



Cancer Predisposition Clinic

Familial Hemophagocytic Lymphohistiocytosis (HLH)

Also called: Familial Erythrophagocytic Lymphohistiocytosis

What is HLH?

HLH is not one condition. It is the name for a group of rare conditions in which the immune system no longer works properly.

In healthy people, white blood cells are the part of the immune system that helps to fight infection. Two important kinds of white blood cells are called “cytotoxic T cells” and “natural killer” cells. One way these white blood cells help fight infections is by killing cells that have been infected with viruses or other germs. These cells also make chemicals called “cytokines” and release them into the blood. Cytokines attract cells to the site of infection, and they help to regulate the immune response.

In patients with HLH, cytotoxic T cells and natural killer cells do not kill as well as they should. They also release too many cytokines. As a result, too many activated immune cells build up and damage parts of the body, such as the liver, spleen, bone marrow and brain. Without treatment, HLH can lead to severe organ damage and death.

There are two major types of HLH. One type is called “**familial**” (or **primary**) **HLH**. It is an inherited condition, which means that it can be passed from generation to generation in a family. Signs and symptoms of familial HLH usually begin within a few weeks to months after birth. A second type is called “**acquired**” (or **secondary**) **HLH**. Doctors currently do not think acquired HLH is inherited. Instead, it is thought to result from specific infections, cancers and autoimmune disorders. This type usually occurs in older children and adults.

HLH is diagnosed in fewer than 1 out of every 50,000–100,000 children per year. The condition occurs equally often in boys and girls. Since HLH causes symptoms similar to many other disorders, doctors think that more children develop HLH than are recognized and reported.

What symptoms are seen in people with HLH?

Some of the more common symptoms of HLH include the following:

- Frequent, high fevers
- Enlargement of the spleen or liver
- Easy bruising or bleeding
- Feeling very tired

- Headaches, irritability or other neurological changes
- Red skin rash or tiny, red pinpoint dots on the skin
- Pale skin

What causes HLH?

Doctors do not completely understand why certain people develop acquired HLH.

Doctors do know that familial HLH is caused by changes in 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.

Most cases of familial HLH is caused by changes in the genes *PRF1*, *UNC13D*, *STX11* and *STXBP2*. Genes carry information telling cells within the body how to grow and function. The *PRF1*, *UNC13D*, *STX11* and *STXBP2* genes help white blood cells to kill invading viruses and other pathogens and they work to calm the immune system once it becomes activated. It is harder for people with familial HLH to clear infections and often they develop repeated episodes of hyperinflammation.

Most people have two working copies of each of these genes in the cells of their body. One copy is inherited from the mother and one from the father. A change in the gene that causes it to not work properly is called a mutation. When someone inherits an HLH gene mutation from the mother and another mutation in the same HLH gene from the father, they have familial HLH. In other words, this person has a mutation affecting each of the 2 copies of an HLH gene. Most children with familial HLH inherit the HLH gene mutations from their parents. Parents of a child with familial HLH have a 25% or 1 in 4 chance with each pregnancy of having another child with familial HLH.

To best determine the chances that a person with familial HLH will have children who are also affected with the condition, it is recommended that the person with familial HLH and his/her partner undergo genetic counseling and testing prior to becoming pregnant.

How are people with HLH treated?

Health care providers offer a variety of treatments depending on the underlying cause and severity of symptoms. Because HLH 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 HLH.

Familial HLH—For children with familial HLH, the first step is to suppress the overactive immune system. This is often done using a combination of steroids and chemotherapy, with the goal of putting the condition in remission.

After this initial treatment, children with familial HLH usually undergo an allogeneic stem cell transplant. This procedure replaces their defective immune system with a healthy one from a different person. This offers the best chance of a cure.

Acquired HLH—For children with acquired HLH, the aim is to identify and treat the underlying cause (such as an infection, cancer or autoimmune condition). In many cases, this treatment puts the acquired HLH into remission. However, sometimes health care providers will recommend steroids, chemotherapy, or both.

Health care providers decide to use steroids or chemotherapy based on how severe the HLH is, not based on whether it is familial or acquired.

How is genetic testing for HLH done?

Diagnostic genetic testing

If the health care provider or genetic counselor suspects that a person has HLH, 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.
- Both copies of the person's *PRF1*, *UNC13D*, *STX11* and *STXBP2* genes are checked for possible changes. A genetic specialist compares the two copies of the person's *PRF1*, *UNC13D*, *STX11* and *STXBP2* genes to normal copies of those genes. If there are differences, the specialist decides if those differences are linked to the development of familial HLH.
- If mutations are found in the *PRF1*, *UNC13D*, *STX11* or *STXBP2* genes, the health care provider or genetic counselor will work with the family in the following ways:
 - To help the family understand the risks of familial HLH
 - To work with the affected patient and develop a care plan
 - 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 *PRF1*, *UNC13D*, *STX11* or *STXBP2* genes for all people with familial HLH. About 30–40% of people with the condition do not have any mutations in the *PRF1*, *UNC13D*,

STX11 or *STXBP2* genes. Therefore, a person can still have familial HLH even if no mutations are found. It is likely that there are other genes related to familial HLH that doctors do not yet know about.

Prenatal genetic testing

Parents may undergo prenatal testing to find out if the pregnancy is affected with known *PRF1*, *UNC13D*, *STX11* or *STXBP2* 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 the 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 *PRF1*, *UNC13D*, *STX11* or *STXBP2* 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 *PRF1*, *UNC13D*, *STX11* or *STXBP2* 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 *PRF1*, *UNC13D*, *STX11* or *STXBP2* 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 familial HLH 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 HLH can feel sad, anxious or angry. Parents who pass on *PRF1*, *UNC13D*, *STX11* or *STXBP2* gene mutations to one or more of their children can feel guilty. Some people with *PRF1*, *UNC13D*, *STX11* or *STXBP2* 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 familial HLH?

People of any age with familial HLH should try to limit their exposure to infections of any kind.

It is important to seek medical help if anything unusual appears.

What other information and resources are there for children with familial HLH and their families?

- Histiocytosis Association—Hemophagocytic Syndromes
(www.histio.org/hemophagocyticsyndromes)
- The Histiocytosis Treatment Program at St. Jude Children's Research Hospital
<https://www.stjude.org/treatment/disease/histiocytosis.html>

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/)
- Young People with Cancer: A Parent's Guide
(www.cancer.gov/publications/patient-education/young-people)

Sources:

1. Genetics Home Reference – Familial Hemophagocytic Lymphohistiocytosis
ghr.nlm.nih.gov/condition/familial-hemophagocytic-lymphohistiocytosis

2. GeneReviews – Familial Hemophagocytic Lymphohistiocytosis

www.ncbi.nlm.nih.gov/books/NBK1444/

3. Hemophagocytic Lymphohistiocytosis - UpToDate

<https://www.uptodate.com/contents/clinical-features-and-diagnosis-of-hemophagocytic-lymphohistiocytosis>

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