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Lymphoproliferative Disease, X-Linked

Synonyms: Duncan Disease, XLP

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Summary

Clinical characteristics

X-linked lymphoproliferative disease (XLP) has two recognizable subtypes, XLP1 and XLP2. XLP1 is characterized predominantly by one of three commonly recognized phenotypes:

- Inappropriate immune response to Epstein-Barr virus (EBV) infection leading to hemophagocytic lymphohistiocytosis (HLH) or severe mononucleosis
- Dysgammaglobulinemia
- Lymphoproliferative disease (malignant lymphoma)

XLP2 is most often characterized by HLH (often associated with EBV), dysgammaglobulinemia, and inflammatory bowel disease. HLH resulting from EBV infection is associated with an unregulated and exaggerated immune response with widespread proliferation of cytotoxic T cells, EBV-infected B cells, and macrophages. Dysgammaglobulinemia is typically hypogammaglobulinemia of one or more immunoglobulin subclasses. The malignant lymphomas are typically B-cell lymphomas, non-Hodgkin type, often extranodal, and in particular involving the intestine.

Diagnosis/testing

The diagnosis of XLP is established in a male by identification of a hemizygous pathogenic variant in *SH2D1A* (associated with XLP1) or *XIAP* (associated with XLP2) on molecular genetic testing.

Management

Treatment of manifestations: Treatment of XLP-related HLH is similar to that of other life-threatening genetic hemophagocytic disorders and includes immunosuppressive agents such as steroids and etoposide or anti-thymocyte globulin. Rituximab therapy may also be considered when HLH is associated with EBV infection.

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Hypogammaglobulinemia is treated with IVIG replacement therapy. Lymphoma is treated with standard chemotherapy appropriate to the tumor. Inflammatory bowel disease is treated with immunosuppression. For all clinical phenotypes of XLP, the only curative treatment is allogeneic hematopoietic cell transplantation (HCT), which should be considered in most individuals as early as possible.

Prevention of primary manifestations: Boys with known or suspected XLP and hypogammaglobulinemia should receive regular intravenous (IV) IgG replacement therapy every three to four weeks until definitive treatment can be provided.

Surveillance: Blood should be monitored by EBV-PCR for evidence of EBV infection if symptoms of infection and/or HLH develop; blood counts, hepatic profiles, coagulation studies, and inflammatory markers should be monitored as needed based on clinical status for early evidence of HLH; IgG levels should be monitored as needed based on clinical phenotype.

Agents/circumstances to avoid: Individuals with XLP who come into contact with EBV are at risk until curative treatment with allogeneic HCT has been performed. Individuals are also at risk of developing HLH or inflammatory problems with other infections.

Evaluation of relatives at risk: Molecular genetic testing of at-risk sibs and other relatives for the family-specific pathogenic variant facilitates early diagnosis and treatment.

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 a carrier, the chance of transmitting the *SH2D1A* and *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). Carrier 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

Suggestive Findings

X-linked lymphoproliferative disease (XLP) **should be suspected** in a male with any of the following clinical presentations or laboratory features.

Clinical Presentations

The following are suggestive of XLP:

- Fatal or near-fatal Epstein-Barr virus (EBV) infection / severe fulminant infectious mononucleosis
- Hemophagocytic lymphohistiocytosis (HLH) resulting from EBV or other viral illness (e.g., influenza, cytomegalovirus, adenovirus, varicella), especially in childhood or adolescence; or HLH without an identifiable trigger
- Dysgammaglobulinemia
- Lymphoproliferative disease (malignant lymphoma) (XLP1)
- Inflammatory bowel disease (XLP2)
- Family history of one or more maternally related males with an XLP phenotype

Laboratory Features

Males with XLP do not show any uniform abnormalities on standard immunologic testing; however, the following may be seen:

- Variably decreased or increased numbers of lymphocyte subsets including decreased or increased T cells, B cells, and NK cells. HLH may be associated with T-cell expansion.

  Note: (1) Males with XLP1 have absent invariant natural killer T cells (iNKT cells). (2) Males with XLP2 can have normal or decreased iNKT cell populations [Marsh et al 2009].

- Impaired T-cell restimulation-induced cell death (males with XLP1) or increased susceptibility to T-cell restimulation-induced cell death (XLP2)
- Impaired 2B4-mediated cytotoxicity (XLP1)
- Impaired NOD2 signaling (XLP2)

Acute EBV infection

- EBV detection by polymerase chain reaction (PCR; preferred method)
- Positive heterophile antibodies or monospot testing
- Detection of EBV-specific IgM antibodies
- Atypical lymphocytosis on peripheral blood smear with expansion of CD8 T cells

HLH / fulminant infectious mononucleosis

- Markedly elevated liver transaminases and/or liver dysfunction/coagulopathy, hypofibrinogenemia
- Inverted CD4:CD8 ratio in peripheral blood
- Hemophagocytosis on bone marrow biopsy or in other tissues (e.g., CSF, lymph node)
- Cytopenias
- Splenomegaly
- Elevated plasma levels of soluble IL-2 receptor alpha
- Hypertriglyceridemia
- Hyperferritinemia

Dysgammaglobulinemia. Decreased levels of one or more immunoglobulin subclasses, most frequently manifest by low serum concentration of IgG, with variable serum concentrations of IgM and/or IgA that may also sometimes be abnormally increased

Establishing the Diagnosis

Male proband. Because bone marrow transplantation becomes an option for acutely ill males if an *SH2D1A* or *XIAP* pathogenic variant is identified, molecular genetic testing should be used early in the investigation of a male with the following:

- A severe EBV (or other virus) infection
- Hemophagocytic lymphohistiocytosis (HLH)
- Immunodeficiency involving hypogammaglobulinemia of uncertain etiology
- Recurrence of a B-cell (typically non-Hodgkin) lymphoma

The diagnosis of XLP **is established** in a male proband with:

- Low or absent SH2 domain protein 1A (SAP) expression by flow cytometry (XLP1) or low or absent XIAP expression by flow cytometry (XLP2), and normal perforin flow cytometric screening and CD107a flow cytometric screening (see Differential Diagnosis);

- A hemizygous pathogenic variant in *SH2D1A* or *XIAP* identified by molecular genetic testing (see Table 1).

  Note: Molecular genetic testing of *SH2D1A* or *XIAP* is recommended for all individuals with abnormal SAP and XIAP expression studies, and for individuals in whom clinical suspicion is high.

Female proband. The diagnosis of XLP **is usually established** in a female proband who is symptomatic for XLP and has a heterozygous pathogenic variant in *XIAP* or *SH2D1A* identified on molecular genetic testing.

Molecular testing approaches can include **serial single-gene testing**, use of a **multigene panel**, and **more comprehensive genomic testing**.

Serial single-gene testing

- In males with low or absent SH2 domain protein 1A (SAP) expression by flow cytometry, start with sequence analysis of *SH2D1A*. If no pathogenic variant is identified, gene-targeted deletion/duplication analysis of *SH2D1A* is performed.
- In males with low or absent XIAP expression by flow cytometry, sequence analysis of *XIAP* is performed first. If no pathogenic variant is identified, gene-targeted deletion/duplication analysis of *XIAP* is performed.

A multigene panel that includes *SH2D1A*, *XIAP*, and other genes of interest (see Differential Diagnosis) may also be considered. 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*; thus, clinicians need to determine which multigene panel 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. (3) 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.

More comprehensive genomic testing (when available) including exome sequencing, genome sequencing, and whole mitochondrial sequencing may be considered if serial single-gene testing (and/or use of a multigene panel) fails to confirm a diagnosis in an individual with features of XLP.

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] Detected by Method	
		Sequence analysis [3]	Gene-targeted deletion/duplication analysis [4]
SH2D1A	83%-97% [5]	~75% [6]	~25% [7]

Table 1. continued from previous page.

Gene [1]	Proportion of XLP Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [2] Detected by Method	
		Sequence analysis [3]	Gene-targeted deletion/ duplication analysis [4]
XIAP	12% [8]	~85%	~15% [9]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
5. Sumegi et al [2000], Rigaud et al [2006]
6. 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].
7. 25% are predicted to have deletion of one or more exons or the entire gene [Stenson et al 2003].
8. 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%.
9. 15% 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) has two recognizable subtypes, XLP1 and XLP2.

XLP1

The three most commonly recognized phenotypes are (Table 2):

- An inappropriate immune response to EBV infection resulting in unusually severe and often fatal infectious mononucleosis or hemophagocytic lymphohistiocytosis (HLH) caused by EBV or other viral infection;
- Dysgammaglobulinemia; and
- Lymphoproliferative disease typically of B-cell origin.

Clinical manifestations of XLP vary even among affected members of the same family. Of note, some males with pathogenic variants in *SH2D1A* are asymptomatic and their long-term prognosis is not known.

Prior to EBV infection, most males with XLP1 appear generally healthy and do not have any characteristic clinical findings. In approximately 12% of males with XLP1, dysgammaglobulinemia precedes EBV infection, resulting in varying degrees of hypogammaglobulinemia and recurrent respiratory infections [Sumegi et al 2000].

Pachlopnik Schmid et al [2011] reported mean age at death for individuals with an *SH2D1A* pathogenic variant as 11 years (range 2-69 years). Approximately 50% of affected males reached adulthood; of this group only one had hematopoietic cell transplantation (HCT). In this study, approximately 25% of surviving males were not receiving treatment; 60% received intravenous immunoglobulin (IVIG) only; and 12% were undergoing therapy for lymphoma. Mortality was related to HLH (70%), lymphoma (12%), myelodysplasia (6%), and complications of HCT (12%).

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

Phenotype	% of Individuals with XLP1 with This Phenotype	Mortality Rate
Hemophagocytic lymphohistiocytosis (HLH)	35.2%	65.6%
Dysgammaglobulinemia	50.5%	13%
Lymphoma	24.2%	9%
Fulminant infectious mononucleosis	9.9%	22.2%
Other	15.4%	28.6%

From Booth et al [2011]

Fulminant infectious mononucleosis (FIM)/HLH associated with EBV. The most commonly recognized presentation of XLP is a fatal or near-fatal EBV infection associated with an unregulated and exaggerated immune response with widespread proliferation of cytotoxic T cells, EBV-infected B cells, and macrophages [Gaspar et al 2002]. Affected individuals typically have lymphadenopathy and hepatosplenomegaly with extensive parenchymal damage including fulminant hepatitis, hepatic necrosis, and profound bone marrow failure. Death is generally secondary to liver failure. Hemophagocytosis (phagocytosis identified by microscopy of intact or partially degraded blood cells) in bone marrow and/or CNS may also be seen in association with overwhelming EBV infection. Involvement of other organs may include the spleen ("white pulp" necrosis), heart (mononuclear myocarditis), and kidney (mild interstitial nephritis).

Booth et al [2011] found 65% of persons with XLP to be positive for EBV at diagnosis. In this group, the most common presentation of XLP was FIM/HLH, seen in 69% of individuals positive for EBV. In contrast, persons negative for EBV more typically presented with dysgammaglobulinemia (52%) or lymphoma (25%). HLH in the absence of EBV infection occurred in approximately 21%. The overall mortality rate of approximately 30% did not vary significantly between those who were positive for EBV and those who were not. Mortality was calculated based on whether the individual was alive or deceased at point of data collection. This time span varied between individuals from day 0 (presentation) to 148 months post transplant.

Note: In contrast, EBV infection in individuals who do not have XLP can occur as the well-recognized "infectious mononucleosis" (IM); in young infants, it 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 period the "mono spot" test and EBV IgM titers are found. IgG titers generally develop during the second month and persist for life.

Dysgammaglobulinemia. In approximately one half of males with XLP1, hypogammaglobulinemia of one or more immunoglobulin subclasses is diagnosed prior to EBV infection or in survivors of EBV infection. Some of these males were previously considered to have common variable immunodeficiency. All lymphoid cell lines (including T cells, B cells, and natural killer cells) can be affected. The natural history of individuals diagnosed with the common variable immunodeficiency phenotype and subsequently found to have a pathogenic variant in *SH2D1A* is not well documented at this time. The prognosis for males with this phenotype is more favorable if they are managed with regular IVIG (see Management).

Lymphoproliferative disease (malignant lymphoma). Lymphomas or other lymphoproliferative disease occurs in approximately one third of males with XLP1, some of whom have hypogammaglobulinemia or have survived an initial EBV infection. The lymphomas seen in XLP 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, liver, and kidney [Gaspar et al 2002].

The 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%) [Harrington et al 1987]. Some but not all B-cell lymphomas express the EBV genome, suggesting that the XLP defect alone predisposes to lymphogenesis.

Lymphomas often develop in childhood and may occur prior to EBV exposure. Remission may follow chemotherapy; however, relapse or development of a second lymphoma or other manifestations of XLP is common [Booth et al 2011].

Common variable immunodeficiency (CVID) and hemophagocytic lymphohistiocytosis (HLH). *SH2D1A* pathogenic variants have been described in individuals with phenotypes that overlap with other immunodeficiencies (see Differential Diagnosis) including the following:

- Common variable immunodeficiency (CVID) [Nistala et al 2001, Soresina et al 2002, Aghamohammadi et al 2003, Eastwood et al 2004]
- Familial hemophagocytic lymphohistiocytosis (FHL) [Arico et al 2001, Halasa et al 2003]
- Severe EBV-associated illness [Sumazaki et al 2001]
- B-cell neoplasms [Sandlund et al 2013]

Males with phenotypes that overlap with other immunodeficiencies and an identified *SH2D1A* or *XIAP* pathogenic variant should be considered to have XLP and be managed accordingly.

Other. Less frequent manifestations of XLP1 are aplastic anemia, vasculitis, and lymphoid granulomatosis.

XLP2

Males with XIAP deficiency (XLP2) typically present with HLH (often without EBV infection), recurrent episodes of HLH, splenomegaly, and gastrointestinal disease and may be better described as having an X-linked form of familial HLH rather than XLP. To date, neither lymphoproliferative disease [Pachlopnik Schmid et al 2011] nor common variable immunodeficiency (CVID) has been reported in males with XIAP deficiency [Salzer et al 2008]. Of note, some males with a pathogenic variant in *XIAP* are asymptomatic and their long-term prognosis is not known.

Pachlopnik Schmid et al [2011] reported mean age at death for males with an *XIAP* pathogenic variant as 16 years (range 1-52 years). Approximately 43% reached adulthood; none of this group had HCT. In this study, approximately 60% of surviving males were not receiving treatment; 12% received IVIG only; 12% were undergoing treatment for colitis; and 18% were undergoing treatment for HLH. Mortality was related to HLH (30%), complications of HCT (30%), colitis (23%), liver failure (8%), and pneumonia (8%).

Table 3. Clinical Phenotypes of XIAP Deficiency (XLP2)

Phenotype	% of All Individuals w/XLP2 with This Phenotype [1]	Age of Onset
Hemophagocytic lymphohistiocytosis (HLH)	83%	0-23 yrs [1]
Recurrent HLH	67%	Typically <1 yr after initial illness [2]
Splenomegaly	85%	0-45 yrs [1]
Hypogammaglobulinemia	30%	0-26 yrs [1]
Colitis ± liver disease	13%	4-41 yrs [1]

1. Combined from series reported to date including Rigaud et al [2006], Marsh et al [2010], Zhao et al [2010], and Pachlopnik Schmid et al [2011]
2. Pachlopnik Schmid et al [2011]

Hemophagocytic lymphohistiocytosis (HLH) poses a significant risk for mortality to males with XLP2: 33% of the originally described XLP2 cohort died from HLH between ages six months and 40 years [Rigaud et al 2006]. Recurrences of HLH are common, particularly within a year of onset of the initial HLH episode [Pachlopnik Schmid et al 2011].

Colitis, a serious complication of XLP2, has a mortality rate of 60% in symptomatic individuals [Pachlopnik Schmid et al 2011].

Dysgammaglobulinemia. Approximately one third of males with XLP2 have hypogammaglobulinemia of one or more immunoglobulin subclasses, which, if untreated, may result in life-threatening infections. The prognosis for males with this phenotype is more favorable if they are managed with regular IVIG (see Management, Treatment of Manifestations).

Transient hypogammaglobulinemia has been reported in a minority of affected males.

In addition, hypergammaglobulinemia has been reported in two males with XIAP deficiency [Pachlopnik Schmid et al 2011].

Genotype-Phenotype Correlations

No strong correlation exists between *SH2D1A* and *XIAP* genotype and XLP1 and XPL2 phenotype, respectively. Considerable variability in phenotype can be present even within a family [Sumegi et al 2002, Rigaud et al 2006, Filipovich et al 2010].

Nomenclature

In the past, the following terms were used to describe XLP1:

- 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 XLP is one per one million males. This may be an underestimate given the severity and often rapidly fatal initial presentation, variable expression, clinical overlap with other immunologic disorders, and lack of a functional assay for diagnosis.

As in many X-linked recessive disorders, females are rarely affected. To the authors' best knowledge, only one affected female (with skewed X-chromosome inactivation) has been reported [Holle et al 2015]. This may be an underestimate of affected females due to the variable clinical presentation of XLP as well as underutilization of testing in the female population.

XLP has been reported in families of European, African, Asian, and Middle Eastern descent; no evidence exists for a racial or ethnic predilection.

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

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

- **Common variable immunodeficiency** (CVID; OMIM Phenotypic Series 607594) is characterized by humoral immune deficiency with onset after age 24 months and usually in young adulthood, resulting in increased susceptibility to infections and diminished responses to protein and polysaccharide vaccines. The most common infections are sinopulmonary. Overall prevalence is approximately one in 30,000 live births and occurs equally in males and females [Stiehm & Johnston 2005]. The genetic etiology of most CVID is currently unknown. XLP should be considered in males with CVID and hypogammaglobulinemia identified during the first decade of life, particularly in the presence of other symptoms or a positive family history.
- **Hemophagocytic lymphohistiocytosis (HLH)** has numerous causes:
  - Familial hemophagocytic lymphohistiocytosis (FHL), a group of rare autosomal recessive disorders, is characterized by excessive immune activation with uncontrolled T-lymphocyte and macrophage activation. Familial HLH may also be triggered by EBV infection. These disorders are lethal in childhood unless treated with bone marrow transplantation. Four genes (*PRF1*, *UNC13D* [*MUNC13-4*], *STXBP2*, and *STX11*), representing approximately 60% of the genetic basis of FHL, have been identified to date.
  - Secondary EBV-associated HLH is commonly diagnosed in Asia [Imashuku 2002]; it also accounts for approximately 30% of individuals with HLH identified in North America. Individuals with EBV-associated HLH typically have symptomatic presentation beyond infancy [Filipovich 2001] and may achieve prolonged remission with therapy, thus not requiring curative BMT.
  - Arico et al [2001] found pathogenic variants in *SH2D1A* in four of 25 males (16%) who had previously been diagnosed with HLH, suggesting that XLP should be considered in males presenting with HLH who have no family history of affected females. Similarly, Marsh et al [2010] published a series of young males who presented with HLH and an *XIAP* pathogenic variant, prompting the conclusion that XIAP deficiency may be most appropriately classified as an X-linked form of hemophagocytic lymphohistiocytosis rather than an X-linked lymphoproliferative disease.
- **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. Aplastic anemia is an uncommon but serious complication of severe EBV-associated illness.
- **Recurrent lymphoma.** XLP1 should be suspected in boys treated for lymphoma with standard chemotherapy who develop a second distinct lymphoma (not relapse) after achieving initial remission [Sandlund et al 2013]. To date, lymphoma as a complication of XLP2 has not been reported.
- **Chediak-Higashi syndrome** is characterized by partial oculocutaneous albinism, a mild bleeding tendency, and severe immunodeficiency. Mutation of *LYST*, encoding a protein involved in intracellular vesicle formation, is causative, resulting in failure to fuse lysosomes properly with phagosomes. Chediak-Higashi syndrome can be differentiated from XLP based on the presence of huge secretory lysosomes in the neutrophils and lymphocytes and giant melanosomes on skin biopsy. Inheritance is autosomal recessive.
- **Griscelli syndrome type 2** (GS2; OMIM 607624) is a disorder of cytotoxic T lymphocytes caused by mutation of *RAB27A*, encoding a small GTPase, which controls the movement of vesicles within cells [Ménasché et al 2002]. GS2 is usually associated with neurologic abnormalities in addition to partial albinism with fair skin and silvery-gray hair. Inheritance is autosomal recessive.
- **ITK deficiency** (lymphoproliferative syndrome 1; OMIM 613011). Pathogenic variants in *ITK* have been reported in association with an autosomal recessive form of lymphoproliferative disease [Huck et al 2009,

Stepensky et al 2011]. Presentation has been quite variable in the few individuals reported to date and has included fatal hemophagocytic lymphohistiocytosis, hypogammaglobulinemia, and autoimmune-mediated renal disease, often following EBV infection. In contrast to XLP1, four out of five individuals with ITK deficiency developed Hodgkin disease, as opposed to Burkitt lymphoma.

- **CD27 deficiency** (lymphoproliferative syndrome 2; OMIM 615122). Pathogenic variants in *TNFRSF7* have been reported in association with an autosomal recessive form of lymphoproliferative disease [van Montfrans et al 2012, Salzer et al 2013]. This condition is characterized by EBV viremia, hypogammaglobulinemia, and T-cell dysfunction.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with X-linked lymphoproliferative disease (XLP), the following evaluations are recommended:

- Physical examination to evaluate for rashes, lymphadenopathy, hepatosplenomegaly, and neurologic dysfunction
- Evaluation of blood and bone marrow compartments (CBC and bone marrow biopsy)
- Determination of the extent of liver involvement by measuring serum concentration of transaminases, bilirubin, triglycerides, sodium, and lactate dehydrogenase
- Identification of potential infectious cofactors (especially viral infection or reactivation) that would require specific treatment
- Testing to assess immune function including lymphocyte subset analysis (T cell, B cell, NK cell) and serum concentrations of IgG, IgM, and IgA
- Establishing the presence or extent of CNS involvement by evaluating the CSF and performing neuroimaging and neuropsychological assessment
- Evaluation of inflammatory factors including serum concentrations of ferritin, sIL2Rα, and other cytokines
- Evaluation and monitoring of PT, PTT, and fibrinogen
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

No formal management guidelines exist; the following are general considerations.

Individuals with XLP who develop fulminant EBV infection / HLH often improve with early treatment (e.g., based on HLH-1994 protocol) similar to that used in other life-threatening genetic hemophagocytic disorders including familial hemophagocytic lymphohistiocytosis (FHL) [Henter et al 1997, Jordan et al 2011], typically consisting of etoposide and steroids. Rituximab (anti-CD20 antibody) [Milone et al 2005, Lee et al 2006] as well as IVIG may also be considered.

Allogeneic HCT is the only curative therapy and should be strongly considered in individuals with confirmed XLP1 as early in life as is feasible [Lankester et al 2005]. Successful outcomes have been reported with the use of matched sib donors and marrow or umbilical cord blood from unrelated donors [Gross et al 1996, Filipovich 2001, Lankester et al 2005]. Overall survival appears to be approximately 80%, regardless of conditioning regimen used. However, survival of affected individuals who received a transplant was increased if they were transplanted prior to an episode of HLH [Booth et al 2011].

The outcomes of allogeneic HCT for males with XLP2 are less certain at this time. Early evidence suggests that reduced-intensity conditioning regimens should be considered due to very poor early experience with myeloablative preparative regimens [Marsh et al 2013].

Hypogammaglobulinemia is treated with IVIG.

Lymphoma associated with XLP1 is treated with the standard chemotherapy appropriate to the tumor diagnosis. Once lymphoma remission is achieved, the individual should quickly proceed to allogeneic HCT.

Colitis associated with XLP2 is treated symptomatically and with immunosuppression similar to that used for inflammatory bowel disease of other etiologies.

Prevention of Primary Manifestations

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

HCT is the only curative therapy and should be considered in children with confirmed XLP as early in life as possible.

Surveillance

No formal surveillance guidelines exist; the following are general considerations:

- Blood should be monitored by EBV-PCR for evidence of EBV infection if symptoms of infection or HLH develop.
- Blood counts, hepatic profiles, coagulation studies, and inflammatory markers (ferritin, soluble IL2R) should be monitored as needed based on clinical status for early evidence of HLH.
- IgG levels should also be monitored as needed based on clinical phenotype.

Agents/Circumstances to Avoid

Individuals with XLP who come into contact with EBV are at risk until curative treatment with allogeneic HCT has been performed. Individuals are also at risk of developing HLH or inflammatory problems with other infections.

Evaluation of Relatives at Risk

Once the pathogenic variant has been identified in a proband, molecular genetic testing of at-risk sibs and other maternal male relatives is appropriate for medical management and for consideration of presymptomatic bone marrow transplantation.

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

Therapies Under Investigation

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. Note: There may not be clinical trials for this disorder.

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.

Risk to Family Members

Parents of a 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 (carrier). Female carriers of XLP are typically asymptomatic with no immunologic or biochemical markers of the disorder (in rare cases, heterozygous females may be symptomatic due to skewed X-chromosome inactivation).

  Note: If a woman has more than one affected son and no other affected relatives and if the *SH2D1A* or *XIAP* pathogenic variant cannot be detected in her leukocyte DNA, she has germline mosaicism. Germline mosaicism has been reported [Schuster et al 1993]; the frequency of germline mosaicism in XLP is currently unknown.
- If the proband is the only affected family member (i.e., a simplex case), the mother may be a carrier or the affected male may have a *de novo* pathogenic variant, in which case the mother is not a carrier.

Sibs of a proband

- The risk to sibs depends on the genetic status of the mother.
- If the mother of the proband has a *SH2D1A* or *XIAP* pathogenic variant, the chance of transmitting the 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 carriers. Female carriers of XLP are typically asymptomatic with no immunologic or biochemical markers of the disorder (in rare cases, heterozygous females may be symptomatic due to skewed X-chromosome inactivation).
- Germline mosaicism has been demonstrated [Schuster et al 1993]. Thus, even if the pathogenic variant has not been identified in DNA extracted from the mother's leukocytes, her offspring are still at increased risk.

Offspring of a proband

- It is likely that in the near future some affected males will live to reproduce following bone marrow transplantation given that reduced-intensity conditioning regimens – which may not render them infertile – are being more frequently used. However, the likelihood of this is unknown at the present time.
- Affected males would transmit the *SH2D1A* or *XIAP* pathogenic variant to:
  - All of their daughters, who would be heterozygotes and typically unaffected;
  - None of their sons.

Other family members of a proband

- The proband's maternal relatives and their offspring may be at risk of being carriers (if female) or of being affected with XLP (if male).
- The exact risk to the proband's maternal relatives depends on the family relationships.

Heterozygote (Carrier) Detection

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.

Identification of female heterozygotes requires either (a) prior identification of the pathogenic variant in the family or (b) 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. Females who are heterozygous (carriers) for an *SH2D1A* or *XIAP* pathogenic variant are asymptomatic and have no immunologic or biochemical markers of the disorder.

Note: X-chromosome inactivation studies are not suitable for determining carrier status [Harris et al 1992].

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, clarification of carrier status, 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.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown).

Prenatal Testing and Preimplantation Genetic Testing

Once the *SH2D1A* or *XIAP* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for XLP 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.

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. Lymphoproliferative Disease, X-Linked: 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 Lymphoproliferative Disease, X-Linked (View All in OMIM)

300079	INHIBITOR OF APOPTOSIS, X-LINKED; XIAP
300490	SH2 DOMAIN PROTEIN 1A; SH2D1A
300635	LYMPHOPROLIFERATIVE SYNDROME, X-LINKED, 2; XLP2
308240	LYMPHOPROLIFERATIVE SYNDROME, X-LINKED, 1; XLP1

SH2D1A

Gene structure. *SH2D1A* has four exons (NM_002351.4) that span more than 25 kb. See Table A for a detailed summary of gene and protein information.

Pathogenic variants. More than 113 *SH2D1A* pathogenic variants that result in the XLP-associated phenotype have been identified. Pathogenic variants have been found in all four exons and include deletions and insertions that lead to absence of a functional protein, pathogenic variants that interfere with transcription and splicing, nonsense variants predicted to result in protein truncation, and missense variants that affect protein function [Sumegi et al 2002]. One half of these pathogenic variants are single-nucleotide substitutions, one quarter are splicing defects or frameshift variants, and one quarter are large (i.e., [multi]exon or whole-gene) deletions. These pathogenic variants result in improper processing of the *SH2D1A* message and lead to truncated or unstable protein [Morra et al 2001, Li et al 2003, Stenson et al 2003, Erdõs et al 2005, Friedlander et al 2008, Marsh et al 2009, Snow et al 2009, Marsh et al 2010, Gifford et al 2014].

Normal gene product. *SH2D1A* codes for SH2 domain protein 1A (signaling lymphocyte activation molecular [SLAM]-associated protein, or SAP), a small 125-amino acid protein (NP_002342.1) involved in the intracellular signaling of the SLAM family of receptors [Veillette 2006, Ma et al 2007].

Abnormal gene product. Pathogenic variants in *SH2D1A* lead to changes in the amino acid sequence and truncation or absence of SAP, which disrupts binding to SLAM family receptors and resultant signal transduction pathways [Sayos et al 1998, Morra et al 2001]. Loss of functional SAP causes intrinsic defects in lymphocyte function including lymphocyte cytotoxicity, cytokine production by T cells, T cell-dependent humoral immune responses, and development of NKT cells [Veillette 2006, Ma et al 2007]. It is likely that additional functions that could be disturbed by certain pathogenic variants of *SH2D1A* will be defined in the future.

***XIAP* (*BIRC4*)**

Gene structure. *XIAP* has seven exons (NM_001167.3) that encode a 497-amino acid protein. See Table A for a detailed summary of gene and protein information.

Pathogenic variants. Three pathogenic variants in *XIAP* were described in the original cohort of individuals with XLP2. Two families were found to have pathogenic nonsense variants resulting in early stop codons within exon 1, and the third family was described with a deletion spanning exon 2 [Rigaud et al 2006]. To date more than 70 pathogenic variants have been identified in *XIAP*, including nonsense and missense variants and deletions [Marsh et al 2010, Pachlopnik Schmid et al 2011].

Normal gene product. *XIAP* encodes E3 ubiquitin-protein ligase XIAP. As the name implies, XIAP is known to inhibit apoptosis through interaction with caspase-3, -7, and -9. XIAP also has a C-terminal ring finger domain with E3 ubiquitin ligase activity. XIAP is involved in signaling pathways involving nuclear factor-kappa beta, JNK, and TGF-β, and is also involved in intracellular copper homeostasis [Mufti et al 2007].

Abnormal gene product. The majority of *XIAP* pathogenic variants lead to an absence of protein expression [Rigaud et al 2006, Marsh et al 2009]. How this results in the XLP phenotype remains to be definitively explained, but an increased sensitivity of XIAP-deficient lymphocytes to apoptosis and decreased populations of NKT cells have been postulated to contribute to disease pathogenesis [Rigaud et al 2006, Latour 2007, Marsh et al 2009].

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Published Guidelines / Consensus Statements

American Society of Human Genetics Social Issues Subcommittee on Familial Disclosure. ASHG statement. Professional disclosure of familial genetic information. Available online.1998. Accessed 1-24-22.

Committee on Bioethics, Committee on Genetics, and American College of Medical Genetics and Genomics Social, Ethical, Legal Issues Committee. Ethical and policy issues in genetic testing and screening of children. Available online. 2013. Accessed 1-24-22.

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