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Lymphoproliferative Disease, X-Linked

[*Duncan Disease, XLPD*]

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Summary

Disease characteristics. The three most commonly recognized phenotypes of X-linked lymphoproliferative disease (XLP) are an inappropriate immune response to Epstein-Barr virus (EBV) infection resulting in unusually severe and often fatal infectious mononucleosis, dysgammaglobulinemia, and/or lymphoproliferative disorders typically of B-cell origin. Clinical manifestations of XLP vary even among affected members of the same family. The most common presentation is a near-fatal or fatal EBV infection associated with an unregulated and exaggerated immune response with widespread proliferation of cytotoxic T cells, EBV-infected B cells, and macrophages. Affected individuals typically have lymphadenopathy and hepatosplenomegaly with extensive parenchymal damage. In untreated males, mortality is higher than 90%; death is generally secondary to liver failure. In about one-third of males with XLP, hypogammaglobulinemia of one or more immunoglobulin subclasses is diagnosed prior to EBV infection or in rare survivors of EBV infection. The prognosis for males with this phenotype is more favorable if they are managed with regular IV IgG. Lymphomas or other lymphoproliferative disease occur in about one-third of males with XLP, 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, and particularly involving the intestine. Median survival overall for individuals with XLP is age ten years.

Diagnosis/testing. The diagnosis of XLP should be considered in males with any of the following: fatal or near-fatal Epstein-Barr virus (EBV)-induced infectious mononucleosis, especially in childhood or adolescence; immunodeficiency involving decreased T cells, B cells, and natural killer (NK) cells in association with hypogammaglobulinemia; lymphoma (generally, B-cell non-Hodgkin lymphoma); or presumptive diagnosis of common variable immunodeficiency (CVID) or hemophagocytic lymphohistiocytosis (HLH) with early mortality, especially in association with EBV. *SH2D1A*, encoding SH2 domain protein 1A, is

the only gene associated with XLP. Sequencing of the entire coding region of *SH2D1A* and exon/intron boundaries identifies about 97% of *SH2D1A* mutations in affected males who have two or more maternally related family members with an XLP phenotype and about 75% of *SH2D1A* mutations in obligate carrier females.

Management. Treatment for individuals with XLP who develop fulminant EBV infections with hemophagocytosis consists of etoposide, steroids, cyclosporin A often accompanied by rituximab (anti-CD20 antibody), and IV IgG for control of EBV infection. Once the individual is stabilized, allogeneic hematopoietic stem cell transplantation (HSCT) should be undertaken. HSCT is the only curative therapy and should be undertaken as soon as possible after confirmation of the diagnosis. For those who present with lymphoma, standard chemotherapy appropriate to the tumor diagnosis should be followed by allogeneic HSCT once lymphoma remission is achieved. Surveillance includes monitoring for evidence of EBV infection by EBV PCR at least every six months and more frequently if infectious-type symptoms develop.

Genetic counseling. XLP is inherited in an X-linked recessive manner. *De novo* mutations in *SH2D1A* are very rare; therefore, mothers of males with proven mutations in *SH2D1A* are very likely to be carriers of XLP. If the mother is a carrier, the chance of transmitting the disease-causing mutation in each pregnancy is 50%. Male sibs who inherit the mutation will be affected; female sibs who inherit the mutation will be carriers. Female carriers of XLP are asymptomatic and have no immunologic or biochemical markers of the disorder. Germline mosaicism has been reported in XLP; therefore, even if the disease-causing mutation is not identified in the mother, her offspring are at an increased risk for XLP. Carrier testing of at-risk female relatives is available if the mutation has been identified in an affected family member. Prenatal testing is possible for pregnancies of women who are carriers of a known *SH2D1A* mutation.

Diagnosis

Clinical Diagnosis

The diagnosis of X-linked lymphoproliferative disease (XLP) should be considered in males with any of the following:

- Fatal or near-fatal Epstein-Barr virus (EBV)-induced infectious mononucleosis or other viral illness (e.g. influenza, adenovirus), especially in childhood or adolescence
- Immunodeficiency involving decreased T cells, B cells, and natural killer (NK) cells in association with hypogammaglobulinemia
- Lymphoma (generally, B-cell non-Hodgkin lymphoma)
- Family history of one or more maternally-related males with an XLP phenotype or diagnosis
- Presumptive diagnosis of common variable immunodeficiency (CVID)
- Diagnosis of hemophagocytic lymphohistiocytosis (HLH) with early mortality, especially in association with EBV

The diagnosis of XLP is established in males with a mutation in *SH2D1A*.

Testing

Prior to an encounter with EBV, no uniform abnormalities are observed on laboratory testing of individuals with XLP. The following are seen in some individuals:

- Decreased numbers of lymphocyte subsets including decreased T cells, B cells, and NK cells

- Variably decreased NK cell function
- Dysgammaglobulinemia, most frequently manifest by low serum concentration of IgG with elevated serum concentration of IgM and/or IgA

Evidence of acute EBV infections is supported by the following:

- Heterophil antibodies or monospot testing
- EBV detection by polymerase chain reaction (PCR)
- Detection of EBV-specific IgM antibodies
- Atypical lymphocytosis on peripheral blood smear

Specific tests that suggest the diagnosis of XLP in males with severe EBV infections include the following:

- Markedly elevated liver transaminases
- Inverted CD4:CD8 ratio in peripheral blood
- Liver biopsy consistent with widespread necrosis during severe EBV infection
- Bone marrow biopsy with evidence of hemophagocytosis during severe EBV infection
- Positive EBV viral capsid antigen (VCA) titer, but negative Epstein-Barr virus nuclear antigen (EBNA) titer

Expression of SH2 domain protein 1A (signaling lymphocyte activation molecule [SLAM]-associated protein, or SAP) detected by flow cytometry is abnormally low or absent in individuals with XLP. Thus, SAP expression can be used as a rapid screen for XLP in individuals with EBV-induced HLH [Tabata et al 2005].

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene. *SH2D1A*, encoding SH2 domain protein 1A, is the only gene associated with XLP.

Molecular genetic testing: Clinical uses

- Confirmatory diagnosis
- Carrier testing
- Prenatal diagnosis

Molecular genetic testing: Clinical method

- **Sequence analysis** of the entire coding region of *SH2D1A* and exon/intron boundaries identifies nucleotide substitutions, small deletions, small insertions, small insertions/deletions, and small inversions. PCR-based sequencing can detect:
  - About 97% of *SH2D1A* mutations in affected males who have two or more maternally related family members with an XLP phenotype [Sumegi et al 2000];

- About 75% of mutations in obligate carrier females [Stenson et al 2003].

Note: Large deletions account for about 25% of mutations in families with XLP. Because males have one X chromosome, the absence of amplification of a region of a gene under stringent laboratory conditions implies that a large deletion or rearrangement is present. Because females have two X chromosomes, amplification of a region occurs even in the presence of a large deletion because of the contribution of the second X chromosome; thus, PCR-based sequencing does not accurately detect a large deletion.

Molecular genetic testing: Research

- **Deletion detection.** Southern blot analysis and multiplex ligation-dependent probe amplification (MLPA) can detect large deletions that are not detected by sequence analysis in females.

Table 1 summarizes molecular genetic testing for this disorder.

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

Test Methods	Mutations Detected	Mutation Detection Rate		Test Availability
		Affected Males	Carrier Females	
Gene amplification and sequence analysis	Nucleotide substitutions, small deletions/insertions, small inversions in *SH2D1A*	97%	75%	Clinical Testing
	Large deletions in *SH2D1A*		N/A	
Southern blot analysis/ MLPA analysis	Large deletions/insertions in *SH2D1A* in a female	N/A	25%	Research only

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

Testing Strategy for a Proband

SAP expression by flow cytometry may be used as a screening test prior to molecular genetic testing of *SH2D1A*; however, from a practical standpoint, waiting for results of SAP expression studies may delay molecular genetic testing by a week or more and may require additional blood draws and shipment of samples.

Because bone marrow transplantation becomes an option for acutely ill patients if a *SH2D1A* mutation is identified, *SH2D1A* molecular genetic testing should be used early in the investigation of the following:

- A severe EBV (or other virus) infection in a male child or adolescent
- Hemophagocytic lymphohistiocytosis (HLH) in a young male in whom molecular testing for *PRF1* and *UNC13D* is normal
- Recurrence of a B-cell (typically non-Hodgkins) lymphoma in a young male
- Immunodeficiency involving decreased T cells, B cells, and natural killer (NK) cells associated with hypogammaglobulinemia of uncertain etiology

If the immediate survival of the affected individual is in question, collection of materials for future characterization of underlying genetic defects is appropriate.

Genetically Related (Allelic) Disorders

No other phenotypes are known to be associated with mutations in *SH2D1A*.

Clinical Description

Natural History

The three most commonly recognized phenotypes of XLP are an inappropriate immune response to EBV infection resulting in unusually severe and often fatal infectious mononucleosis, dysgammaglobulinemia, and/or lymphoproliferative disorders typically of B-cell origin (see Table 2). Clinical manifestations of XLP vary even among affected members of the same family.

Table 2. Clinical Phenotypes of X-Linked Lymphoproliferative Disease

Phenotype	% of Individuals with XLP with this Phenotype	Mean Age of Onset (Years)	Survival Rate (%)
Fulminant infectious mononucleosis	58	5	4
Dysgammaglobulinemia	31	9	55
Lymphoproliferative disease	30	6	35
Aplastic anemia	3	8	50
Vasculitis/lymphomatoid granulomatosis	3	6.5	29

From Gaspar et al 2002

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

Median survival overall for individuals with documented XLP is age ten years. Survival into adulthood without allogeneic bone marrow transplantation (BMT) (also called hematopoietic stem cell transplantation [HSCT]) is unusual. The natural history of individuals diagnosed with the common variable immunodeficiency (CVID) phenotype and subsequently found to have a mutation in *SH2D1A* is not well documented at this time.

Fulminant infectious mononucleosis. The most common presentation 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 tissues may include spleen ("white pulp" necrosis), heart (mononuclear myocarditis), and kidney (mild interstitial nephritis). Mortality associated with EBV infection in individuals with XLP is higher than 90%.

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 about 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 about one-third of males with XLP, hypogammaglobulinemia of one or more immunoglobulin subclasses is diagnosed prior to EBV infection or in rare survivors of EBV infection. Some of these males were previously considered to have common variable immunodeficiency. All lymphoid cell lines can be affected including T cells, B cells, and natural killer (NK) cells. The prognosis for males with this phenotype is more favorable if they are managed with regular IV IgG (see Management).

Lymphoproliferative disease (malignant lymphoma). Lymphomas or other lymphoproliferative disease occurs in about one-third of males with XLP, 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. About 75% of lymphomas occur in the ileocecal region. Other sites include the central nervous system, liver, and kidney [Harrington et al 1987, Gaspar et al 2002]. The lymphomas can be histologically classified as Burkitt's lymphomas (53% of all B-cell lymphomas), immunoblastic lymphomas (12% of all cases), small cleaved or mixed-cell lymphomas (12%), and unclassifiable lymphomas (5% of all cases) [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. Although remission may follow chemotherapy, relapse or development of a second lymphoma or other manifestations of XLP is common [Gaspar et al 2002].

Common variable immunodeficiency (CVID) and hemophagocytic lymphohistiocytosis (HLH). *SH2D1A* mutations have been described in individuals with phenotypes that overlap with other immunodeficiencies including 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], and severe EBV-associated illness [Sumazaki et al 2001] (see Differential Diagnosis). These cases appear to represent the clinical variability of XLP; thus, a male with an identified *SH2D1A* mutation should be considered to have XLP and be managed accordingly.

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

Genotype-Phenotype Correlations

No good correlation exists between genotype and phenotype in XLP. Large deletions do not appear to be associated with a more severe phenotype. Considerable variability in phenotype can be present even within a family [Sumegi et al 2002].

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

Prevalence

The estimated prevalence of XLP is about 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.

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

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

The differential diagnosis of XLP includes the following:

- **Common variable immunodeficiency (CVID).** CVID is defined as low serum concentration of two out of three immunoglobulins (IgG, IgA, IgM) and abnormal production of specific antibodies. Symptoms include recurrent infections (especially of the respiratory tract) at any age. CVID has an estimated incidence of one in 50,000 and occurs equally in males and females. 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.
- **HLH.** Hemophagocytic lymphohistiocytosis 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 loci have been identified to date and clinical and/or research molecular testing is available.
  - 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 mutations 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 and no family history of affected females.
- **Severe EBV-associated illness.** About one in 1000 persons infected with EBV develop severe EBV-associated illness. XLP 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. Since mutations in *SH2D1A* have rarely been found in situations in which only one male is known to be affected in a family, it appears likely that some individuals with clinical symptoms consistent with XLP have an XLP-like disorder that has not yet been genetically defined.
- **Recurrent lymphoma.** XLP should be suspected in boys treated for lymphoma with standard chemotherapy who develop a second distinct lymphoma (not relapse) after achieving initial remission.
- **Chediak-Higashi syndrome** is characterized by partial albinism, abnormal platelet function, and severe immunodeficiency. The causative gene is *CHS1* [Barbosa et al

1996, Nagle et al 1996], encoding a protein involved in intracellular vesicle formation; mutations in *CHS1* result 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)** is a disorder of cytotoxic T lymphocytes caused by mutations in a small GTPase, *RAB27A*, which controls the movement of vesicles within cells [Menasche et al 2002]. GS2 is usually associated with neurologic abnormalities in addition to partial albinism with fair skin and silvery-grey hair. Inheritance is autosomal recessive.

Management

Evaluations at Initial Diagnosis to Establish the Extent of Disease

- Physical examination to evaluate for rashes, lymphadenopathy, hepatosplenomegaly, and neurologic dysfunction
- Evaluation of blood and bone marrow compartments (CBC and BM biopsy)
- Determination of the extent of liver involvement by measuring serum concentration of transaminases, bilirubin, triglycerides, sodium, and lactate dehydrogenase
- Identification of potential infectious co-factors (especially viral infection or reactivation) that would require specific treatment
- Testing to assess immune function including lymphocyte subsets (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 neuropsychologic assessment
- Evaluation of inflammatory factors including serum concentrations of ferritin, sIL2Rα, and other cytokines
- Evaluation and monitoring of PT, PTT, and fibrinogen

Treatment of Manifestations

Individuals with XLP who develop fulminant EBV infection with hemophagocytosis often improve with early treatment (e.g., the HLH-2004 protocol) similar to that used in other life-threatening genetic hemophagocytic disorders such as familial hemophagocytic lymphohistiocytosis (FHL) [Henter et al 1997], consisting of etoposide, steroids, cyclosporin A often accompanied by rituximab (anti-CD20 antibody), and IV IgG for control of EBV infection. Once the individual is stabilized, allogeneic hematopoietic stem cell transplantation (HSCT) should be undertaken.

For individuals with XLP who present with lymphoma, standard chemotherapy appropriate to the tumor diagnosis should be completed. Once lymphoma remission is achieved, the individual should quickly proceed to allogeneic HSCT.

Allogeneic BMT (also called HSCT) is the only curative therapy and should be undertaken in confirmed cases of XLP as early in life as feasible [Lankester et al 2005]. Successful outcomes have been reported with the use of matched sibling donors and marrow or umbilical cord blood from unrelated donors [Gross et al 1996, Filipovich 2001].

Prevention of Primary Manifestations

It is recommended that boys with known or suspected XLP receive regular intravenous (IV) IgG replacement therapy until definitive treatment can be provided even though earlier attempts to prevent EBV infection with the use of IV IgG and/or acyclovir prophylaxis have not been completely effective [Seemayer et al 1995].

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

Surveillance

Blood should be monitored by EBV PCR for evidence of EBV infection at least every six months and more frequently if the individual develops symptoms of infection.

Testing of Relatives at Risk

Once the disease-causing mutations have been identified in a proband, molecular genetic testing of at-risk siblings and other at-risk maternal male relatives is appropriate for medical management and consideration of presymptomatic bone marrow transplantation.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

X-linked lymphoproliferative disease is inherited in an X-linked recessive manner.

Risk to Family Members

Parents of a proband

- The father of an affected male will not have XLP, nor will he be a carrier of the *SH2D1A* mutation.
- In a family with more than one affected individual, the mother of an affected male is an obligate carrier. Female carriers of XLP are asymptomatic and have no immunologic or biochemical markers of the disorder.
- If pedigree analysis reveals that the proband is the only affected family member, the mother may be a carrier or the affected male may have a *de novo* gene mutation and, thus, the mother is not a carrier.
- If a woman has more than one affected son and the disease-causing mutation cannot be detected in DNA extracted from her leukocytes, she has germline mosaicism.

Sibs of a proband

- The risk to sibs depends upon the carrier status of the mother.
- If the mother is a carrier, the chance of transmitting the disease-causing mutation in each pregnancy is 50%. Male sibs who inherit the mutation will be affected; female sibs who inherit the mutation will be carriers. Female carriers of XLP are asymptomatic and have no immunologic or biochemical markers of the disorder.
- Germline mosaicism has been demonstrated [Schuster et al 1993]. Thus, even if the disease-causing mutation 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, affected males will live to reproduce following bone marrow transplantation and that the chemotherapy regimen used prior to BMT will not render them infertile.

Males will pass the disease-causing mutation to all of their daughters and none of their sons. Female carriers of XLP are asymptomatic and have no immunologic or biochemical markers of the disorder.

Other family members of a proband. The proband's other 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.

Carrier Detection

Carrier testing of at-risk female relatives is available on a clinical basis if the mutation has been identified in the proband.

If sequencing has not been performed on an affected male in the family, direct sequencing of the coding regions of *SH2D1A* is clinically available and detects about 75% of female carriers of XLP.

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Prenatal testing is possible for pregnancies of women who are carriers. The usual procedure is to determine the sex by performing chromosome analysis on fetal cells obtained by chorionic villus sampling (CVS) at about 10-12 weeks' gestation or by amniocentesis usually performed at about 15-18 weeks' gestation. If the karyotype is 46,XY and if the *SH2D1A* disease-causing mutation has been identified in a family member, DNA from fetal cells can be analyzed for the known disease-causing mutation.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified in an affected family member in a research or clinical laboratory. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Lymphoproliferative Disease, X-Linked

Gene Symbol	Chromosomal Locus	Protein Name
SH2D1A	Xq25	SH2 domain protein 1A

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Lymphoproliferative Disease, X-Linked

300490	SH2 DOMAIN PROTEIN 1A; SH2D1A
308240	LYMPHOPROLIFERATIVE SYNDROME, X-LINKED

Table C. Genomic Databases for Lymphoproliferative Disease, X-Linked

Gene Symbol	Locus Specific	Entrez Gene	HGMD
SH2D1A	SH2D1A	4068 (MIM No. 308240)	SH2D1A

For a description of the genomic databases listed, click here.

Normal allelic variants: The *SH2D1A* gene has four exons that span over 25 kb. No normal allelic variants of the *SH2D1A* gene are associated with a change in the amino acid sequence of this protein. Population studies of DNA from 50 normal females from southern Ohio identified several variants in the intronic sequence, but these are highly unlikely to have any pathologic effect on the SH2D1A protein [Zhang et al, unpublished].

Pathologic allelic variants: Over 60 pathologic mutations have been identified in the *SH2D1A* gene. Mutations have been found in all four exons. Mutations include deletions and insertions that lead to absence of a functional protein, mutations that interfere with transcription and splicing, nonsense mutations that lead to protein truncation, and missense mutations that affect protein function [Sumegi et al 2002]. One-half of these mutations are single nucleotide substitutions, one-quarter of the mutations are splicing defects or frame shift mutations, and one-quarter are large deletions. These mutations 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; Erdos et al 2005; Zhang et al 2006, unpublished].

Normal gene product: *SH2D1A* codes for a small, 128-amino acid protein, SH2 domain protein 1A (signalling lymphocyte activation molecular [SLAM]-associated protein, or SAP). The exact function of the protein is not known; recent studies suggest a probable role in signal transduction of activated T cells [Sayos et al 1998]. Northern blot analysis with probes generated from cDNA showed expression of an approximately 2.5-kb mRNA at high levels in thymus and lung, with a low level of expression in spleen and liver [Coffey et al 1998]. SAP is expressed in T cells, NK cells, NKT cells, eosinophils, platelets, and some B cells [Veillette 2006].

Abnormal gene product: *SH2D1A* mutations lead to changes in the amino acid sequence and truncation or absence of SAP, which disrupts binding to SLAM [Sayos et al 1998, Morra et al 2001]. SAP controls the signal-transduction pathways initiated by interactions between SLAM

molecules at the interface between T and B cells. Mutations in *SH2D1A* could also interfere with 2B4 binding on the basis of its strong homology to SLAM [Benoit et al 2000]. It is likely that additional functions that could be disturbed by certain mutations of *SH2D1A* will be defined in the future.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

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Fax: 410-321-9165
Email: idf@primaryimmune.org
www.primaryimmune.org

Jeffrey Modell Foundation/National Primary Immunodeficiency Resource Center
747 Third Avenue 34A
New York NY 10017
Phone: 800-533-3844; 212-819-0200
Fax: 212-764-4180
Email: info@jmfworld.org
www.info4pi.org

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

American Society of Human Genetics and American College of Medical Genetics (1995) Points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents

American Society of Human Genetics Social Issues Subcommittee on Familial Disclosure (1998) ASHG statement. Professional disclosure of familial genetic information. *Am J Hum Genet* 62:474-83 [Medline]

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Suggested Readings

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Chapter Notes

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