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X-Linked Lymphoproliferative Disease

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Summary

Clinical characteristics

X-linked lymphoproliferative disease (XLP) in general is characterized by an inappropriate immune response to Epstein-Barr virus (EBV) infection leading to hemophagocytic lymphohistiocytosis (HLH) or severe mononucleosis, dysgammaglobulinemia, and lymphoproliferative disease (malignant lymphoma). The condition primarily affects males. XLP has two recognizable subtypes, XLP1 (due to pathogenic variants in *SH2D1A*) and XLP2 (due to pathogenic variants in *XIAP*). HLH / fulminant infectious mononucleosis is the most common presentation regardless of subtype. HLH is characterized as an acute illness with prolonged and high fever, bi- or trilineage cytopenias, and hepatosplenomegaly, which is often severe or fatal. Death is generally secondary to liver failure or multisystem organ dysfunction. In those with XLP1, dys- or hypogammaglobulinemia can lead to varying degrees of humoral immune dysfunction associated with bronchiectasis and recurrent respiratory infections that, if untreated, may result in death. Lymphoproliferative disease (malignant lymphoma) and other lymphoproliferative diseases are specific to XLP1 and often develop in childhood, usually following EBV exposure. Rarer findings in those with XLP1 can include aplastic anemia, vasculitis, and lymphoid granulomatosis. Males with XLP2 are more likely to have HLH without EBV infection, recurrent episodes of HLH (which is not typically seen in those with XLP1), splenomegaly, and gastrointestinal disease, including enterocolitis and perirectal abscesses or fistulae. Rarely, individuals with XLP2 and inflammatory bowel disease have been reported to develop inflammatory liver disease, which can progress to fatal liver failure. Transient hypogammaglobulinemia has been rarely observed in those with XLP2. To date, neither lymphoproliferative disease nor common variable immunodeficiency has been reported in males with XLP2.

Heterozygous females rarely have symptoms. There are, however, increasing numbers of reports of affected females with unfavorable (skewed) X-chromosome inactivation favoring the X chromosome with the pathogenic variant who develop HLH, inflammatory bowel disease, and erythema nodosum.

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Diagnosis/testing

The diagnosis of XLP1 or XLP2 can be established in a male proband who has a hemizygous germline pathogenic variant in *SH2D1A* (XLP1) or *XIAP* (XLP2) identified on molecular genetic testing. These males typically have low or absent SAP or XIAP protein expression, respectively, by flow cytometry. Female probands with a heterozygous pathogenic variant in *SH2D1A* or *XIAP* identified on molecular genetic testing and skewed X-chromosome inactivation toward expression of the chromosome with the pathogenic *SH2DA1* or *XIAP* variant have been reported; such individuals may be symptomatic.

Management

Targeted therapy: The only known curative therapy for XLP1 is allogeneic hematopoietic stem cell transplant (HSCT), which should be strongly considered in all males as early in life as is feasible, particularly in those who have not developed symptoms; HSCT is not recommended for asymptomatic heterozygous females. For individuals with XLP2, many manifestations of disease can be improved with HSCT; however, there are more complications in these individuals.

Supportive care: Standard treatment for liver dysfunction/failure, hypogammaglobulinemia (IVIG or IgG), fulminant EBV infection / HLH (including etoposide and steroids and consideration of rituximab), lymphoma, colitis, aplastic anemia, and vasculitis.

Surveillance: At each visit, obtain history of any neurologic changes; physical exam for evidence of hepatosplenomegaly, lymphadenopathy, and neurologic changes; monitor for signs and symptoms of colitis and cholangitis in those with XLP2. Based on clinical status / evaluation for early evidence of HLH, monitor for liver dysfunction with hepatic profiles and coagulation; measurement of complete blood count; measurement of serum inflammatory markers (ferritin, soluble IL2R). As needed, measurement of serum IgG levels based on phenotype or in those with recurrent respiratory infections; EBV-PCR in blood for evidence of EBV infection if a person has symptoms of infection or HLH develops.

Agents/circumstances to avoid: Individuals with XLP who come into contact with EBV are at risk of developing HLH and/or lymphoproliferation. Individuals are also at risk of developing HLH or inflammatory problems secondary to other infections.

Genetic counseling

XLP is inherited in an X-linked manner. The risk to the sibs of a male proband depends on the genetic status of the mother: if the mother is heterozygous for an *SH2D1A* or *XIAP* pathogenic variant, the chance of transmitting the *SH2D1A* or *XIAP* pathogenic variant in each pregnancy is 50%. Male sibs who inherit the pathogenic variant will be affected; female sibs who inherit the pathogenic variant will be heterozygotes and will typically not be affected (in rare cases, heterozygous females may be symptomatic due to skewed X-chromosome inactivation). Genetic testing of at-risk female relatives is most informative if the pathogenic variant has been identified in the proband. Prenatal testing is possible for a pregnancy at increased risk if the familial pathogenic variant is known.

Diagnosis

For the purposes of this *GeneReview*, the terms "male" and "female" are narrowly defined as the individual's biological sex at birth as it determines clinical care [Caughey et al 2021].

No consensus clinical diagnostic criteria for X-linked lymphoproliferative disease (XLP) have been published. XLP has traditionally been separated into two recognizable subtypes: XLP1, due to pathogenic variants in *SH2D1A*, and XLP2, due to pathogenic variants in *XIAP* (see Clinical Description).

Suggestive Findings

XLP **should be suspected** in a proband (most typically a male but rarely a female) with any of the following clinical, supportive laboratory, or family history findings.

Clinical Findings

General clinical findings suggestive of either XLP1 or XLP2. Fever and/or hepatomegaly, splenomegaly, lymphadenopathy, and rash resembling **hemophagocytic lymphohistiocytosis (HLH)**

Further clinical findings suggestive of XLP1

- Lymphoma, most often B-cell non-Hodgkin lymphoma of the Burkitt subtype, with or without a prior history of Epstein-Barr virus (EBV) infection
- Vasculitis of the central nervous system or lungs in individuals with or without a prior history of EBV infection

Further clinical findings suggestive of XLP2

- Inflammatory bowel disease, often resembling Crohn disease
- Recurrent splenomegaly, with or without concurrent fever
- Uveitis
- Skin abscesses and other skin disorders
- Arthritis
- Liver disease
- Autoimmune disorders

Laboratory Findings

Supportive laboratory findings suggestive of either XLP1 or XLP2

- Laboratory evidence of hemophagocytic lymphohistiocytosis (HLH):
  - Bi- or trilineage cytopenias
  - Hyperferritinemia
  - Elevated levels of soluble interleukin-2 receptor alpha (IL2RA CD25)
  - Hypertriglyceridemia
  - Markedly elevated liver transaminases and/or liver dysfunction/coagulopathy, hypofibrinogenemia
  - Inverted CD4:CD8 ratio in peripheral blood
  - Hemophagocytosis in the bone marrow, spleen, lymph node, or cerebral spinal fluid
  - Elevated levels of pro-inflammatory cytokines, such as interferon-gamma (IFNG), chemokine ligand 9 (CXCL9; in XLP1), or interleukin-18 (IL-18; in XLP2 plasma IL-18 levels may remain elevated between HLH episodes)
- Laboratory evidence of an acute Epstein-Barr virus (EBV) infection, such as EBV detection by polymerase chain reaction (PCR) (the preferred method) or positive heterophile antibodies or monospot testing
- Decreased levels of one or more immunoglobulin subclasses (dysgammaglobulinemia), most frequently manifested by low serum concentration of immunoglobulin G (IgG), with variable serum concentrations of IgM and/or IgA that may also sometimes be abnormally increased

Further suggestive laboratory findings in XLP1

- Low or absent SAP protein expression by flow cytometry
- Absent or greatly reduced invariant natural killer T (iNKT) cells [Ralph et al 2022]
- Impaired 2B4-mediated cytotoxicity of $CD8^+$ T or NK cells
- Reduced levels of $CD27^+$ memory B cells

- Decreased apoptosis of T lymphocytes in response to stimulation of the cell death receptors FAS/CD95 or TRAIL-R, or when activated via the T cell receptor (also known as decreased T cell restimulated cell death)

Further suggestive laboratory findings in XLP2

- Low or absent XIAP protein expression by flow cytometry
- Increased apoptosis of T lymphocytes in response to stimulation of the cell death receptors FAS/CD95 or TRAIL-R, or when activated via the T-cell receptor (also known as increased T cell restimulated cell death)

Family History

Family history is consistent with X-linked inheritance (e.g., no male-to-male transmission). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

Male proband. The diagnosis of XLP1 or XLP2 can be **established** in a male proband with **one of the following** identified on molecular genetic testing (see Table 1):

- A hemizygous germline pathogenic (or likely pathogenic) variant in *SH2D1A* (XLP1)
- A hemizygous germline pathogenic (or likely pathogenic) variant in *XIAP* (XLP2)

Note: (1) Because bone marrow transplantation becomes an option for affected males if an *SH2D1A* or *XIAP* pathogenic variant is identified, molecular genetic testing should be used early in the investigation of a male with any of the suggestive findings above. (2) Molecular genetic testing of *SH2D1A* or *XIAP* is recommended for all individuals with concerning clinical features suggestive of XLP, especially those with low or absent SAP or XIAP expression, respectively. While decreased SAP or XIAP expression is highly suggestive, identification of a germline pathogenic variant in *SH2D1A* or *XIAP* remains the gold standard.

Female proband. XLP is an X-linked condition that does not typically affect females. However, female probands with a heterozygous pathogenic (or likely pathogenic) variant in *SH2D1A or XIAP* identified on molecular genetic testing and skewed X-chromosome inactivation toward expression of the chromosome with the pathogenic *SH2DA1* or *XIAP* variant have been reported; such individuals may be symptomatic [Rigaud et al 2006, Aguilar et al 2014, Yang et al 2015].

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in the 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 a hemizygous or heterozygous *SH2D1A* or *XIAP* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of XLP has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of XLP, molecular genetic testing approaches can include **serial single-gene testing** (typically done in males) or use of a **multigene panel** (for males or females).

Serial single-gene testing

- In males with low or absent SAP expression by flow cytometry, sequence analysis of *SH2D1A* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.
- In males with low or absent XIAP expression by flow cytometry, sequence analysis of *XIAP* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.
- For symptomatic female probands in whom XLP is considered to be likely, sequencing of *SH2D1A* and/or *XIAP* followed by deletion/duplication analysis of *SH2D1A* and/or *XIAP* (if no pathogenic variant is identified by sequence analysis in either gene) may be undertaken.

  In females who have been found to have a heterozygous pathogenic variant in *XIAP* or *SH2D1A*, low or absent XIAP or SAP expression in ~50% or more of peripheral blood T cells by flow cytometry can suggest X-chromosome skewing favoring expression of the chromosome with the pathogenic *XIAP* or *SH2D1A* variant.

A primary immunodeficiency or HLH multigene panel that includes *SH2D1A*, *XIAP*, and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) 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. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) 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.

Option 2

When a person has atypical phenotypic features but XLP remains a consideration, comprehensive genomic testing may be performed.

Comprehensive 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 1. Molecular Genetic Testing Used in X-Linked Lymphoproliferative Disease

Gene [1]	Proportion of XLP Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [2] Identified by Method	
		Sequence analysis [3]	Gene-targeted deletion/ duplication analysis [4]
SH2D1A	83%-97% [5]	~79% [6]	~21% [7]
XIAP	12% [8]	~80%	~19% [9]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. 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. Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.
6. Sumegi et al [2000], Rigaud et al [2006], Stenson et al [2020]
7. Sequence analysis of the entire coding region and exon/intron boundaries identifies pathogenic variants in approximately 75% of obligate carrier females [Stenson et al 2003].
8. 21% of all reported pathogenic variants are predicted to have deletion of one or more exons or the entire gene [Stenson et al 2003].
9. Filipovich et al [2010]. Note: The incidence of *XIAP* pathogenic variants in males who present with an HLH phenotype (as opposed to an XLP phenotype) is likely less than 10%.
10. 19% of all reported pathogenic variants are predicted to have deletion of one or more exons or the entire gene [Stenson et al 2003].

Clinical Characteristics

Clinical Description

X-linked lymphoproliferative disease (XLP) in general is characterized by an inappropriate immune response to Epstein-Barr virus (EBV) infection leading to hemophagocytic lymphohistiocytosis (HLH) or severe mononucleosis, dysgammaglobulinemia, and lymphoproliferative disease (malignant lymphoma). The condition primarily affects males, although females rarely may have symptoms.

- Prior to EBV infection, most males appear healthy and do not exhibit any characteristic clinical findings.
- Clinical findings vary among individuals with XLP, even in the same family.
- Rarely, males may be asymptomatic; however, they generally develop one or more clinical findings over the course of their life [Jiang et al 2020].
- There is no way to reliably predict which clinical findings will develop in an individual with XLP.

XLP has two recognizable subtypes, XLP1 (due to pathogenic variants in *SH2D1A*) and XLP2 (due to pathogenic variants in *XIAP*).

XLP1

Table 2 summarizes the most commonly recognized phenotypes within *SH2D1A*-related XLP (also known as XLP1) and the frequency of affected individuals with the feature.

Table 2. Clinical Phenotypes of *SH2D1A*-Related XLP (XLP1)

Phenotype	% of Persons w/XLP1 w/Phenotype
Hemophagocytic lymphohistiocytosis (HLH) or fulminant infectious mononucleosis (FIM)	45%-58%
Dysgammaglobulinemia	50.5%

Table 2. continued from previous page.

Phenotype	% of Persons w/XLP1 w/Phenotype
Lymphoma	24.2%
Other	15.4%

Booth et al [2011], Pachlopnik Schmid et al [2011]

HLH / fulminant infectious mononucleosis (FIM) is the most common presentation and usually is characterized by acute illness with prolonged and high fever, bi- or trilineage cytopenias, and hepatosplenomegaly. This is often a severe or fatal condition and is typically associated with EBV infection in between 51%-100% of individuals with XLP1 [Booth et al 2011].

- Rash and lymphadenopathy are less common but may also occur.
- Individuals may exhibit liver dysfunction and neurologic abnormalities.
- Death is generally secondary to liver failure or multisystem organ dysfunction (see Prognosis).

Laboratory/pathology findings in HLH may include the following:

- Hemophagocytosis (phagocytosis identified by microscopy revealing intact or partially degraded blood cells) in the bone marrow, liver, spleen, lymph nodes, and/or cerebral spinal fluid (CSF)
- Pleiocytosis with increased numbers of mononuclear cells and elevated protein levels in the CSF

Dys- or hypogammaglobulinemia can lead to varying degrees of humoral immune dysfunction associated with bronchiectasis and recurrent respiratory infections that, if untreated, may result in death. Dysgammaglobulinemia can develop at any time, although it generally follows EBV infection.

- Hypogammaglobulinemia of one or more immunoglobulin subclasses may be diagnosed prior to EBV infection or in survivors of EBV infection.
- Some of these affected males were previously considered to have common variable immunodeficiency (see Genetically Related Disorders).
- The prognosis for males with dys- or hypogammaglobulinemia is more favorable when managed with regular intravenous immunoglobulin (IVIG) infusions (see Management).
- Hypogammaglobulinemia is usually progressive in XLP1.

Lymphoproliferative disease (malignant lymphoma) and other lymphoproliferative diseases often develop in childhood and usually follow EBV exposure. This finding is specific to XLP1. Lymphomas are typically high-grade B-cell lymphomas, non-Hodgkin type, often extranodal, particularly involving the intestine. Approximately 75% of lymphomas occur in the ileocecal region. Other sites include the central nervous system (CNS), liver, and kidney.

- Lymphomas can be histologically classified as Burkitt lymphoma (53% of all B-cell lymphomas), immunoblastic lymphomas (12% of all lymphomas), small cleaved or mixed-cell lymphomas (12%), and unclassifiable lymphomas (5%).
- Hodgkin and T-cell lymphomas have also rarely been reported.
- Remission may follow treatment with chemotherapy; however, relapse or development of a second primary lymphoma or other clinical manifestation of XLP1 may occur [Booth et al 2011, Zhou et al 2016].

Other

- **Aplastic anemia** and bone marrow failure have been reported to occur in ~3% of individuals with XLP1. It remains unknown whether aplastic anemia is secondary to EBV infection and/or HLH, but it is typically

diagnosed after EBV infection. Aplastic anemia of unclear etiology can occur many years following a prior EBV infection.

- **Vasculitis** has been reported to occur in EBV-positive as well as EBV-negative individuals with XLP1 [Booth et al 2011, Kanegane et al 2012].
  - It is most often observed in the CNS but can also occur in the lungs or other organs.
  - Symptoms of CNS vasculitis include headaches, disorientation, seizures, focal deficits, memory problems, stroke, and hemorrhage.
  - Retinal involvement can lead to visual disturbances and blindness.
  - Pathology of CNS vasculitis reveals clonal or non-clonal T-cell infiltration of vessel walls.
- **Lymphoid granulomatosis (LG)** can affect the lungs and CNS of individuals with XLP1. LG is associated with EBV-driven accumulation of B cells and may range from a benign lymphoid proliferation to frank B-cell malignancy. LG of the lungs can present with pulmonary symptoms (cough, shortness of breath, or pulmonary hemorrhage).

XLP2

Males with *XIAP*-related XLP (also known as XLP2) are more likely to have HLH without EBV infection, recurrent episodes of HLH, splenomegaly, and gastrointestinal disease (see Table 3). To date, neither lymphoproliferative disease nor common variable immunodeficiency (CVID) has been reported in males with XLP2 [Salzer et al 2008, Pachlopnik Schmid et al 2011].

Table 3. Clinical Phenotypes of *XIAP*-Related XLP (XLP2)

Phenotype	% of Persons w/XLP2 w/Phenotype	Age of Onset
Hemophagocytic lymphohistiocytosis (HLH)	37%-90%	Age 0-23 yrs
Recurrent HLH	67%-83%	Typically <1 yr after initial illness
Splenomegaly	56%	Age 0-45 yrs
Hypogammaglobulinemia	16%	Age 0-26 yrs
Colitis ± liver disease	25%-30%	Age 4-41 yrs

Rigaud et al [2006], Marsh et al [2010], Zhao et al [2010], Pachlopnik Schmid et al [2011], Aguilar & Latour [2015]

HLH. Similar to XLP1, HLH is also the most common presentation in those with XLP2. HLH is associated with EBV infection in 33%-83% of individuals with XLP2 [Marsh et al 2010, Pachlopnik Schmid et al 2011, Yang et al 2012, Speckmann et al 2013].

- The prevalence of HLH is 37%-90% in individuals with XLP2 [Marsh et al 2010, Pachlopnik Schmid et al 2011, Yang et al 2012, Speckmann et al 2013].
- Unlike XLP1, recurrence of HLH in individuals with XLP2 is common; repeated episodes may be seen in 67%-83% of affected individuals, often within a year of onset of the initial HLH episode [Marsh et al 2010, Pachlopnik Schmid et al 2011, Yang et al 2012, Speckmann et al 2013].
- HLH poses a significant risk for mortality to males with XLP2. Of the originally described XLP2 cohort, 33% died from HLH between ages six months and 40 years [Rigaud et al 2006].

Splenomegaly can be seen alone, without evidence of HLH or incomplete HLH (fever and cytopenias only). Treatment of this finding typically is not necessary unless there are other concerns, such as platelet trapping. Transient splenomegaly can be seen after vaccinations (see Management).

Hypogammaglobulinemia/hypergammaglobulinemia. Transient hypogammaglobulinemia has rarely been reported in males with XLP2. However, in two males with XLP2, hypergammaglobulinemia was reported [Pachlopnik Schmid et al 2011].

Enterocolitis occurs in between 20%-35% of males with XLP2. Symptoms of colitis include abdominal pain, diarrhea, or rectal bleeding. Affected individuals can also develop perirectal abscesses or fistulae.

- Enterocolitis resembles and is often misdiagnosed as Crohn disease.
  - Approximately 5% of individuals with signs and symptoms of inflammatory bowel disease are ultimately diagnosed with XLP2.
  - Pathologic examination of the colon reveals inflammatory infiltrates in the lamina propria with ulceration, apoptotic crypt cells, and crypt abscesses.
- Enterocolitis can lead to gastrointestinal hemorrhage and has a mortality rate of 10%-60% [Pachlopnik Schmid et al 2011, Aguilar & Latour 2015].
- Enterocolitis has been reported to resolve following allogenic hematopoietic stem cell transplant (HSCT) [Ono et al 2017, Morita et al 2022] (see Management).
- Rarely, individuals with XLP2 and inflammatory bowel disease have also been reported to develop inflammatory liver disease, which can progress to fatal liver failure [Pachlopnik Schmid et al 2011, Speckmann et al 2013, Aguilar & Latour 2015].

Prognosis

Advances in the recognition, diagnosis, and management of XLP1 and XLP2 have led to improved outcomes, although mortality rates still remain high.

XLP1

- In one of the largest series to date, Booth et al [2011] reported that 71% of individuals with XLP1 were alive at the time of publication.
- Survival was greater for those who underwent allogeneic HSCT (81.4%) vs those who did not (62.5%).
- Regardless of whether affected individuals underwent allogeneic HSCT or not, survival was lowest for individuals with XLP1 who developed HLH.
- Combined data from this and other reports reveal an overall mortality rate of 29%-66% for individuals with XLP1 [Shadur et al 2019].

XLP2. The overall mortality rate for individuals with XLP2 ranges from 14% to 43%. Mortality rate following HLH appears to be lower in individuals with XLP2 (ranging from 0% to 23%) compared to those with XLP1.

- A large study of 167 individuals with XLP2 revealed that for individuals reaching adulthood who did not undergo allogeneic HSCT, survival probabilities were 86% at age 30 years and 37% at age 52 years, with poorer outcomes for those who developed disease features before age five years or with new disease features as adults [Yang et al 2022].
- Enterocolitis appears to have the highest risk for mortality in XLP2.

Heterozygous Females

As in many X-linked disorders, females rarely have symptoms. There are, however, increasing numbers of reports of affected females with unfavorable (skewed) X-chromosome inactivation toward the X chromosome with the pathogenic variant in *SH2D1A* or *XIAP* who develop HLH, inflammatory bowel disease, and erythema nodosum [Aguilar & Latour 2015, Dziadzio et al 2015, Holle et al 2015, Yang et al 2015]. This may be an underestimate of affected females due to the variable clinical presentation of XLP as well as underutilization of molecular genetic testing in the female population.

Genotype-Phenotype Correlations

No strong correlation exists between the *SH2D1A* and *XIAP* genotype and the XLP1 and XPL2 phenotype, respectively. Considerable variability in phenotype can be present even within a family [Filipovich et al 2010, Aguilar & Latour 2015].

Nomenclature

In the past, the following terms were used to describe XLP:

- Epstein-Barr virus infection, familial fatal
- EBV susceptibility (EBVS)
- X-linked progressive combined variable immunodeficiency 5
- Purtilo syndrome
- Duncan disease

Prevalence

The estimated prevalence of XLP1 is one in every one to two million males. The prevalence of XLP2 is less well characterized but believed to be less than XLP1. These frequencies may be an underestimate given the severity and often rapidly fatal initial presentation, variable expression, and clinical overlap with other immunologic disorders [Tangye 2014].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *SH2D1A* or *XIAP.*

Although *SH2D1A* and *XIAP* pathogenic variants have been described in individuals with phenotypes that overlap other immunodeficiencies (e.g., common variable immunodeficiency [Morra et al 2001, Nistala et al 2001, Soresina et al 2002, Aghamohammadi et al 2003, Eastwood et al 2004], autoimmune lymphoproliferative syndrome (ALPS) and ALPS-like syndromes [López-Nevado et al 2021], and familial hemophagocytic lymphohistiocytosis [Arico et al 2001, Halasa et al 2003, Chen et al 2020, Loganathan et al 2020, El-Mallawany et al 2022]), males with phenotypes that overlap other immunodeficiencies and an identified *SH2D1A* or *XIAP* pathogenic variant should be considered to have X-linked lymphoproliferative disease and be managed accordingly.

Differential Diagnosis

The differential diagnosis of X-linked lymphoproliferative disease (XLP) includes the following hereditary and acquired disorders:

- **Common variable immunodeficiency** and other hereditary disorders with immunodeficiency (See Table 4.)
- **Hemophagocytic lymphohistiocytosis (HLH).** HLH is traditionally subdivided into familial HLH (fHLH), caused by inherited pathogenic variants in one of several genes required for lymphocyte-mediated cytotoxicity (see Table 4), and secondary HLH, triggered by an underlying infection, malignancy, or autoimmune disease. Individuals with fHLH often present in infancy, and the only curative treatment is hematopoietic stem cell transplant (HSCT) [Cron et al 2023]. Epstein-Barr virus (EBV) is the most common infectious trigger of secondary HLH [Koumadoraki et al 2022] and is particularly common in Asia. Individuals with EBV-associated HLH typically present in childhood. High remission rates are seen with prompt initiation of HLH-directed immunosuppressive therapy [El-Mallawany et al 2022].

- **Typical EBV infection "infectious mononucleosis" (IM).** In young infants, IM can pass for a self-limited viral illness. IM may have an acute or insidious onset. Common manifestations are fever, malaise, and pharyngitis typically lasting one to four weeks. Variable lymphadenopathy and splenomegaly may persist for weeks or even months. A truncal macular eruption is observed in approximately 25% of individuals during the first two weeks, during which time the "mono spot" test and EBV immunoglobulin M (IgM) titers are found. IgG titers generally develop during the second month and persist for life.
- **Severe EBV-associated illness.** Approximately one in 1,000 persons infected with EBV develops severe EBV-associated illness. XLP1 and XLP2 should be considered in males with severe EBV-associated illness who fail to respond to conventional therapies, develop secondary symptoms, or have a family history of severe EBV-associated illness [Lino & Ghosh 2021]. Aplastic anemia is an uncommon but serious complication of severe EBV-associated illness.
- **Recurrent lymphoma.** XLP1 should be suspected in males treated for lymphoma with standard chemotherapy who develop a second distinct lymphoma (not relapse) after achieving initial remission [Sandlund et al 2013, Tangye 2014]. To date, lymphoma as a complication of XLP2 has not been reported.
- **Multisystem inflammatory syndrome in children (MIS-C).** MIS-C occurs as a complication of infection with SARS-CoV-2, the virus that causes COVID-19. Individuals with MIS-C develop potentially life-threatening inflammation of multiple organ systems, including the cardiovascular and gastrointestinal systems, and have elevated systemic inflammatory markers. XLP should be considered in individuals who develop significant and persistent inflammation in the setting of SARS-CoV-2 infection [Prader et al 2021].
- **Sepsis.** Sepsis is characterized by life-threatening inflammation arising in response to infection that leads to hemodynamic collapse and associated end-organ failure. Individuals with HLH caused by XLP may develop severe hyperinflammation that mimics sepsis [Mischler et al 2007].

Table 4. Genes of Interest in the Differential Diagnosis of X-Linked Lymphoproliferative Disease

Gene(s)	Disorder	MOI	Clinical Features	Comment
ADA2 *CARD11* *CTLA4* *DEF6* *IL12RB1* *IL2RA* *IL2RB* *KRAS* *NRAS* *PIK3CD* *PIK3R1* *PRKCD* *STAT1* *STAT3* *STK4* *TET2* *TNFAIP3* *TNFRSF9* *TPP2*	ALPS-like syndrome [1]	AD AR	Benign & chronic lymphoproliferation, autoimmunity, & ↑ risk of lymphoma	Inherited gain- or loss-of-function pathogenic variants in these genes lead to immune regulatory disorders that phenocopy multiple features of XLP, incl hypogammaglobulinemia, inflammation, predisposition to infection, & lymphoma.
AP3B1	*AP3B1*-related Hermansky-Pudlak syndrome	AR	Strong susceptibility to EBV infection, incl severe infection, & development of EBV-assoc Hodgkin & non-Hodgkin lymphomas [2]	XLP should be considered in persons presenting w/severe EBV infection.
BTK	X-linked agammaglobulinemia	XL	↑ susceptibility to bacterial infection	XLP should be considered in males w/ hypogammaglobulinemia identified in 1st decade of life.

Table 4. continued from previous page.

Gene(s)	Disorder	MOI	Clinical Features	Comment
CD19 *CD81* *CR2* *ICOS* *IKZF1* *IL21* *IRF2BP2* *LRBA* *MS4A1* *NFKB1* *NFKB2* *TNFRSF13B* *TNFRSF13C*	CVID (OMIM PS607594)	AD AR	• Humoral immune deficiency w/age of onset most commonly between 16 & 20 yrs resulting in ↑ susceptibility to infections & ↓ responses to protein & polysaccharide vaccines • The most common infections are sinopulmonary. • Overall prevalence is approximately one in 20,000 to 50,000 live births. • Occurs equally in males & females. [3]	• The genetic etiology of most CVID is currently unknown. • XLP should be considered in males w/CVID & hypogammaglobulinemia identified during 1st decade of life, particularly in presence of other signs or positive family history. • Persons w/CVID occasionally present with HLH-like phenotype. [4]
CD27 *CD70* *CORO1A* *CTPS1* *MAGT1* *RASGRP1*	EBV-assoc lymphoproliferative disorders [5]	AR XL	Strong susceptibility to EBV infection, incl severe infection, & development of EBV-assoc Hodgkin & non-Hodgkin lymphomas	XLP should be considered in persons presenting w/severe EBV infection.
CDC42	*CDC42*-related HLH [2]	AD	Cytopenias, hepatosplenomegaly, ↑ transaminases, recurrent fevers, rashes, failure to thrive, & HLH [2]	XLP should be considered in males who meet criteria for HLH.
FAS *FASLG*	ALPS-FAS & ALPS-FASLG [6]	AD AR [7]	Accumulation of autoreactive lymphocytes leading to lymphadenopathy, hepatosplenomegaly, autoimmune cytopenias, & ↑ risk for lymphoma	ALPS phenocopies many features of XLP. XLP should be considered in males presenting w/benign or malignant lymphoproliferation.
ITK	ITK deficiency (lymphoproliferative syndrome 1) (OMIM 613011)	AR	Presentation is quite variable in the few persons reported to date & incl fatal HLH, hypogammaglobulinemia, & autoimmune-mediated renal disease, often following EBV infection.	In contrast to XLP1, 4/5 persons w/ITK deficiency developed Hodgkin lymphoma, as opposed to Burkitt lymphoma.
LYST	Chediak-Higashi syndrome (CHS)	AR	• Partial oculocutaneous albinism, a mild bleeding tendency, & severe immunodeficiency • ~85% of persons w/classic CHS develop HLH.	CHS can be differentiated from XLP by the presence of huge secretory lysosomes in neutrophils & lymphocytes & giant melanosomes on skin biopsy in persons w/ CHS.
MVK	Hyper-IgD syndrome (OMIM 260920)	AR	High serum IgD levels w/assoc febrile episodes, lymphadenopathy, & abdominal pain	XLP shares clinical features w/hyper-IgD syndrome but can be differentiated by the presence of hypogammaglobulinemia.
NLRC4	*NLRC4*-related HLH [2]	AD	Enterocolitis & HLH [2]	XLP should be considered in males who meet criteria for HLH.

Table 4. continued from previous page.

Gene(s)	Disorder	MOI	Clinical Features	Comment
PRF1 *STX11* *STXBP2* *UNC13D*	Familial HLH (fHLH)	AR [8]	• Excessive immune activation w/uncontrolled T lymphocyte & macrophage activation • Familial HLH may also be triggered by EBV infection • Familial HLH is lethal in childhood unless treated w/ HSCT.	XLP should be considered in males who meet criteria for HLH. HLH in persons w/XLP commonly occurs in the setting of infection w/EBV, while an underlying infectious trigger is often not identified in persons w/fHLH.
RAB27A	Griscelli syndrome type 2 (GS2) (OMIM 607624)	AR	• Disorder of cytotoxic T lymphocytes • Usually assoc w/ neurologic abnormalities in addition to partial albinism w/fair skin & silvery-gray hair • Many persons w/GS2 develop HLH.	Persons w/GS2 can present w/HLH, similar to persons w/XLP, but XLP is not assoc w/ albinism or neurologic abnormalities.

AD = autosomal dominant; ALPS = autoimmune lymphoproliferative syndrome; AR = autosomal recessive; CVID = common variable immunodeficiency; EBV = Epstein-Barr virus; HLH = hemophagocytic lymphohistiocytosis; HSCT = hematopoietic stem cell transplant; Ig = immunoglobulin; MOI = mode of inheritance; XL = X-linked; XLP = X-linked lymphoproliferative disease

1. López-Nevado et al [2021]

2. Canna & Marsh [2020]

3. Remiker et al [2024]

4. Dowdell et al [2010], Malkan et al [2015], Yao et al [2022]

5. Latour & Winter [2018]

6. ALPS-FAS refers to autoimmune lymphoproliferative syndrome (ALPS) associated with biallelic or heterozygous germline pathogenic variants in *FAS*. ALPS-FASLG refers to ALPS associated with biallelic or heterozygous germline pathogenic variants in *FASLG*.

7. In most individuals with ALPS-FAS and some individuals with ALPS-FASLG, inheritance is autosomal dominant. In most individuals with ALPS-FASLG and individuals with severe ALPS associated with biallelic *FAS* pathogenic variants, inheritance is autosomal recessive.

8. Autosomal dominant inheritance of *STXBP2*-related fHLH has been suggested by rare reports of symptomatic individuals with heterozygous gain-of-function variants.

Management

No clinical practice guidelines for X-linked lymphoproliferative disease (XLP) have been published.

Evaluations Following Initial Diagnosis

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

Table 5. X-Linked Proliferative Disease: Recommended Evaluations Following Initial Diagnosis [1]

System/Concern	Evaluation	Comment
Gastroenterology /Hepatology	Physical exam to assess for hepatosplenomegaly	• Consider liver imaging if there is hepatomegaly w/ abnormal serum transaminases or bilirubin. • Consider MR cholangiopancreatography if there is concern for cholangitis in those w/XLP2 (*XIAP*-related XLP) & colitis. [2]
	Serum transaminases, bilirubin, triglycerides, lactate dehydrogenase, prothrombin time, PTT, fibrinogen	To assess for liver dysfunction/failure & coagulopathy
	Serum triglyceride levels	To evaluate for HLH
	Assess for signs & symptoms of colitis & cholangitis (rare) [2]	In persons w/XLP2; consider referral to gastroenterologist.
Hematology / Spleen / Lymph nodes / Oncology	Physical exam to assess for hepatosplenomegaly & lymphadenopathy	• Splenomegaly can be seen in setting of HLH or incomplete HLH (fever & cytopenias only). • Splenomegaly & lymphadenopathy should prompt further investigation for lymphoma in those w/XLP1 (*SH2D1A*-related XLP). • In persons w/XLP2, transient splenomegaly can be seen after vaccinations.
	CBC, lactate dehydrogenase, uric acid	To assess for anemia, thrombocytopenia, neutropenia, & ↑ cell turnover
	Consider bone marrow biopsy in those w/cytopenias.	To assess for bone marrow dysfunction/failure (such as aplastic anemia) & evidence of hemophagocytosis &/or malignancy
	Assess for signs & symptoms of lymphoma.	In those w/XLP1
Immunologic	Lymphocyte subset analysis (T cell, B cell, NK cell) & serum concentrations of IgG, IgM, & IgA	To assess immune function & for evidence of dysgammaglobulinemia
	Measurement of serum concentrations of ferritin, soluble IL2RA, & other cytokines if concerns for HLH	To evaluate for evidence & severity of inflammation
Infection	Assessment of previous infectious disease history	• To evaluate for history of recurrent bacterial infections to aid in decisions for Ig replacement therapy, if needed • To evaluate for history of previous viral infections, such as EBV
	• Identification of possible active infections (esp viral infection or reactivation such as EBV, CMV, HSV, adenovirus, HHV6) that would require specific treatment • Eval of infection status of EBV & other infections [3]	To determine active viral infection, viral blood PCR is recommended.

Table 5. continued from previous page.

System/Concern	Evaluation	Comment
Neurologic	Neurologic eval to assess for presence of infection, inflammation, vasculitis, CNS HLH, &/or CNS lymphoma	• If abnormal neurologic exam or symptoms: evaluate CSF cell count w/differential, glucose, protein, culture (& meningitis PCR panel if available), & cytology. Consider CNS imaging w/MRI of brain w/ & w/o contrast (± MR angiography if concern for vasculitis). • Elevation of CSF mononuclear cells, often w/assoc elevation of protein, is sufficient to determine CNS involvement of HLH w/o need to demonstrate hemophagocytosis. • CNS lymphoma & vasculitis can be seen in persons w/ XLP1.
Respiratory	Assess for cough, shortness of breath, & signs/symptoms of pulmonary hemorrhage.	To screen for possible lymphoid granulomatosis in those w/ XLP1.
Genetic counseling	By genetics professionals [4]	To inform affected persons & their families re nature, MOI, & implications of XLP to facilitate medical & personal decision making
Family support & resources	By clinicians, wider care team, & family support organizations	Assessment of family & social structure to determine need for: • Community or online resources such as Parent to Parent • Social work involvement for parental support • Home nursing referral

CBC = complete blood count; CMV = cytomegalovirus; CNS = central nervous system; CSF = cerebrospinal fluid; EBV = Epstein-Barr virus; FIM = fulminant infectious mononucleosis; HLH = hemophagocytic lymphohistiocytosis; HHV6 = human herpes virus 6; HSV = herpes simplex virus; Ig = immunoglobulin; IL2RA = interleukin-2 receptor alpha; MOI = mode of inheritance; MR = magnetic resonance; PCR = polymerase chain reaction; PTT = partial thromboplastin time; XLP = X-linked lymphoproliferative disease

1. Unless otherwise specified, all recommendations listed in this table pertain to individuals diagnosed with either XLP1 or XLP2.

2. Those with XLP1 generally do not develop cholitis.

3. Consider evaluation of CMV, HSV, varicella, hepatitis B virus, and hepatitis C virus infection status.

4. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Targeted Therapy

In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure. —ED

The only known curative therapy for XLP1 (*SH2D1A*-related XLP) is allogeneic hematopoietic stem cell transplant (HSCT). For individuals with XLP2 (*XIAP*-related XLP), many manifestations of disease can be improved with HSCT; however, there are more complications in these individuals (see Table 6).

Table 6: X-Linked Proliferative Disease: Targeted Treatment

Targeted Treatment	XLP1	XLP2
Allogeneic hematopoietic stem cell transplant (HSCT) [1]	• Should be strongly considered in all males as early in life as is feasible, particularly in those who have not yet developed symptoms. [2, 3] • In those who have developed HLH, HSCT should be pursued as soon as the person is clinically stable & HLH has been adequately controlled (i.e., remission). • HSCT is not recommended for asymptomatic heterozygous females.	• Those w/XLP2 appear to experience more complications following allogeneic HSCT, incl ↑ rates of acute & chronic graft-vs-host disease. [4] • High mortality has been observed when using myeloablative conditioning regimens in persons w/XLP2. [5] • Those w/XLP2 who develop HLH have better outcomes if their HLH is in remission prior to HSCT. [6] • There are reports of improvement of enterocolitis following HSCT. [7]

HLH = hemophagocytic lymphohistiocytosis

1. Successful outcomes have been reported with the use of matched-sib donors and marrow or umbilical cord blood from unrelated donors [Marsh et al 2014]. Limited data are available regarding the use of haploidentical donors.

2. Overall survival is approximately 70%-80% [Marsh et al 2014], with improved outcomes following reduced-intensity conditioning.

3. Survival of affected individuals who received a transplant may be increased if they were transplanted prior to developing HLH or other symptoms of disease [Booth et al 2011, Tamura et al 2018, Tomomasa et al 2022]; however, one report reveals similar overall survival for affected individuals with or without a history of HLH [Marsh et al 2014].

4. Ono et al [2017], Arnold et al [2022]

5. Early evidence suggests that reduced-intensity conditioning regimens are effective and should be considered due to very poor early experience with myeloablative preparative regimens [Marsh et al 2013]. Survival (57%-90%) has been better using reduced-intensity or reduced-toxicity regimens.

6. Worthey et al [2011], Marsh et al [2013], Ono et al [2021], Arnold et al [2022]

7. Ono et al [2021]

Supportive Care

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 7).

Table 7. X-Linked Proliferative Disease: Treatment of Manifestations [1]

Manifestation/Concern	Treatment	Considerations/Other
Liver damage/ dysfunction/failure	Standard treatment per infectious disease specialist &/or hepatologist	Liver dysfunction is typically secondary to active viral infection (i.e., EBV) or HLH. Directed EBV or HLH therapy should be considered if present.
Hypogammaglobulinemia	Standard treatment w/IVIG therapy; [2] subcutaneous IgG is also an option.	• IVIG therapy should be considered in affected persons w/hypogammaglobinemia. • IVIG replacement should be strongly considered in persons w/ hypogammaglobulinemia & recurrent respiratory infections or evidence of impaired vaccine response. [3] • Decision to start Ig replacement is supported by presence of low Ig levels (IgG) &/or if there is a history of recurrent respiratory infections. • If it is unclear if a person needs IgG replacement therapy, vaccine response can be tested. [4]

Table 7. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Fulminant EBV infection / HLH	Standard treatment based on HLH-1994 protocol, which may include: • Etoposide & steroids [5] • Consideration of rituximab (anti-CD20 antibody) if person has active EBV infection [6] • Consideration of IVIG therapy If affected person has refractory disease, consider alemtuzumab or anti-thymocyte antibody. [7]	• Other therapies to consider incl cytokine-directed therapy, such emapalumab & ruxolitinib. • Persons w/XLP2 may benefit from anakinra (IL-1 beta antagonist) or IL-18 binding agents due to inflammasomapathy. [8] • Once HLH is controlled, those w/XLP1 should quickly proceed to allogeneic HCST (see Targeted Therapy). • Those w/XLP2 who develop HLH should undergo careful consideration to determine if HSCT is needed (see Targeted Therapy).
Lymphoma (* Only relevant to persons w/XLP1)	Standard chemotherapy appropriate to specific tumor diagnosis	Once lymphoma remission is achieved, affected person should quickly proceed to allogeneic HCST.
Colitis (*Only relevant to persons w/XLP2)	• Symptomatic therapy, which typically incl immunosuppression, such as 5-amino salicylic acid, azathioprine, steroids, cyclosporine, & infliximab (anti-TNF therapies) [9] • HSCT can be curative for severe colitis & should be considered on a case-by-case basis. [9]	Treatment is similar to that used for inflammatory bowel disease of other etiologies. Referral to gastroenterologist for mgmt of colitis is highly recommended.
Aplastic anemia (*Only relevant to persons w/XLP1)	• Supportive care w/transfusions as needed • Antimicrobial prophylaxis if neutropenic or lymphopenic • Consider HSCT.	The etiology of aplastic anemia in those w/XLP1 is unclear. The role of immunosuppression for treatment of aplastic anemia secondary to XLP is unclear but can be considered.
Vasculitis (CNS, lung, systemic) (*Only relevant to those w/XLP1)	• There is no definitive immunosuppressive therapy for vasculitis, & it is often difficult to treat. Agents that have been reported incl steroids, IVIG, & rituximab. [10] • If unresponsive to immunosuppression, HSCT can be considered. [11]	
Family/Community	• Ensure appropriate social work involvement to connect families w/ local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	Ongoing assessment of need for palliative care involvement &/or home nursing

Table 7. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Ethics consultation	Clinical ethics services	• Assess health care decisions in the context of the best interest of the affected person & values & preferences of the family. • For difficult life-prolonging decisions or for clarification of treatment options, consider further consultation w/independent clinical teams. [12]

CNS = central nervous system; EBV = Epstein-Barr virus; FIM = fulminant infectious mononucleosis; HLH = hemophagocytic lymphohistiocytosis; HSCT = hematopoietic stem cell transplant; Ig = immunoglobulin; IL = interleukin; IVIG = intravenous immunoglobulins; TNF = tumor necrosis factor; XLP = X-linked lymphoproliferative disease

1. Unless otherwise specified, all recommendations listed in this table pertain to individuals diagnosed with either XLP1 or XLP2.

2. It is recommended that males with known or suspected XLP and hypogammaglobulinemia receive regular intravenous IgG replacement therapy every three to four weeks until definitive treatment can be provided.

3. Hanitsch et al [2020]

4. Pachlopnik Schmid et al [2011], Panchal et al [2018], Hanitsch et al [2020]

5. Booth et al [2011], Bergsten et al [2017], Ehl et al [2018], Böhm et al [2024]

6. Milone et al [2005], Chellapandian et al [2013]

7. Mahlaoui et al [2007]

8. There is limited data available for anti-cytokine therapy in individuals with XLP1 or XLP2 [Locatelli et al 2020, Geerlinks et al 2022, Maccari et al 2023].

9. Pachlopnik Schmid et al [2011], Worthey et al [2011], Ono et al [2021]

10. Talaat et al [2009]

11. Talaat et al [2009], Marsh et al [2014]

12. Linney et al [2019]

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 8 are recommended.

Table 8. X-Linked Proliferative Disease: Recommended Surveillance [1]

System/Concern	Evaluation	Frequency
Gastroenterology/ Hepatology	Monitor for liver dysfunction w/hepatic profiles (serum transaminases, bilirubin, triglycerides, lactate dehydrogenase) & coagulation studies (prothrombin time, PTT, fibrinogen)	As needed based on clinical status / eval for early evidence of HLH
	Monitor for signs & symptoms of colitis & cholangitis, in those w/XLP2.	At each visit
Hematology / Spleen / Lymph nodes / Oncology	Physical exam for evidence of hepatosplenomegaly & lymphadenopathy	
	Measurement of CBC	As needed based on clinical status / eval for early evidence of HLH
Immunologic	Measurement of serum IgG levels	As needed based on phenotype. Serial immunoglobulin evals are recommended if person has recurrent respiratory infections.
	Measurement of serum inflammatory markers (ferritin, soluble IL2RA)	As needed based on clinical status / eval for early evidence of HLH
Infection	EBV-PCR in blood for evidence of EBV infection	If symptoms of infection or HLH develop

Table 8. continued from previous page.

System/Concern	Evaluation	Frequency
Neurologic	History & physical exam for evidence of any neurologic changes	At each visit
Family/Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	

CBC = complete blood count; EBV = Epstein-Barr virus; FIM = fulminant infectious mononucleosis; HLH = hemophagocytic lymphohistiocytosis; Ig = immunoglobulin; IL2RA = interleukin-2 receptor alpha; PCR = polymerase chain reaction; PTT = partial thromboplastin time

1. Unless otherwise specified, all recommendations listed in this table pertain to individuals diagnosed with either XLP1 or XLP2.

Agents/Circumstances to Avoid

Infections. Individuals with XLP who come into contact with Epstein-Barr virus (EBV) are at risk of developing HLH and/or lymphoproliferation. Individuals are also at risk of developing HLH or inflammatory problems secondary to other infections.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk sibs and other maternal male relatives of an affected individual in order to identify as early as possible those who would benefit from medical management and consideration of presymptomatic bone marrow transplantation in males [Tamura et al 2018, Yang et al 2022]. Evaluations can include:

- Targeted molecular genetic testing if the pathogenic variant in the family is known;
- Flow cytometry to measure SAP and XIAP protein expression if the pathogenic variant in the family is not known.

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

Therapies Under Investigation

The following therapies are under investigation for XLP:

- NCT03512314 (OLE-NLRC4/XIAP.2016.001). Open-label extension study with tadekinig alfa (r-hIL-18BP) to monitor safety and tolerability in patients with interleukin (IL)-18-driven monogenic autoinflammatory conditions (including XIAP deficiency, i.e., XLP2)
- NCT01494103. Administration of donor T cells with the caspase-9 suicide gene after HSCT to determine whether this helps with recovery
- NCT06160791. Testing the effects of ruxolitinib with a de-intensified HLH-1994 conditioning regimen on the treatment of HLH in adults
- NCT04641442. Study to evaluate the efficacy, safety and tolerability of MAS825 in patients with monogenic IL-18-driven autoinflammatory diseases (including XIAP deficiency, i.e., XLP2)
- NCT04551131. Use of a response-adapted ruxolitinib-containing regimen for the treatment of HLH in children

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for 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

X-linked lymphoproliferative disease (XLP) is inherited in an X-linked manner. XLP primarily affects males, although females rarely may have symptoms.

Risk to Family Members

Parents of a male proband

- The father of an affected male will not have XLP, nor will he be hemizygous for the *SH2D1A* or *XIAP* pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote. Females who are heterozygous for an *SH2D1A* or *XIAP* pathogenic variant are typically asymptomatic with no immunologic or biochemical markers of the disorder (rarely, heterozygous females may be symptomatic due to skewed X-chromosome inactivation) [Holle et al 2015, Suryaprakash et al 2021]. Note: If a female has more than one affected child and no other affected relatives and if the familial pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism.
- If a male is the only affected family member (i.e., a simplex case):
  - The mother may be a heterozygote;
  - The affected male may have a *de novo* pathogenic variant, in which case the mother is not a heterozygote (the frequency of *de novo* pathogenic variants is unknown);
  - The mother may have somatic/germline mosaicism. Germline mosaicism has been reported [Schuster et al 1993, Tomomasa et al 2023].
- Molecular genetic testing of the mother is recommended to evaluate her genetic status and inform recurrence risk assessment.

Sibs of a male proband. The risk to sibs depends on the genetic status of the mother:

- If the mother of the proband has an *SH2D1A* or *XIAP* pathogenic variant, the chance of transmitting the pathogenic variant in each pregnancy is 50%.
  - Males who inherit the pathogenic variant will be affected.
  - Females who inherit the pathogenic variant will be heterozygotes. Females rarely have symptoms; however, there are increasing numbers of reports of affected females with skewed X-chromosome inactivation who develop HLH, inflammatory bowel disease, and erythema nodosum (see Clinical Description, Heterozygous Females).
- If the proband represents a simplex case and if the pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is presumed to be low but greater than that of the general population because of the possibility of maternal germline mosaicism (maternal germline mosaicism has been reported [Schuster et al 1993, Tomomasa et al 2022]).

Offspring of a male proband

- Historically, affected males have not been known to reproduce owing to poor survival. However, survival outcomes for affected males are improving, resulting in larger numbers of affected individuals surviving

into adulthood [Pachlopnik Schmid et al 2011, Yang et al 2022]. Reduced-intensity conditioning regimens are increasingly being used for individuals with XLP1 and XLP2 undergoing HSCT [Marsh et al 2014, Ono et al 2017, Arnold et al 2022], which may be associated with higher rates of fertility preservation.

- Affected males would transmit the *SH2D1A* or *XIAP* pathogenic variant to:
  - All of their daughters, who would be heterozygotes (see Clinical Description, Heterozygous Females);
  - None of their sons.

Other family members. The maternal aunts and maternal cousins of a male proband may be at risk of having an *SH2D1A* or *XIAP* pathogenic variant.

Note: Molecular genetic testing may be able to identify the family member in whom a *de novo* pathogenic variant arose, information that could help determine genetic risk status of the extended family.

Heterozygote Detection

Identification of female heterozygotes requires either prior identification of the XLP-related pathogenic variant in the family or, if an affected male is not available for testing, molecular genetic testing first by sequence analysis, and if no pathogenic variant is identified, by gene-targeted deletion/duplication analysis. Molecular genetic testing of at-risk female relatives to determine their genetic status is most informative if the *SH2D1A* or *XIAP* pathogenic variant has been identified in the proband.

Note: Females who are heterozygous for an *SH2D1A* or *XIAP* pathogenic variant rarely have symptoms; however, there are increasing numbers of reports of affected females with unfavorable X-chromosome inactivation who develop HLH, inflammatory bowel disease, and erythema nodosum (see Clinical Description, Heterozygous Females).

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 XLP-related pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible. In pregnancies where the fetus is found to be unaffected, prenatal identification of an HLA-matched potential stem cell donor for an affected sib may be considered.

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.

- **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
- **Jeffrey Modell Foundation/National Primary Immunodeficiency Resource Center**
  Email: info@jmfworld.org
  info4pi.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. X-Linked Lymphoproliferative Disease: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SH2D1A	Xq25	SH2 domain-containing protein 1A	CCHMC - Human Genetics Mutation Database (SH2D1A) SH2D1Abase: Mutation registry for X-linked lymphoproliferative syndrome (XLP)	SH2D1A	SH2D1A
XIAP	Xq25	E3 ubiquitin-protein ligase XIAP	XIAP @ LOVD CCHMC - Human Genetics Mutation Database (XIAP) Mutation registry for X-linked lymphoproliferative syndrome (XIAP)	XIAP	XIAP

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 X-Linked Lymphoproliferative Disease (View All in OMIM)

300079	INHIBITOR OF APOPTOSIS, X-LINKED; XIAP
300490	SH2 DOMAIN PROTEIN 1A; SH2D1A
300635	LYMPHOPROLIFERATIVE SYNDROME, X-LINKED, 2; XLP2

Table B. continued from previous page.

308240	LYMPHOPROLIFERATIVE SYNDROME, X-LINKED, 1; XLP1

Molecular Pathogenesis

SH2D1A encodes SH2 domain-containing protein 1A (signaling lymphocytic activation molecule [SLAM]-associated protein, or SAP), a ligand that binds to members of the SLAM family of receptors [Panchal et al 2018]. Pathogenic variants in *SH2D1A* disrupt the binding of SAP to SLAM receptors, leading to intrinsic defects in lymphocyte function that include lymphocyte cytotoxicity, cytokine production by T cells, T cell-dependent humoral immune responses, and development of natural killer T (NKT) cells [Panchal et al 2018].

XIAP encodes E3 ubiquitin-protein ligase XIAP (XIAP), which belongs to the inhibitor of apoptosis (IAP) family of proteins. Its three baculovirus IAP repeat (BIR) domains inhibit caspase activity, thereby inhibiting apoptosis. The ubiquitin-associated (UBA) domain binds to polyubiquitin chains, resulting in a role for XIAP in ubiquitin-dependent signaling. Finally, the really interesting new gene (RING) domain functions as an E3 ubiquitin ligase, allowing XIAP to target proteins for proteasomal degradation [Mudde et al 2021].

The majority of *XIAP* pathogenic variants lead to an absence of protein expression [Rigaud et al 2006, Marsh et al 2009]. T cells from individuals with XIAP deficiency express elevated levels of caspases, which are normally inhibited by XIAP, and therefore undergo activation-induced cell death at a higher rate. This contributes to impaired expansion of virus-specific T cells in the setting of infection. XIAP is also involved in activation of the innate immune response, autophagic elimination of intracellular bacteria, and regulation of the NACHT, LRR and PYD domains-containing protein 3 (NLRP3) inflammasome. Its absence therefore results in abnormal pathogen persistence due to an ineffective immune response as well as uncontrolled inflammasome activation, leading to an hemophagocytic lymphohistiocytosis (HLH) phenotype [Mudde et al 2021].

Mechanism of disease causation. Loss of function

Table 9. X-Linked Lymphoproliferative Disease: Gene-Specific Laboratory Considerations

Gene [1]	Special Consideration
SH2D1A	Large deletions have been reported.
XIAP	Large deletions, incl protein-coding & promoter regions, have been reported.

1. Genes from Table 1 in alphabetic order

Chapter Notes

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Clinical Immunology Society

Histiocyte Society

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