Familial Hemophagocytic Lymphohistiocytosis (HLH)

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.

There are four genes that, if any one of them gets a mutation, can cause familial HLH. These genes include PRF1, UNC13D, STX11 and STXBP2. Mutations in these genes are believed to cause about 60–70% of familial HLH cases. For the remaining 30–40% of people with familial HLH, doctors cannot find any mutations in the four genes listed. Therefore, there are very likely to be other genes that doctors have not identified yet that can also cause familial HLH.

Most people without familial HLH carry two working copies of the PRF1, UNC13D, STX11 and STXBP2 genes in their cells. One copy of each gene is inherited from the mother, and one copy of each gene is inherited from the father. Cells from people with familial HLH usually carry two changed copies of just one of these four genes. One changed copy is inherited from the mother, and one changed copy is inherited from the father.

The parents of a child with familial HLH have a 25% (1 in 4) chance of having another child with the condition. They have a 50% (1 in 2) chance of having a child who carries just one copy of PRF1, UNC13D, STX11 or STXBP2 with a mutation. That child would be a carrier. Carriers do not show the signs of familial HLH, but they can pass on the mutated gene to their own children. There is a 25% (1 in 4) chance of the parents having a child with no mutations in PRF1, UNC13D, STX11 or STXBP2. That child would not have familial HLH and would not be a carrier. Children with two normal copies of the PRF1, UNC13D, STX11 or STXBP2 genes would only pass on normal copies of these genes to their own children.

A person with familial HLH will definitely pass one mutation in PRF1, UNC13D, STX11 or STXBP2 to each of his or her children. This person’s chance of having a child with familial HLH depends on whether or not his or her partner also carries a mutation in PRF1, UNC13D, STX11 or STXBP2. If the partner carries a mutation in the same gene as the affected person, the chance of having a child with the condition is 50% (1 in 2). The chance of having a child who is a carrier is 50% (1 in 2). If the partner does not carry a mutation in PRF1, UNC13D, STX11 or STXBP2, then none of their children will have familial HLH. However, all of the children will be carriers.

How are people with HLH treated?

Doctors 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 doctor that knows this condition well. Only a doctor 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 doctors will recommend steroids, chemotherapy, or both.

Doctors 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 doctor 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 doctor 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 that doctors can find. 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 diagnosis (PGD). This special type of genetic testing is done along with in vitro fertilization (IVF). PGD 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 doctor 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?

- HLH Support [www.hlhsupport.org](http://www.hlhsupport.org)
- Histiocytosis Association—Hemophagocytic Syndromes [www.histio.org/hemophagocyticsyndromes](http://www.histio.org/hemophagocyticsyndromes)
- The HLH Treatment Team, Children’s Hospital of Philadelphia [www.chop.edu/centers-programs/hlh-treatment-team](http://www.chop.edu/centers-programs/hlh-treatment-team)
- The HLH Treatment Team, Cincinnati Children’s Hospital Medical Center [https://go.cincinnatichildrens.org/service/hlh/treatment.php?gclid=Cj0KEQjws1WvBRCnzevvor2g4L8BEiQAAN234e3pWf3Zj97R0svLUnXW_ohPa8IG8bUXQ0bYv75Le_gAn-I8P8HAQ](https://go.cincinnatichildrens.org/service/hlh/treatment.php?gclid=Cj0KEQjws1WvBRCnzevvor2g4L8BEiQAAN234e3pWf3Zj97R0svLUnXW_ohPa8IG8bUXQ0bYv75Le_gAn-I8P8HAQ)

More resources about genetic testing and hereditary cancer:


Sources:
1. Children’s Hospital of Philadelphia – Hemophagocytic Lymphohistiocytosis [www.chop.edu/conditions-conditions/hemophagocytic-lymphohistiocytosis-hlh#.Vd8512fb15s](http://www.chop.edu/conditions-conditions/hemophagocytic-lymphohistiocytosis-hlh#.Vd8512fb15s)