



# Cancer Predisposition Clinic

## **X-linked Lymphoproliferative Syndrome**

*Also called: Duncan disease; Purtilo syndrome; X-linked progressive combined variable immunodeficiency*

### **What is X-linked lymphoproliferative syndrome (XLP)?**

X-linked lymphoproliferative syndrome (XLP) is a very rare disorder in which the immune system does not work properly. People with XLP have an increased chance to develop a severe reaction called fulminant infectious mononucleosis (FIM). With FIM too many immune cells become activated and build up in different parts of the body, including the liver, spleen, bone marrow and brain. This reaction is sometimes also called “hemophagocytic lymphohistiocytosis” (HLH). FIM/HLH usually presents with the following signs and symptoms:

- High fever
- Enlarged spleen
- Low levels of blood cells, including white blood cells (immune cells), red blood cells (cells that carry oxygen to body tissues), and platelets (cells that help the blood to clot).
- Improper levels of certain chemicals or proteins in the blood
- Inflammation (swelling) in the liver, bone marrow and brain

Without treatment, FIM/HLH can lead to severe organ damage and death.

People with XLP are almost always male. The condition is diagnosed in fewer than 1 out of 1,000,000 boys or young men per year. How severe the condition is will be hard to predict and can be different in different people who have it, even among members of the same family.

There are two types of XLP: XLP-1 and XLP-2. People with XLP-1 develop FIM/HLH after becoming infected with the Epstein-Barr virus. Normally, the Epstein-Barr virus causes a person to develop infectious mononucleosis, or “mono”. Having “mono” is very common among children and teenagers. People with “mono” have a sore throat, swollen glands, fever and tiredness. They usually get better on their own after one to several weeks. In contrast, a person with XLP-1 usually cannot properly eliminate the Epstein-Barr virus, and instead, they are at risk to develop FIM/HLH.

People with XLP-2 are also at increased risk to develop HLH. Those with XLP-2 may develop HLH following infection with a variety of viruses and other pathogens, not just Epstein Barr virus.

## **What other symptoms are seen in people with X-linked lymphoproliferative syndrome?**

Boys with XLP may develop other medical problems. The risk of developing these problems varies depending on whether a boy has XLP-1 or XLP-2. Not all boys with XLP develop these problems. It is not possible to predict which boys with XLP-1 or XLP-2 will develop specific health problems.

X-linked lymphoproliferative syndrome type 1 (XLP-1):

- Cancer of the immune cells (lymphoma)
- Too few antibodies in the bloodstream (hypogammaglobulinemia). Antibodies are proteins which are needed to help fight infections.
- Failure of the bone marrow to produce enough blood cells (aplastic anemia)
- Inflammation (swelling) of small blood vessels (vasculitis) in the lungs, eyes, brain or other organs

X-linked lymphoproliferative syndrome type 2 (XLP-2):

- Enlarged spleen (splenomegaly)
- Too few antibodies in the bloodstream (hypogammaglobulinemia)
- Failure of the bone marrow to produce enough blood cells (aplastic anemia)
- Inflammation (swelling) of the large intestine (colitis)
- Inflammation (swelling) of small blood vessels (vasculitis) in the lungs, eyes, brain or other organs

## **What is the cancer risk for people with X-linked lymphoproliferative syndrome?**

About 25% of people with XLP-1 (1 in 4) will develop immune cell cancer (lymphoma) during their lifetimes. People with XLP-2 have no greater a cancer risk than what is seen in the general population.

## **What causes X-linked lymphoproliferative syndrome?**

Most cells in the body have 46 chromosomes each. Chromosomes are made of DNA and contain our genes. Genes carry information telling cells within the body how to function. Sometimes a gene becomes changed and no longer works properly. These changes are called mutations.

Usually each cell has two copies of every chromosome (these are numbered 1 through 22), along with a pair of sex chromosomes, called “X” and “Y.” Females have two X chromosomes, one inherited from their mother and one inherited from their father. Males have one X chromosome inherited from their mother and one Y chromosome inherited from their father. Because males only have one X chromosome, their cells contain only one copy of the genes that are on the X chromosome. That gene copy is inherited from their mother. They do not inherit any copy of those particular genes from their father.

Mutations in one of two genes can cause X-linked lymphoproliferative syndrome. Both of those genes are on the X chromosome. Mutations in a gene called *SH2D1A* cause XLP-1. The *SH2D1A* gene produces a protein called SAP, which controls how white blood cells combat infections such as Epstein-Barr virus. SAP also controls how a person produces antibodies and cytokines, molecules that help the body respond to infection and damage. When changes in the *SH2D1A* gene are present, usually less SAP protein is produced. Sometimes, an abnormal protein is produced, but it is unable to function properly.

Mutations in a gene called *XIAP* (also known as *BIRC4*) cause XLP-2. The *XIAP* gene produces a protein known as X-linked inhibitor of apoptosis (XIAP), which helps to prevent cell death and to control how the immune system works. When changes in the *XIAP* gene are present, usually less XIAP protein is produced. It is not yet understood how this causes the features of XLP-2.

Because the *SH2D1A* and *XIAP* genes reside on the X chromosome, a change in either of these genes will affect females and males differently.

Females:

- A female with two working copies of *SH2D1A* or *XIAP* will not have X-linked lymphoproliferative syndrome. She also cannot pass a mutation in either of these genes on to her children.
  
- A female with one working copy and one mutated copy of either *SH2D1A* or *XIAP* does not have X-linked lymphoproliferative syndrome. She is called a “carrier”. Despite having a mutation in one of her two gene copies, carrier females generally do not develop XLP-1. To date, only very rare females have shown the signs and symptoms of XLP-2. Female carriers have a 50% (1 in 2) chance to pass the mutated copy of the *SH2D1A* or *XIAP* gene on to her children. If the mother passes the mutated copy of the *SH2D1A* or *XIAP* gene to a daughter, that daughter will be a carrier. If the mother passes the mutated copy of the *SH2D1A* or *XIAP* gene to a son, that son will have X-linked lymphoproliferative disease. the son will be at risk to develop the health problems related to this condition.

Males:

- A male whose copy of *SH2D1A* or *XIAP* is working will not have X-linked lymphoproliferative syndrome. He also cannot pass a mutation on to his children.
  
- A male whose copy of *SH2D1A* or *XIAP* is mutated will have X-linked lymphoproliferative syndrome. If he has any daughters, he will pass the mutation on to them, and they will be carriers. He will not pass the mutation on to any sons he might have, because a man always passes his Y chromosome on to his sons.

### **How are children with X-lined lymphoproliferative syndrome screened for cancer?**

Children with X-linked lymphoproliferative syndrome are not usually screened for lymphoma because the age at which it may develop can vary widely. People with the condition should watch closely for general signs or symptoms of lymphoma, including the following:

- One or more firm or enlarged lymph nodes (glands)
- Feeling tired
- Fever
- Weight loss
- Night sweats
- Trouble breathing

If any of these signs or symptoms occur and do not go away in a reasonable period of time, it is important to be checked by a health care provider who knows X-linked lymphoproliferative syndrome well. These could be the signs of possible lymphoma.

### **How are people with X-linked lymphoproliferative syndrome treated?**

Health care providers offer a variety of treatments depending on the underlying cause and severity of symptoms. Because XLP is a very complex condition, parents should seek out a health care provider that knows this condition well. Only a health care provider who is familiar with the condition should offer treatment for XLP.

Currently, the only way to cure XLP is with a stem cell transplant. The transplant replaces the abnormal immune system with a normal immune system from a person who does not have XLP. Hemophagocytic lymphohistiocytosis (HLH) is often treated with immune suppressing medicines, such as steroids and chemotherapy. The goal is to stabilize the person until a stem cell transplant can be performed. Lymphoma is treated with chemotherapy. Colitis is treated with immune suppressing medicines such as steroids. Hypogammaglobulinemia (too few antibodies in the blood) is treated with infusions of antibodies every three to four weeks.

### **How is genetic testing for X-linked lymphoproliferative syndrome done?**

If the health care provider or genetic counselor suspects XLP in a child, one of them will perform a test that looks at the levels of the SAP or XIAP protein in the child's white blood cells. The health care provider or genetic counselor may also recommend testing of the *SH2D1A* and *XIAP* genes.

### **Diagnostic genetic testing**

If the health care provider or genetic counselor suspects that a person has X-linked lymphoproliferative syndrome or may be a carrier for the condition, diagnostic testing may take place as follows:

- A blood sample is collected.
- DNA is isolated from the cells in the sample. A person's genes are made of DNA.
- All copies of the person's *SH2D1A* and *XIAP* genes are checked for possible changes (two copies for females, one copy for males). A genetic specialist compares the person's *SH2D1A* and *XIAP* genes to normal copies of those genes. If there are differences, the specialist decides if they might cause a certain condition such as X-linked lymphoproliferative syndrome.

- If mutations are found in the *SH2D1A* or *XIAP* genes, the genetic counselor will work with the family in the following ways:
  - To help the family understand the risks of X-linked lymphoproliferative syndrome
  - To find out if other family members should consider testing for the mutation
  - To help with decisions about prenatal genetic testing.

It is important to remember that genetic testing does not always find mutations in the *SH2D1A* or *XIAP* genes for all people with symptoms that suggest XLP. There are other medical conditions that can look like this disorder. These include the following:

- Lymphoproliferative syndrome caused by mutations in the *ITK* gene (also known as ITK deficiency): Mutations in the *ITK* gene cause symptoms similar to those seen in XLP, including hypogammaglobulinemia, anemia, swollen lymph nodes, enlarged liver and spleen, and lymphoma. XLP-1 and XLP-2 only affect boys and are caused by mutations in genes on the X chromosome. On the other hand, ITK deficiency is caused by mutations affecting both copies of the *ITK* gene, which is located on chromosome 5.
- X-linked immunodeficiency with magnesium defect, Epstein-Barr virus infection, and neoplasia (XMEN) caused by mutations in the *MAGT1* gene. Patients with mutations in *MAGT1* often develop recurrent infections (including Epstein Barr virus). They also see defects involving immune system cells and lymphoma. Like XLP1 and XLP2, XMEN is inherited on the X chromosome.

Because these some other immunodeficiency syndromes share several features with XLP, the health care provider or genetic counselor might recommend more genetic testing of the *ITK* and *MAGT1* genes depending on the patient's personal and family history.

### **Prenatal genetic testing**

Parents may undergo prenatal testing to find out if the pregnancy is affected with known *SH2D1A* or *XIAP* gene mutations in the family. Testing may take place either before pregnancy occurs or during pregnancy.

People considering prenatal testing should work with a genetic counselor to review the pros and cons of testing. The genetic counselor can also help parents consider how they wish to handle the results of the testing.

**Testing that occurs before pregnancy**— Testing that happens before pregnancy is called preimplantation genetic testing (PGT). This special type of genetic testing is done along with in vitro fertilization (IVF). PGT offers a way to test embryos for known *SH2D1A* or *XIAP* gene mutations before placing them into the uterus.

**Testing that occurs during pregnancy**—Testing can be used to see if a pregnancy is affected with known *SH2D1A* or *XIAP* gene mutations. A doctor gathers cells from the pregnancy in one of two ways:

- **Chorionic villus sampling (CVS)**—during the first trimester (first three months)
- **Amniocentesis**—during the second trimester or later (last six months)

Collected tissue can be checked for the presence of the *SH2D1A* or *XIAP* gene mutations identified in the family.

Both of these tests carry minor risks and should be discussed with an experienced doctor or genetic counselor.

### **Special concerns**

Genetic testing for XLP is a complex process. Those thinking about testing should take time to consider the benefits and risks. They should discuss the process with a genetic counselor before testing is done. If they choose testing, they should review the test results with the health care provider or genetic counselor to be sure they understand the meaning of the results.

Sometimes children or adults with XLP can feel sad, anxious or angry. Parents who pass on *SH2D1A* or *XIAP* gene mutations to one or more of their children can feel guilty. Some people with *SH2D1A* or *XIAP* gene mutations could have trouble getting disability coverage, life insurance or long-term care insurance in some states. [Read more about genetic discrimination.](#)

### **Are there other special health care needs for children with X-linked lymphoproliferative syndrome?**

People of any age with XLP should be watched closely for fever and the other signs and symptoms of FIM/HLH (please see above). If any of these occur, it is important to seek medical help right away since early treatment ensures the best chances for cure.

### **What other information and resources are there for children with X-linked lymphoproliferative syndrome and their families?**

- XLP Research Trust  
([www.xlpresearchtrust.org/](http://www.xlpresearchtrust.org/))
- National Organization for Rare Disorders— X-linked Lymphoproliferative Syndrome  
([rarediseases.org/rare-diseases/x-linked-lymphoproliferative-syndrome/](http://rarediseases.org/rare-diseases/x-linked-lymphoproliferative-syndrome/))
- Jeffrey Modell Foundation  
([www.info4pi.org](http://www.info4pi.org))

More resources about genetic testing and hereditary cancer:

- Making Sense of Your Genes: A Guide to Genetic Counseling  
([www.ncbi.nlm.nih.gov/books/NBK115508/](http://www.ncbi.nlm.nih.gov/books/NBK115508/))
  - Young People with Cancer: A Parent's Guide  
([www.cancer.gov/publications/patient-education/young-people](http://www.cancer.gov/publications/patient-education/young-people))
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**Sources:**

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<https://www.ncbi.nlm.nih.gov/books/NBK1406/>
3. National Organization for Rare Disorders – X-linked lymphoproliferative syndrome  
<https://rarediseases.org/rare-diseases/x-linked-lymphoproliferative-syndrome/>
4. UpToDate – X-linked lymphoproliferative disease  
<https://www.uptodate.com/contents/x-linked-lymphoproliferative-disease>

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