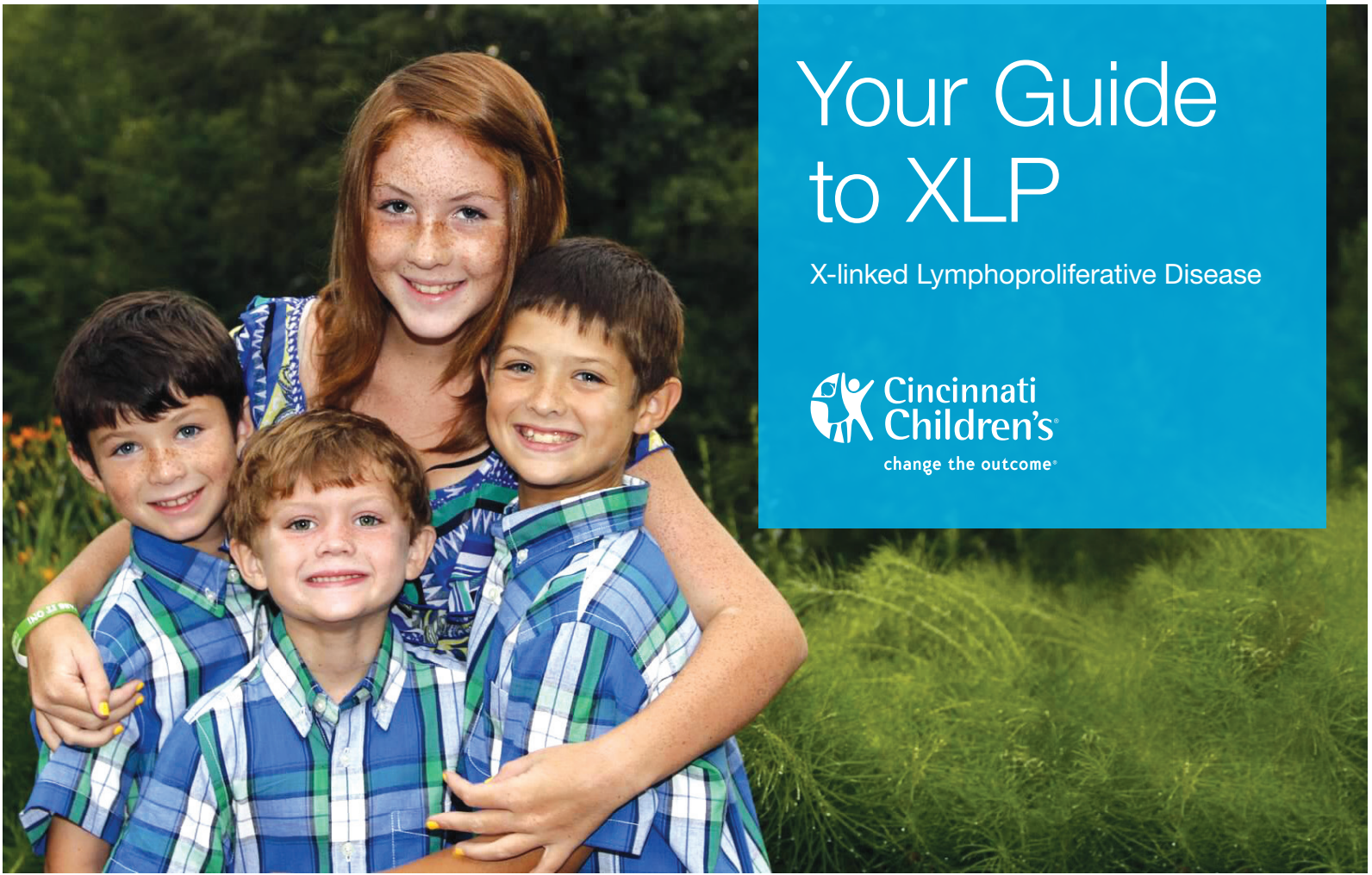

Your Guide to XLP

X-linked Lymphoproliferative Disease

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What is XLP?

XLP stands for X-linked lymphoproliferative disease. XLP is a genetic condition where the immune system doesn't work as it should. XLP mainly affects male patients. There are 2 types of XLP: XLP1 and XLP2.

What causes XLP?

XLP can be caused by variations in the genetic makeup of a person. Genes are part of our genetic makeup and provide the instructions our cells need to perform their different roles within our bodies. XLP can be caused by changes or mutations in either of two genes: SH2D1A or XIAP/BIRC4. When these genes are defective, the immune system doesn't function correctly, and the symptoms of XLP develop.

What are the differences between XLP1 and XLP2?

XLP1
Caused by mutations in SH2D1A
Results in either absence or poor function of the protein SAP
Often referred to as the protein defect it causes, SAP deficiency
Associated with HLH, lymphoma, and hypogammaglobulinemia, and other more rare manifestations

XLP2
Caused by mutations in XIAP/BIRC4
Results in either absence or poor function of the protein XIAP
Often referred to as the protein defect it causes, XIAP deficiency
Associated with HLH, hypogammaglobulinemia, recurrent fevers, recurrent low blood counts, splenomegaly and inflammatory bowel disease
Not associated with lymphoma

What are the symptoms of XLP?

The symptoms of XLP and the ages of onset vary greatly among patients, even among patients in the same family. Some symptoms of XLP1 and XLP2 include:

- **HLH**: Patients with XLP1 and XLP2 can both develop hemophagocytic lymphohistiocytosis (HLH). Symptoms of HLH include persistent fevers, rash, enlarged liver and/or spleen, enlarged lymph nodes, anemia, low platelets, low white blood cells, bleeding or easy bruising, jaundice, hepatitis, liver failure, respiratory problems, seizures and altered mental function. Patients may also have general symptoms of a virus infection at the start of illness, such as sore throat and fatigue.
- **Hypogammaglobulinemia**: Patients with XLP1 and XLP2 can both develop low antibody levels (hypogammaglobulinemia). Low antibody levels can lead to recurrent infections such as ear infections, sinus infections, pnueumonia, blood stream infections and other illnesses.
- **Lymphoma**: Only patients with XLP1 develop lymphoma. Patients with lymphoma may develop fatigue, fevers, easy bruising, pale appearance, body aches, weight loss and swollen lymph nodes in the neck, armpit, groin or abdomen.
- **Recurrent fevers, splenomegaly and low blood counts**: Patients with XLP2 are likely to develop recurring fevers, low blood counts and enlarged spleens, but without the full picture of HLH.
- **Inflammatory bowel disease**: Patients with XLP2 are also at risk of developing inflammatory bowel disease, which is often diagnosed as Crohn's disease. Symptoms may include abdominal pain, diarrhea or gastrointestinal bleeding.

What is HLH?

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening systemic inflammatory syndrome that may be triggered by viruses or other problems. A common virus associated with HLH in patients with XLP is Epstein-Barr virus (EBV), the virus that causes mono.

XLP Diagnosis & Treatment

Complications Associated with XLP1

	PERCENTAGE OF PATIENTS
HLH	45-58%
Low Antibody Levels	31-67%
Lymphoma	21-30%

Table 1. Manifestations of SAP deficiency (XLP1). Based on Seemayer et al 1995, Pachlopnik Schmid et al 2011, Kanegane et al 2012, Booth et al 2011.

Complications Associated with XLP2

	PERCENTAGE OF PATIENTS
HLH	67-90%
Incomplete HLH (Splenomegaly +/- Low Blood Counts +/- Fever)	33-87%
Low Antibody Levels	22-33%
Inflammatory Bowel Disease	17-22%

Table 2. Manifestations of XIAP deficiency (XLP2). Based on Pachlopnik Schmid et al 2011, Yang et al 2012, Marsh et al 2010.

How are XLP1 and XLP2 diagnosed?

Both disorders are usually diagnosed by genetic testing and/or protein testing by flow cytometry. Testing is usually done with blood samples.

Are there other names for XLP1 and XLP2?

It is sometimes debated whether patients with XIAP/BIRC4 mutations should be classified as having XLP1 or XLP2. We often refer to these diseases simply by the protein defect they cause. XLP1 may be referred to as SAP deficiency and XLP2 may be referred to as XIAP deficiency. Both disorders are sometimes lumped with other diseases which cause hemophagocytic lymphohistiocytosis (HLH).

What is the treatment for HLH, XLP1 and XLP2?

Patients need treatment of HLH when it occurs. Treatment can involve steroids, other immune suppressive medications, monoclonal antibody therapies and chemotherapy. Patients with XLP1 who develop lymphoma need current standard-of-care lymphoma treatment. Low antibody levels are often treated with immunoglobulin replacement (IVIG or subcutaneous antibody replacement). Immune suppression is often needed for patients with inflammatory bowel disease. The only cure for XLP1 and XLP2 at this time is bone marrow transplant.

Is a bone marrow transplant for XLP the best option for every patient?

Only your doctor can answer this question. Many patients with XLP1 or XLP2 should be considered for a bone marrow transplant. However, the decision to do a transplant should be made only after a thorough evaluation of the patient's health status and after a bone marrow search has been performed to see if a suitable bone marrow or other stem cell donor is available.

Sometimes siblings can be the bone marrow donor. Importantly, patients with XLP2 should almost always be treated with a reduced intensity conditioning regimen in order to avoid toxicities and optimize outcomes. Patients with XLP1 may also be treated with a reduced intensity conditioning regimen.

What about vaccinations for patients with XLP1 and XLP2?

Patients with XLP1 and XLP2 should avoid all live virus vaccines (MMR, rotavirus, chicken pox/varicella).

How is HLH diagnosed?

Only a doctor can diagnose HLH. In addition to the symptoms listed on the previous page, HLH is suspected in some patients who also have characteristic laboratory markers, such as elevated levels of ferritin or the soluble IL-2 receptor or the observation of hemophagocytosis on bone marrow or other biopsy specimens.

Genetics & Resources

How is XLP inherited?

XLP1 and XLP2 are both X-linked diseases, which means the genes which cause them are located on the X chromosome. Affected boys have an X chromosome that has a mutated or “bad copy” of the SH2D1A or XIAP/BIRC4 gene. Mothers or sisters of patients with XLP may also have an X chromosome that has a bad copy of the SH2D1A or XIAP/BIRC4 gene, but since females have two X chromosomes, most females will never have any symptoms of disease because there is a normal copy of the gene on their other X chromosome. Very rarely, female carriers may also develop symptoms of XLP. In most cases, affected patients inherit the X chromosome with the bad copy of the gene from their mother. In some cases, the mutation spontaneously occurs in the affected child.

I am an XLP carrier. What are the chances my children are affected?

Women who have a bad copy of an XLP gene on one of their X chromosomes are called carriers. For these women, every pregnancy has a 50% chance of receiving the X chromosome with the bad copy of the gene. Every male child of an XLP carrier has a 50% chance of being affected by XLP. Every female child has a 50% chance of being a carrier but will probably never be sick, though their future male children may be affected.

My son was diagnosed with XLP. Do my other children need to be tested?

Your physician may recommend testing the patient's mother first to see if she is a carrier and then proceed to evaluate other children in the family. Or your physician may test the other children right away. Testing may even need to be performed in aunts, uncles and cousins within the family. Your physician or genetic counselor can tell you more about testing.

Where can I find more resources on XLP?

Cincinnati Children's Hospital Medical Center
www.cincinnatichildrens.org

XLP Research Trust
www.xlpresearchtrust.org

Matthew and Andrew Akin Foundation
www.matthewandandrew.org

For information about Bone Marrow Transplant:
National Bone Marrow Registry Be the Match
www.bethematch.org

How can Cincinnati Children's help?

To learn more about XLP and HLH or to inquire about treatment at Cincinnati Children's, contact:

HLH Center of Excellence
hlh@cchmc.org
513-803-3872 or 877-920-3590
www.cincinnatichildrens.org/hlh

On the Cover:

Pictured with their sister Julia (a bone marrow donor) are brothers John, Will and Matthew, who were all diagnosed with XLP.

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