, and poor appetite, with individuals becoming acutely ill after only a mild infection. While any organ system may be involved, the most common include the CNS, liver, and spleen (see Table 4b).

**Inborn errors of immunity** and selected disorders such as chronic granulomatous disease, Wiskott-Aldrich syndrome, and DiGeorge syndrome (see 22q11.2 Deletion Syndrome) can in rare cases be associated with the HLH phenotype in the setting of disseminated or severe infections (see Table 4b).

**Table 4b.** Other Hereditary Disorders to Consider in the Differential Diagnosis of Familial Hemophagocytic Lymphohistiocytosis

| Gene(s) / Genetic Mechanism | DiffDx Disorder | MOI | Clinical Features of DiffDx Disorder Distinguishing from fHLH | Case Report Describing Assoc w/HLH |
|---|---|---|---|---|
| **Inborn errors of metabolism** | | | | |
| *BTD* | Biotinidase deficiency | AR | | Kardas et al [2012] |
| *COG6* | *COG6*-CDG & HLH | AR | | Althonaian et al [2018] |
| *CTSA* | Galactosialidosis (OMIM 256540) | AR | | Olcay et al [1998] |
| *G6PC1* | *G6PC1*-related glycogen storage disease type I | AR | | Düzenli Kar et al [2019] |

*Table 4b. continued from previous page.*

| Gene(s) / Genetic Mechanism | DiffDx Disorder | MOI | Clinical Features of DiffDx Disorder Distinguishing from fHLH | Case Report Describing Assoc w/HLH |
|---|---|---|---|---|
| *GALT* | Classic galactosemia | AR | | Kundak et al [2012] |
| *GBA1* (*GBA*) | Gaucher disease | AR | Storage cells in bone marrow | Sharpe et al [2009], Anderson & Taylor [2020] |
| *HADHA* | LCHAD deficiency (See Long-Chain Hydroxyacyl-CoA Dehydrogenase Deficiency / Trifunctional Protein Deficiency.) | AR | | Erdol et al [2016] |
| *LIPA* | Wolman disease (See Lysosomal Acid Lipase Deficiency.) | AR | Cytopenia, organomegaly, full-scale HLH possible; storage cells in bone marrow | Taurisano et al [2014] |
| *MMUT* | *MMUT*-related isolated methylmalonic acidemia | AR | | Gokce et al [2012] |
| *MMACHC* | Cobalamin C disease (See Disorders of Intracellular Cobalamin Metabolism.) | AR | | Wu et al [2005] |
| mtDNA deletion | Pearson syndrome (See Mitochondrial DNA Deletion Syndromes.) | Mat | | Wild et al [2020] |
| *NPC1* | NPC1-related Niemann-Pick disease type C | AR | | Karaman et al [2010] |
| *PCCA* | *PCCA*-related propionic acidemia | AR | | Gokce et al [2012] |
| *SLC7A7* | Lysinuric protein intolerance | AR | | Mauhin et al [2017] |
| *SUMF1* | Multiple sulfatase deficiency | AR | | Ikeda et al [1998] |
| **Immunodeficiencies** | | | | |
| *FAS* | *FAS*-related autoimmune lymphoproliferative syndrome | AD | Autoimmune cytopenia, ↑ vitamin $B_{12}$, ↑ CD4/CD8, double-negative alpha-/beta-positive T cells | Rudman Spergel et al [2013] |
| 22q11.2 | 22q11.2 deletion syndrome | AD | T-cell deficiency, autoimmune cytopenia | Bode et al [2015] |
| *CYBB* | *CYBB*-related chronic granulomatous disease | XL | Abscesses, colitis, mycosis | Bode et al [2015] |
| *WAS* | Wiskott-Aldrich syndrome (See *WAS*-Related Disorders.) | XL | Small platelets, eczema | Bode et al [2015] |
| *CD3E*<br>*IL2RG*<br>*IL7RA*<br>*RAG1* [1] | Severe combined immunodeficiency (See X-Linked Severe Combined Immunodeficiency.) | AR<br>XL | Profound T-cell deficiency | Bode et al [2015] |
| **Other** | | | | |
| *ADAMTS13* | Hereditary thrombotic-thrombocytopenic purpura (Upshaw Schulman syndrome) (OMIM 274150) | AR | Micronangiopathy (fragmentocytes) | Hassenpflug et al [2018] |

*Table 4b. continued from previous page.*

| Gene(s) / Genetic Mechanism | DiffDx Disorder | MOI | Clinical Features of DiffDx Disorder Distinguishing from fHLH | Case Report Describing Assoc w/HLH |
|---|---|---|---|---|
| *TCN2* | Transcobalamin II deficiency (OMIM 275350) (& other errors of vitamin $B_{12}$ metabolism) | AR | Low holotranscobalamin | Unal et al [2014], Ünal et al [2019] |

AD = autosomal dominant; AR = autosomal recessive; CDG = congenital disorders of glycosylation; DiffDx = differential diagnosis; Mat = maternal; MOI = mode of inheritance; XL = X-linked

*1.* See X-Linked Severe Combined Immunodeficiency, Table 3 for other genes known to be associated with classic SCID.

**Nonfamilial/non-genetic HLH** (also known as "secondary" HLH, acquired HLH, or reactive HLH) is usually associated with infection, autoimmune disease, malignancy, or metabolic disease [Risma & Marsh 2019]. The likelihood of nonfamilial HLH increases with increasing age. Nonfamilial HLH may be self-limited because some affected individuals fully recover after treatment with agents that target the underlying trigger. However, in some instances, treatment with HLH-directed agents such as steroids, chemotherapy, or immunomodulatory agents is required to suppress the hyperinflammatory response.

- **Infection** by viruses, bacteria, fungi, or parasites. Infection particularly involving the herpes virus group is usually seen in older children and adolescents. An example is Epstein-Barr virus (EBV)-associated HLH, which is more common in Asians than in those of northern European background or Africans [Marsh 2018].
- **Autoimmune diseases** such as rheumatologic disorders. Systemic-onset juvenile idiopathic arthritis is most common; associated systemic lupus erythematosus and other autoimmune disorders are also seen [Crayne et al 2019].
- **Malignancy**, particularly T- or B-cell neoplasms, including anaplastic large cell lymphoma, lymphoblastic leukemia/lymphoma, Hodgkin lymphoma, and diffuse large B cell lymphoma. Lehmberg et al [2015] reported that the prevalence of malignancy in children of suspected HLH was 8.4%. When HLH is triggered by underlying malignancy, it often develops at or around the time of cancer diagnosis; it also can occur following initiation of chemotherapy, often triggered by intercurrent infections [Lehmberg et al 2015].

# Management

No clinical practice guidelines specifically for familial hemophagocytic lymphohistiocytosis (fHLH) have been published; however, a report by the Steering Committee of the Histiocyte Society provides recommendations on the use of etoposide-containing therapies such as the HLH-94 protocol and hematopoietic stem cell transplantation (HSCT) for individuals with HLH, including those with fHLH [Ehl et al 2018].

## Evaluations Following Initial Diagnosis

To establish the extent of disease and treatment needs in an individual diagnosed with fHLH, the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

**Table 5.** Familial Hemophagocytic Lymphohistiocytosis: Recommended Evaluations Following Initial Diagnosis

| System/Concern | Evaluation | Comment |
|---|---|---|
| **Constitutional** | Measurement of growth parameters | Height, weight |
| | Physical exam | Evaluate for:<br>• Respiratory status & hemodynamic instability;<br>• Rashes, lymphadenopathy, hepatosplenomegaly, altered skin or hair pigmentation (albinism). |
| **CNS involvement** | CSF exam | • Evaluate for ↑ levels of protein & presence of mononuclear cells w/or w/o hemophagocytosis.<br>• CSF neopterin levels can also be measured. [1] |
| | Neuroimaging | Evaluate for presence of white matter changes, hemorrhage, nodular lesions, masses, generalized atrophy, brain edema. |
| | Neurologic eval | General exam to provide baseline in event of neurologic deterioration |
| | Educational assessment | Eval for early intervention / special education |
| **Hematologic** | Blood count & differential | Eval for anemia, leukopenia & thrombocytopenia |
| | Bone marrow aspirate & biopsy | As needed, examine for evidence of hemophagocytosis & rule out other causes for hyperinflammation (e.g., infection, malignancy). |
| **Immunologic** | Eval of inflammatory biomarkers | Such as serum concentrations of ferritin, pro-inflammatory cytokines, & sIL2Rα, if available |
| **Liver** | Assessment of hepatic function | Evaluate serum levels of transaminases, bilirubin (direct, indirect), triglycerides, & lactate dehydrogenase. |
| **Kidneys & electrolytes** | Assessment of renal function | Examine for risk of kidney involvement by measuring serum electrolytes (esp sodium, potassium), BUN, & creatinine. |
| **Coagulation** | Eval of coagulation | Examine for coagulopathy by measuring PT, PTT, INR, & serum fibrinogen levels. |
| **Potential infectious cofactors** | Exam for infections | Blood culture, viral serologies, or PCR exam to identify & treat any infectious triggers |
| **Genetic counseling** | Eval by genetics professionals [2] | To inform affected persons & families re nature, MOI, & implications of fHLH to facilitate medical & personal decision making |
| **Family support & resources** | Assess need for:<br>• Community or online resources such as Parent to Parent;<br>• Social work involvement;<br>• Home nursing. | Evaluate in order to provide support to affected persons, parents, & other family members. |

BUN = blood urea nitrogen; CNS = central nervous system; CSF = cerebrospinal fluid; MOI = mode of inheritance
*1.* Elevated CSF neopterin, a marker of neuroinflammation, has been rarely reported in children with fHLH [Howells et al 1990].
*2.* Medical geneticist, certified genetic counselor, certified advanced genetic nurse

# Treatment of Manifestations

## Overview

For a detailed explanation of the treatment for fHLH, see Canna & Marsh [2020] and Jordan et al [2011] (full text).

Given the complexity of fHLH diagnosis and treatment, management should be coordinated by or in consultation with a multidisciplinary team of specialists with expertise in fHLH, including specialists from hematology/oncology, bone marrow and stem cell transplantation, immunology, rheumatology, infectious diseases, critical care, neurology, nephrology, pathology, and medical genetics.

**Chemoimmunotherapy.** The Histiocyte Society HLH-94 and HLH-2004 protocols have substantially increased the survival for individuals with HLH, including those with fHLH. Use of the HLH-94 protocol resulted in a 54% five-year probability of survival following treatment with etoposide and dexamethasone, delayed cyclosporine, and intrathecal (IT) methotrexate for individuals with central nervous system (CNS) involvement, followed by hematopoietic stem cell transplantation (HSCT) [Trottestam et al 2011]. Nevertheless, 29% of affected individuals died before HSCT, and 19% developed late neurologic sequelae. To reduce pretransplant mortality and neurologic complications, the HLH-2004 protocol added up-front cyclosporine and included IT corticosteroids. Although use of the HLH-2004 protocol resulted in a five-year estimated survival of 62%, neither treatment modification significantly improved overall outcome [Bergsten et al 2017]. Therefore, the HLH-94 protocol remains the current standard of care in most centers.

For individuals with relapsed/refractory fHLH, data are limited on the utility of specific salvage therapies.

- Case reports and retrospective case series describe the use of the anti-CD52 antibody alemtuzumab and anti-thymocyte globulin; however, there are no published prospective trials using these agents.
- A retrospective study of alemtuzumab revealed that 64% of individuals with relapsed/refractory fHLH responded and 77% survived to become candidates for HSCT [Marsh et al 2013].

These less-than-perfect outcomes of older treatment regimens prompted investigation of alternative therapeutic strategies. Toward this end, a recent report describes 27 individuals with relapsed/refractory fHLH treated with dexamethasone, the IFN-gamma neutralizing antibody emapalumab, and, when needed, other agents [Locatelli et al 2020]. Sixty-three percent of participants exhibited reduction in the signs of active disease with 70.4% proceeding to HSCT.

**Allogeneic HSCT.** Cure for fHLH can only be obtained via allogeneic HSCT, which generally requires prior chemoimmunotherapy (usually with steroids and etoposide-based chemotherapy regimens such as the HLH-94 protocol) to dampen inflammation.

HLA typing and initiation of the stem cell donor search should be started as soon as fHLH is suspected. HSCT should be undertaken in children with molecularly confirmed fHLH as early in life as is feasible, both for symptomatic children who have achieved clinical remission of active disease (or as close to remission of active disease as possible) following treatment with chemoimmunotherapy as well as presymptomatic children who have not yet experienced a flare of active inflammation (usually identified based on a positive family history of fHLH) [Lucchini et al 2018].

In the past, fully myeloablative conditioning regimens containing busulfan and cyclophosphamide were associated with exceptionally high risks of toxicities and mortality in individuals with fHLH. Although reduced-intensity conditioning regimens containing alemtuzumab, fludarabine, and melphalan (which have come into favor over the last decade), are associated with reduced toxicities and improved overall survival, they are associated with high rates of mixed chimerism and secondary graft failure [Marsh et al 2011, Allen et al 2018].

Experience with reduced toxicity myeloablative conditioning approaches is growing and results appear promising [Richards et al 2018, Contreras et al 2020, Felber et al 2020, Naik et al 2020, Chandra et al 2021, Goode et al 2021]. A recent comparison found that survival with sustained engraftment was higher and toxicity lower for patients treated with reduced toxicity myeloablative regimens containing either (1) busulfan and fludarabine or (2) fludarabine, melphalan, and thiotepa, when compared to reduced-intensity conditioning

regimens containing alemtuzumab, fludarabine, and melphalan, or fully myeloablative conditioning regimens containing busulfan and cyclophosphamide [Marsh et al 2022].

Management of neurologic manifestations, respiratory dysfunction, GI tract manifestations, renal impairment, and other system dysfunctions is per standard of care by primary care health care providers or specialty clinicians.

### Supportive Care

The following supportive care measures should accompany treatment with chemoimmunotherapy and allogenic HSCT:

- Antibiotics or antiviral agents to treat or prevent infections
- Antipyretics, intravenous fluids, electrolyte replacement, nutrition support, transfusion of packed red blood cells and platelets, infusions of immunoglobulin, fresh frozen plasma and/or cryoprecipitate

## Surveillance

Individuals responding to treatment and HSCT are technically not at risk for other organ system involvement. Surveillance focuses on potential complications of HSCT.

Surveillance for changes in neurologic manifestations, respiratory function, GI tract manifestations, renal function, and other systems is per standard of care by primary care health care providers or specialty clinicians.

## Agents/Circumstances to Avoid

The following should be avoided:

- Live vaccines
- Exposure to infections
- Acetaminophen in individuals with liver failure
- Nonsteroidal anti-inflammatory drugs in individuals with thrombocytopenia
- Areas of construction or soil manipulation, which increase the risk for fungal infection for individuals with neutropenia
- Transfusion of non-irradiated blood products in individuals undergoing chemoimmunotherapy and/or allogeneic HSCT, per institutional guidelines

## Evaluation of Relatives at Risk

**For early diagnosis and treatment.** Molecular genetic testing of at-risk sibs for the family-specific pathogenic variants is appropriate to identify those who are affected before symptoms occur. (Note: Such testing is not useful in accurately predicting the age of onset, severity, type of symptoms, or rate of progression in asymptomatic individuals.)

Sibs found to have biallelic fHLH-causing pathogenic variants should be carefully monitored for the development of manifestations of active disease (i.e., expectant/watchful waiting), particularly during febrile episodes. Any manifestations of possible active disease should prompt evaluation for splenomegaly, anemia, leukopenia, thrombocytopenia, transaminitis, hypofibrinogenemia/coagulopathy, hypertriglyceridemia, and elevated blood levels of ferritin and soluble IL-2r. If any parameters are abnormal, consultation with a clinician with expertise in fHLH should be initiated.

**For matched sib donor HSCT.** Potential sib donors should be tested for the presence of the family-specific pathogenic variants to ensure that only those without biallelic fHLH-causing pathogenic variants are evaluated further.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

## Pregnancy Management

If a pregnant woman is diagnosed with fHLH, treatment should be tailored and if possible, incorporate non-cytotoxic drugs such as steroids [Dunn et al 2012]. Because etoposide is thought to interfere with mitosis, thus inhibiting DNA synthesis, and has been used to terminate ectopic pregnancies, it has only rarely been used to treat HLH during pregnancy [Parrott et al 2019]. There have been reports of infants exposed to etoposide in the second and third trimesters of pregnancy who have had a normal outcome and others who have experienced anemia, thrombocytopenia, leukopenia, and neutropenia.

Underlying triggers, such as infection, malignancy, and autoimmune disease, should be sought and treated as appropriate.

See MotherToBaby for more information about medication use in pregnancy.

## Therapies Under Investigation

Emapalumab (NI-0501) – an anti-interferon gamma antibody – was approved by the FDA in 2018 for children and adults with fHLH who have refractory, recurrent, or progressive disease or intolerance of conventional HLH therapy [Locatelli et al 2020]. The drug is under investigation for individuals with newly diagnosed fHLH as well as individuals with nonfamilial HLH.

Ruxolitinib – a janus kinase (JAK) 1 and 2 inhibitor – was shown to sensitize immune cells to glucocorticoid-induced apoptosis in vitro and dampen hyperinflammation in a mouse fHLH model [Albeituni et al 2019, Meyer et al 2020]. Several case reports and small case series have described its use in children and adults with active disease (of whom ~6/200 had fHLH) [Keenan et al 2021]; additional larger studies are ongoing.

Alemtuzumab – an anti-CD52 monoclonal antibody – in a pilot trial has shown promising results as frontline treatment for children with fHLH [Moshous et al 2019]. It is under investigation in France.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

# Genetic Counseling

*Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional.* —ED.

## Mode of Inheritance

Familial hemophagocytic lymphohistiocytosis (fHLH) caused by loss-of-function variants in *PRF1*, *STXBP2*, *STX11*, or *UNC13D* is inherited in an autosomal recessive manner.

Note: Autosomal dominant inheritance of *STXBP2*-fHLH is suggested by rare reports of symptomatic individuals with heterozygous gain-of-function variants (see Molecular Genetics, **Gene-specific laboratory technical considerations**). Autosomal dominant inheritance will not be discussed further in this section.

## Risk to Family Members

**Parents of a proband**

- The parents of an affected child are obligate heterozygotes (i.e., presumed to be carriers of one fHLH-causing pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an fHLH-causing pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - One of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017].
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

**Sibs of a proband**

- If both parents are known to be heterozygous for an fHLH-causing pathogenic variant, each sib of an affected individual has a 25% chance of inheriting biallelic pathogenic variants, a 50% chance of inheriting one pathogenic variant and being an asymptomatic carrier, and a 25% chance of inheriting neither of the familial fHLH-causing pathogenic variants.
- Sibs who inherit biallelic fHLH-causing pathogenic variants are at risk of developing fHLH; however, intrafamilial clinical variability may be observed and the age of onset, severity, type of symptoms, and rate of progression in asymptomatic sibs cannot be predicted.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

**Offspring of a proband.** The offspring of an individual with fHLH are obligate heterozygotes (carriers) for an fHLH-causing pathogenic variant.

**Other family members.** Each sib of the proband's parents is at a 50% risk of being a carrier of an fHLH-causing pathogenic variant.

## Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the fHLH-causing pathogenic variants in the family.

## Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

**Family planning**

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

## Prenatal Testing and Preimplantation Genetic Testing

Once the fHLH-causing pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Such testing is not useful in accurately predicting age of onset, severity, type of symptoms, or rate of progression; however, expectant management is warranted for newborns with the same genotype as the symptomatic proband, as hematopoietic stem cell transplantation prior to onset of symptoms may improve outcome.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

## Resources

*GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.*

- **MedlinePlus**
  Familial hemophagocytic lymphohistiocytosis
- **Histiocytosis Association**
  **Phone:** 856-589-6606
  **Fax:** 856-589-6614
  **Email:** info@histio.org
  histio.org
- **Immune Deficiency Foundation**
  **Phone:** 800-296-4433
  **Fax:** 410-321-9165
  **Email:** idf@primaryimmune.org
  primaryimmune.org
- **European Society for Immunodeficiencies (ESID) Registry**
  **Email:** esid-registry@uniklinik-freiburg.de
  ESID Registry

## Molecular Genetics

*Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information.* —ED.

**Table A.** Familial Hemophagocytic Lymphohistiocytosis: Genes and Databases

| Gene | Chromosome Locus | Protein | Locus-Specific Databases | HGMD | ClinVar |
|---|---|---|---|---|---|
| *PRF1* | 10q22.1 | Perforin-1 | CCHMC - Human Genetics Mutation Database (PRF1)<br>PRF1base: Mutation registry for Familiar haemophagocytic lymphohistiocytosis, type II (FHL2) | PRF1 | PRF1 |
| *STX11* | 6q24.2 | Syntaxin-11 | CCHMC - Human Genetics Mutation Database (STX11)<br>STX11base: Mutation registry for Familial haemophagocytic lymphohistiocytosis 4 (FHL4) | STX11 | STX11 |
| *STXBP2* | 19p13.2 | Syntaxin-binding protein 2 | CCHMC - Human Genetics Mutation Database (STXBP2) | STXBP2 | STXBP2 |

*Table A. continued from previous page.*

| | | | | | |
|---|---|---|---|---|---|
| *UNC13D* | 17q25.1 | Protein unc-13 homolog D | CCHMC - Human Genetics Mutation Database (UNC13D)<br>UNC13Dbase: Mutation registry for Familial hemophagocytic lymphohistiocytosis 3 | UNC13D | UNC13D |

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

**Table B.** OMIM Entries for Familial Hemophagocytic Lymphohistiocytosis (View All in OMIM)

| | |
|---|---|
| 170280 | PERFORIN 1; PRF1 |
| 601717 | SYNTAXIN-BINDING PROTEIN 2; STXBP2 |
| 603552 | HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS, FAMILIAL, 4; FHL4 |
| 603553 | HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS, FAMILIAL, 2; FHL2 |
| 605014 | SYNTAXIN 11; STX11 |
| 608897 | UNC13 HOMOLOG D; UNC13D |
| 608898 | HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS, FAMILIAL, 3; FHL3 |
| 613101 | HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS, FAMILIAL, 5, WITH OR WITHOUT MICROVILLUS INCLUSION DISEASE; FHL5 |

## Molecular Pathogenesis

The result of biallelic pathogenic variants in *PRF1*, *UNC13D* (formerly *MUNC13-4*), *STX11*, and *STXBP2* is defective perforin-mediated killing of target cells, also known as lymphocyte cytotoxicity [de Saint Basile et al 2010]. Lymphocyte cytotoxicity is important for killing of infected and malignant cells, as well as maintenance of immune homeostasis.

*PRF1* encodes perforin, which is predominately expressed by lymphocytes of the $CD8^+$ T-cell and NK-cell lineages [Stepp et al 1999]. Perforin is essential for cell-mediated cytotoxicity. Perforin is stored in specialized secretory lysosomal vesicles commonly termed cytotoxic granules. Besides perforin, cytotoxic granules contain granzymes and other proteins that promote target cell death. Upon recognition of a susceptible target cell, cytotoxic lymphocytes release granule contents toward the target cells in a regulated manner, whereupon perforin subunits rapidly form pores in the target cell membrane that serve as conduits for entry of granzymes into the target cell [Lopez et al 2013]. Granzymes are serine proteases that induce apoptosis (cell death) of the target cells. The process of granzyme-mediated lymphocyte cytotoxicity is important for control of infection, protection against cancer, and downregulation of the immune response. Failure to carry out this process can lead to overactivation of the immune response resulting in the signs and symptoms of familial hemophagocytic lymphohistiocytosis (fHLH).

*UNC13D*, *STX11*, and *STXBP2* encode the cytoplasmic proteins Munc13-4, syntaxin-11, and Munc18-2, respectively. They are expressed in most hematopoietic cells. Deficiency in any one of these proteins results in defective exocytosis of secretory lysosome contents, a prerequisite for lymphocyte cytotoxicity. Deficiencies in these proteins also result in defective exocytosis from other hematopoietic cells, including platelets, neutrophils, and mast cells. Nonetheless, the phenotypes of individuals harboring biallelic pathogenic variants in *UNC13D*, *STX11*, and *STXBP2* are largely the same as that associated with pathogenic variants in *PRF1*.

At the cellular level, syntaxin-11 is a membrane-associated SNARE protein that interacts with other SNARE proteins to drive membrane fusion. Signals from activating receptors recruit syntaxin-11 from recycling endosomes to the plasma membrane in a VAMP-8 dependent manner [Marshall et al 2015]. Munc18-2 regulates

syntaxin-11 trafficking and function, whereas Munc13-4 primes vesicle exocytosis, in part by sensing elevated intracellular $Ca^{2+}$ concentrations required for cytotoxic granule exocytosis [Boswell et al 2012]. Notably, cytokine activation of lymphocytes can bypass a requirement for syntaxin-11 in exocytosis, explaining a typically later onset and somewhat milder course of disease in individuals with syntaxin-11 deficiency [Bryceson et al 2007, Sepulveda et al 2013].

Marsh et al [2010] noted that pathogenic missense variants in *STX11* are associated with preserved NK cell function compared to nonsense variants, which resulted in abrogation of NK cell function.

**Mechanism of disease causation.** The vast majority of fHLH is associated with autosomal recessive loss-of-function pathogenic variants in the four well-described fHLH genes (*PRF1*, *STXBP2*, *STX11*, and *UNC13D*).

However, two reports provide evidence for three *STXBP2* variants with gain of function: p.Arg65Trp, p.Arg65Gln [Spessott et al 2015], and p.Arg190Cys [Benavides et al 2020], which impair lymphocyte cytotoxicity and act in dominant-negative manner. The variants reported by Spessott et al [2015] are associated with late-onset fHLH.

**Gene-specific laboratory technical considerations: *UNC13D*.** Two deep intronic variants (c.118-308C>T and c.118-307G>A) and one large gene inversion have been identified as causative of early-onset fHLH [Meeths et al 2011, Entesarian et al 2013].

A large 253-kb inversion straddles the *UNC13D* 3' end and adjacent sequences, abolishing protein expression; the breakpoints have been mapped and the inversion is detectable by targeted analysis for pathogenic variants (see Table 2).

The deep intronic variants lie within an intron 1 region that is typically not sequenced; detection will require specific primers. The c.118-308C>T and c.118-307G>A variants disrupt a lymphocyte-specific enhancer and alternative transcriptional start site, specifically impairing gene transcription in lymphocytes [Cichocki et al 2014].

The deep intronic (c.117+143A>G) variant disrupts an enhancer and has been associated with reduced gene transcription and macrophage activation in a single individual [Schulert et al 2018].

**Table 6.** Familial Hemophagocytic Lymphohistiocytosis: Notable Pathogenic Variants by Gene

| Gene | Reference Sequences | DNA Nucleotide Change | Predicted Protein Change | Comment [Reference] |
|---|---|---|---|---|
| *PRF1* | NM_001083116.1<br>NP_001076585.1 | c.50delT | p.Leu17ArgfsTer34 | High frequency in African American population [Lee et al 2006] |
| | | c.272C>T | p.Ala91Val | • Variant assoc w/late-onset (adult) fHLH [Carvelli et al 2020, Miller et al 2020]<br>• Common variant in population studies of healthy persons; functional effects were studied [Chia et al 2009]. |
| | | c.1090_1091delCT | p.L364fsTer | Seen only in persons of Japanese descent [Trizzino et al 2008] |
| | | c.1122G>A | p.W374Ter | High prevalence in Turkish persons [Zur Stadt et al 2006] |

*Table 6. continued from previous page.*

| Gene | Reference Sequences | DNA Nucleotide Change | Predicted Protein Change | Comment [Reference] |
|---|---|---|---|---|
| *STXBP2* | NM_006949.2 NP_008880.2 | c.193C>T | p.Arg65Trp | Dominant-negative variant assoc w/late-onset fHLH [Spessott et al 2015] |
| | | c.194G>A | p.Arg65Gln | Putative dominant-negative variant assoc w/ late-onset fHLH [Spessott et al 2015] |
| | | c.568C>T | p.Arg190Cys | Dominant-negative variant assoc w/fHLH in 1 infant [Benavides et al 2020] |
| | | c.1247-1G>C | Mixed RNA/protein products | Hypomorphic allele [Meeths et al 2010] |
| *STX11* | AL135917 | g.25560_44750del | -- | Gene deletion [zur Stadt et al 2005] |
| *UNC13D* | NM_199242.2 | c.117+143A>G | -- | Disruption of enhancer → ↓ gene transcription [Schulert et al 2018] |
| | | c.118-308C>T | -- | • Disruption of lymphocyte-specific enhancer [Meeths et al 2011]<br>• Frequent cause of disease in persons of northern European background [Meeths et al 2011] & Koreans [Seo et al 2013] |
| | | c.118-307G>A | -- | Disruption of lymphocyte-specific enhancer [Entesarian et al 2013] |
| | | (253-kb inversion) [1] | -- | • 3' gene inversion that disrupts protein expression<br>• High prevalence in Scandinavia & commonly found in North America [Meeths et al 2011, Qian et al 2014] |
| | | c.754-1G>C | -- | Predominantly found in Korean persons [Seo et al 2013] |
| | | c.1596+1G>C | -- | Most common *UNC13D* variant in Japan [Yamamoto et al 2004] |

Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.
*GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
*1.* Variant designation that does not conform to current naming conventions

# Chapter Notes

## Author Notes

The authors of this chapter are members of The North American Consortium for Histiocytosis or The European Consortium for Histiocytosis, multi-institutional consortia in North America and Europe aimed at developing and implementing clinical and translational studies and biological research on histiocytic diseases including fHLH.

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## Acknowledgments

We respectfully acknowledge all the patients, their families, and our medical colleagues from the Histiocyte Society and elsewhere, who have contributed to our understanding of HLH over the years.

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## Revision History

- 30 September 2021 (bp) Comprehensive update posted live
- 17 January 2013 (me) Comprehensive update posted live
- 7 September 2010 (cd) Revision: sequence analysis of *STXBP2* for familial hemophagocytic lymphohistiocytosis 5 available clinically
- 11 March 2010 (me) Comprehensive update posted live
- 9 March 2007 (cd) Revision: clinical testing and prenatal diagnosis available for FHL4
- 22 March 2006 (me) Review posted live
- 21 April 2005 (jj, af, rw) Original submission

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