X-linked lymphoproliferative disease

Description

X-linked lymphoproliferative disease (XLP) is a disorder of the immune system and blood-forming cells that is found almost exclusively in males. More than half of individuals with this disorder experience an exaggerated immune response to the Epstein-Barr virus (EBV). EBV is a very common virus that eventually infects most humans. In some people it causes infectious mononucleosis (commonly known as " mono"). Normally, after initial infection, EBV remains in certain immune system cells (lymphocytes) called B cells. However, the virus is generally inactive (latent) because it is controlled by other lymphocytes called T cells that specifically target EBV-infected B cells.

People with XLP may respond to EBV infection by producing abnormally large numbers of T cells, B cells, and other lymphocytes called macrophages. This proliferation of immune cells often causes a life-threatening reaction called hemophagocytic lymphohistiocytosis. Hemophagocytic lymphohistiocytosis causes fever, destroys blood-producing cells in the bone marrow, and damages the liver. The spleen, heart, kidneys, and other organs and tissues may also be affected. In some individuals with XLP, hemophagocytic lymphohistiocytosis or related symptoms may occur without EBV infection.

About one-third of people with XLP experience dysgammaglobulinemia, which means they have abnormal levels of some types of antibodies. Antibodies (also known as immunoglobulins) are proteins that attach to specific foreign particles and germs, marking them for destruction. Individuals with dysgammaglobulinemia are prone to recurrent infections.

Cancers of immune system cells (lymphomas) occur in about one-third of people with XLP.

Without treatment, most people with XLP survive only into childhood. Death usually results from hemophagocytic lymphohistiocytosis.

XLP can be divided into two types based on its genetic cause and pattern of signs and symptoms: XLP1 (also known as classic XLP) and XLP2. People with XLP2 have not been known to develop lymphoma, are more likely to develop hemophagocytic lymphohistiocytosis without EBV infection, usually have an enlarged spleen (splenomegaly), and may also have inflammation of the large intestine (colitis). Some

researchers believe that these individuals should actually be considered to have a similar but separate disorder rather than a type of XLP.

Frequency

XLP1 is estimated to occur in about 1 per million males worldwide. XLP2 is less common, occurring in about 1 per 5 million males.

Causes

Mutations in the *SH2D1A* and *XIAP* genes cause XLP. *SH2D1A* gene mutations cause XLP1, and *XIAP* gene mutations cause XLP2.

The *SH2D1A* gene provides instructions for making a protein called signaling lymphocyte activation molecule (SLAM) associated protein (SAP). This protein is involved in the functioning of lymphocytes that destroy other cells (cytotoxic lymphocytes) and is necessary for the development of specialized T cells called natural killer T cells. The SAP protein also helps control immune reactions by triggering self-destruction (apoptosis) of cytotoxic lymphocytes when they are no longer needed.

Some *SH2D1A* gene mutations impair SAP function. Others result in an abnormally short protein that is unstable or nonfunctional, or prevent any SAP from being produced. The loss of functional SAP disrupts proper signaling in the immune system and may prevent the body from controlling the immune reaction to EBV infection. In addition, lymphomas may develop when defective lymphocytes are not properly destroyed by apoptosis.

The *XIAP* gene provides instructions for making a protein that helps protect cells from undergoing apoptosis in response to certain signals. *XIAP* gene mutations can lead to an absence of XIAP protein or decrease the amount of XIAP protein that is produced. It is unknown how a lack of XIAP protein results in the signs and symptoms of XLP, or why features of this disorder differ somewhat between people with *XIAP* and *SH2D1A* gene mutations.

Learn more about the genes associated with X-linked lymphoproliferative disease

- SH2D1A
- XIAP

Inheritance

This condition is generally inherited in an X-linked recessive pattern. The genes associated with this condition are located on the X chromosome, which is one of the two sex chromosomes. In males (who have only one X chromosome), one altered copy of an associated gene in each cell is sufficient to cause the condition. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons.

In females (who have two X chromosomes), a mutation usually has to occur in both copies of the gene to cause the disorder. Because it is unlikely that females will have two altered copies of an associated gene, males are affected by X-linked recessive disorders much more frequently than females. However, in rare cases a female carrying one altered copy of the *SH2D1A* or *XIAP* gene in each cell may develop signs and symptoms of this condition.

Other Names for This Condition

- Duncan disease
- Epstein-Barr virus-induced lymphoproliferative disease in males
- Familial fatal Epstein-Barr infection
- Purtilo syndrome
- Severe susceptibility to EBV infection
- Severe susceptibility to infectious mononucleosis
- X-linked lymphoproliferative syndrome
- XLP

Additional Information & Resources

Genetic Testing Information

- Genetic Testing Registry: X-linked lymphoproliferative disease due to SH2D1A deficiency (https://www.ncbi.nlm.nih.gov/gtr/conditions/C5399825/)
- Genetic Testing Registry: X-linked lymphoproliferative disease due to XIAP deficiency (https://www.ncbi.nlm.nih.gov/gtr/conditions/C1845076/)
- Genetic Testing Registry: X-linked lymphoproliferative syndrome (https://www.ncbi.nlm.nih.gov/gtr/conditions/C0549463/)

Genetic and Rare Diseases Information Center

- X-linked lymphoproliferative disease (https://rarediseases.info.nih.gov/diseases/10915/index)

Patient Support and Advocacy Resources

- National Organization for Rare Disorders (NORD) (https://rarediseases.org/)

Clinical Trials

- ClinicalTrials.gov (https://clinicaltrials.gov/search?cond=%22X-linked lymphoproliferative disease%22)

Catalog of Genes and Diseases from OMIM

- LYMPHOPROLIFERATIVE SYNDROME, X-LINKED, 2; XLP2 (https://omim.org/entry/300635)
- LYMPHOPROLIFERATIVE SYNDROME, X-LINKED, 1; XLP1 (https://omim.org/entry/308240)

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28Lymphoproliferative+Disorders%5BMAJR%5D%29+AND+%28%28x-linked+lymphoproliferative+disease%5BTIAB%5D%29+OR+%28xlp%5BTIAB%5D%29+OR+%28purtilo+syndrome%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D)

References

- Bassiri H, Janice Yeo WC, Rothman J, Koretzky GA, Nichols KE. X-linkedlymphoproliferative disease (XLP): a model of impaired anti-viral, anti-tumor andhumoral immune responses. Immunol Res. 2008;42(1-3):145-59. doi:10.1007/s12026-008-8048-7. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/18815745)
- Latour S. Natural killer T cells and X-linked lymphoproliferative syndrome.Curr Opin Allergy Clin Immunol. 2007 Dec;7(6):510-4. doi:10.1097/ACI.0b013e3282f1bad6. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/17989527)
- Marsh RA, Madden L, Kitchen BJ, Mody R, McClimon B, Jordan MB, Bleesing JJ, Zhang K, Filipovich AH. XIAP deficiency: a unique primary immunodeficiency bestclassified as X-linked familial hemophagocytic lymphohistiocytosis and not asX-linked lymphoproliferative disease. Blood. 2010 Aug 19;116(7):1079-82. doi:10.1182/blood-2010-01-256099. Epub 2010 May 20. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/20489057) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2938130/)
- Marsh RA, Villanueva J, Kim MO, Zhang K, Marmer D, Risma KA, Jordan MB, Bleesing JJ, Filipovich AH. Patients with X-linked lymphoproliferative diseasedue to BIRC4 mutation have normal invariant natural killer T-cell populations.Clin Immunol. 2009 Jul;132(1):116-23. doi: 10.1016/j.clim.2009.03.517. Epub 2009Apr 23. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/19398375) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2729708/)
- Nagy N, Klein E. Deficiency of the proapoptotic SAP function in X-linkedlymphoproliferative disease aggravates Epstein-Barr virus (EBV) inducedmononucleosis and promotes lymphoma development. Immunol Lett. 2010 May4;130(1-2):13-8. doi: 10.1016/j.imlet.2010.01.002. Epub 2010 Jan 18. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/20080127)

- Nagy N, Matskova L, Hellman U, Klein G, Klein E. The apoptosis modulating roleof SAP (SLAM associated protein) contributes to the symptomatology of the Xlinked lymphoproliferative disease. Cell Cycle. 2009 Oct 1;8(19):3086-90. doi:10.4161/cc.8.19.9636. Epub 2009 Oct 27. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/19738428)
- Rigaud S, Fondaneche MC, Lambert N, Pasquier B, Mateo V, Soulas P, Galicier L, Le Deist F, Rieux-Laucat F, Revy P, Fischer A, de Saint Basile G, Latour S. XIAPdeficiency in humans causes an X-linked lymphoproliferative syndrome. Nature. 2006 Nov 2;444(7115):110-4. doi: 10.1038/nature05257. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/17080092)
- Schuster V, Kreth HW. X-linked lymphoproliferative disease is caused bydeficiency of a novel SH2 domain-containing signal transduction adaptor protein.Immunol Rev. 2000 Dec;178:21-8. doi: 10.1034/j.1600-065x.2000.17819.x. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/11213803)
- Snow AL, Marsh RA, Krummey SM, Roehrs P, Young LR, Zhang K, van Hoff J, DharD, Nichols KE, Filipovich AH, Su HC, Bleesing JJ, Lenardo MJ.Restimulation-induced apoptosis of T cells is impaired in patients with X-linkedlymphoproliferative disease caused by SAP deficiency. J Clin Invest. 2009Oct;119(10):2976-89. doi: 10.1172/JCI39518. Epub 2009 Sep 14. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/19759517) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2752081/)
- Woon ST, Ameratunga R, Croxson M, Taylor G, Neas K, Edkins E, Browett P, GaneE, Munn S. Follicular lymphoma in a X-linked lymphoproliferative syndrome carrierfemale. Scand J Immunol. 2008 Aug;68(2):153-8. doi:10.1111/j.1365-3083.2008.02128.x. Erratum In: Scand J Immunol. 2008Sep;68(3):362. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/18702745)
- Zhang K, Wakefield E, Marsh R. Lymphoproliferative Disease, X-Linked. 2004 Feb27 [updated 2016 Jun 30]. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, WallaceSE, Bean LJH, Gripp KW, Amemiya A, editors. GeneReviews(R) [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available fromhttp://www.ncbi.nlm.nih.gov/books/NBK1406/ Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/20301580)

Last updated May 17, 2021