

HYPER-IgM SYNDROME

GENETIC TESTING



What is hyper-IgM syndrome?

Hyper-IgM (HIGM) syndrome is a group of rare, inherited disorders that affect the body's natural defense (immune) system. Symptoms of HIGM syndrome usually appear within the first 2 years of life and may include^{1,2}:

- Recurrent sinus, lung, and ear infections. These infections are usually caused by bacteria.
- Ongoing (chronic) diarrhea that can lead to weight loss and poor nutrition.
- Serious, widespread infections caused by organisms, such as viruses or yeast (fungi), that don't usually cause illness in people with healthy immune systems. These types of infections are called "opportunistic." An opportunistic infection may be the first sign that a child has HIGM syndrome.

People affected with HIGM syndrome may also develop^{1,2}:

- A low white blood cell count (neutropenia), which can lead to open sores (ulcers) in the mouth or rectum and skin infections.
- Enlarged lymph nodes and tonsils.
- Enlarged spleen or liver.
- Conditions (autoimmune disorders) resulting from the immune system launching an attack on healthy cells or tissues. Such conditions may include arthritis, low platelet (a type of blood cell) counts, anemia (low red blood cell counts), inability of the thyroid to produce enough thyroid hormone (hypothyroidism), and kidney disease.
- Cancer of the lymph nodes (lymphoma).
- Digestive tract tumors.
- Nervous system disorders.

Treatments are available for people with HIGM syndrome that can help reduce the number of infections they develop and restore healthy blood cell counts. When treated early enough, the condition can be cured through bone marrow transplantation or umbilical cord blood stem cell transplantation.^{1,2}

What causes hyper-IgM syndrome?

Hyper-IgM syndrome is caused by abnormal changes in certain genes. Genes are found in every cell in your body. They carry the instructions for making proteins that control how each of your cells work. Genes can undergo abnormal changes (called mutations) that may cause cells to stop working the way they should. Gene mutations may result in health problems, and they may be passed from parent to child (inherited).

CD40LG, *AICDA*, *CD40*, and *UNG* are genes that play a role in your immune system cells' ability to make blood proteins called immunoglobulins, which help protect you from infections.¹ When mutations are present in any of these genes, your body cannot make enough of certain immunoglobulins (namely, immunoglobulins G, A, and E—or IgG, IgA, and IgE), but it can still make enough immunoglobulin M (IgM). IgM alone is not enough to prevent bacteria and other organisms from causing infections.

HIGM syndrome is classified according to whether the *CD40LG*, *AICDA*, *CD40*, or *UNG* gene is mutated. The most common type of HIGM syndrome, known as primary HIGM syndrome or HIGM1, is caused by a *CD40LG* gene mutation.^{1,2}

How is hyper-IgM syndrome inherited?

The *CD40LG* gene is located on the X chromosome, which is one of the 2 chromosomes that determine whether a person is male or female. (Females have two X chromosomes, and males have one X and one Y chromosome.)

- Only males who inherit a *CD40LG* mutation are affected by primary HIGM syndrome.^{1,2}
- Females who inherit a *CD40LG* mutation are called "carriers." They are not affected by primary HIGM syndrome, but they have a 50% chance of passing the disorder on to a male child and a 50% chance of passing the mutation on to a female child who will herself become a carrier.²

AICDA, *CD40*, and *UNG* mutations are inherited in an autosomal recessive manner.¹

- This means a child must inherit 2 copies of a gene mutation (1 copy from each parent) in order to be affected with HIGM syndrome and thus has a 1 in 4 (25%) chance of having HIGM syndrome if both parents are carriers.

- These types of HIGM syndrome affect both males and females.

In some cases, the gene mutations that cause HIGM syndrome are *de novo*.² This means the gene mutation occurs for the first time in the affected child instead of being passed from parent to child. In these cases, family members in earlier generations are not at increased risk of having children affected with HIGM syndrome.

It is possible for the mother of a child affected with HIGM syndrome to test negative for the same mutation her child has because she carries the mutation only in her egg cells. This is called germline mosaicism, and it means the brothers and sisters (siblings) of the affected child are at increased risk for HIGM syndrome.²

How is hyper-IgM syndrome diagnosed?

If your young child has had recurring sinus, lung, and/or ear infections, chronic diarrhea, or has developed opportunistic infections, his or her doctor may suspect hyper IgM syndrome. This is especially true if you have a family medical history of HIGM syndrome.

Your child's doctor may order blood tests to gather information about the health of your child's immune system. If your child has HIGM syndrome, his or her blood test results may show^{1,2}:

- Abnormally low levels of IgG and IgA; normal or high levels of IgM.
- Abnormally low white blood cell counts (neutropenia).

Your child's doctor or genetics specialist (geneticist) will combine the above information with your child's symptoms and family history and compare them with those seen in the condition. A genetic test called full gene sequencing can be done to confirm a suspected diagnosis of HIGM syndrome. This test is performed on a sample of blood. It reads the instructions (DNA) that make up the *CD40LG*, *AICDA*, *CD40*, and *UNG* genes and can identify many mutations present in those genes.

What possible results of full gene sequencing can be reported and what do they mean?

- **Negative:** After scanning the *CD40LG*, *AICDA*, *CD40*, and *UNG* genes, no detectable mutations were found. This test does not detect all possible mutations in those genes. For this reason, a negative result cannot

completely rule out the presence of a gene mutation that is causing the child's symptoms.

- **Positive:** After scanning the *CD40LG*, *AICDA*, *CD40*, and *UNG* genes, a mutation was found. Along with the child's signs and symptoms, a positive genetic test result may confirm a diagnosis of HIGM syndrome. The type of HIGM syndrome affecting the child can be identified based on which gene mutation is present. Genetic testing may be recommended for the child's parents. Knowing whether 1 or both parents carry a gene mutation known to cause HIGM syndrome may help make the child's diagnosis more clear and may identify other family members who may be at risk for the disorder.
- **Variant of unknown significance:** After scanning the *CD40LG*, *AICDA*, *CD40*, and *UNG* genes, a mutation was found that has not been reported before. It is unclear if the mutation is the cause of the child's signs and symptoms. Genetic testing of family members may provide more information. If all affected family members have the same mutation, then it is likely to be linked to the inherited disorder. If some affected family members do not have the mutation, it is less likely to be linked to the disorder.

Full gene sequencing test results should be combined with clinical findings and reviewed by a health professional who specializes in medical genetics.

Where can I find more information?

If you have questions or want more information about genetic testing for hyper-IgM syndrome, ask your doctor or genetic counselor. You may search for a genetic counselor in your area using an online address book provided by the National Society of Genetic Counselors at www.nsgc.org.

Other information resources include:

- Immune Deficiency Foundation
Telephone: 800-296-4433
Home page: www.primaryimmune.org
- National Society of Genetic Counselors
Telephone: 312-321-6834
Home page: www.nsgc.org

Note: This material is provided for general information purposes only. It is not intended as a substitute for medical advice and/or consultation with a physician or technical expert.

References

1. Hyper IgM syndrome. Immune Deficiency Foundation Web site. <http://primaryimmune.org/about-primary-immunodeficiency-diseases/types-of-pidd/hyper-igm-syndrome>. Accessed February 4, 2013.
2. Johnson J, Filipovich AH, Zhang K. X-linked hyper IgM syndrome. In: Pagon RA, Bird TD, Dolan CR, et al, eds. *GeneReviews*™ [Internet]. Seattle, WA: University of Washington, Seattle; 1993-. Accessed February 25, 2013.



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