

CTLA4 Haploinsufficiency

Introduction

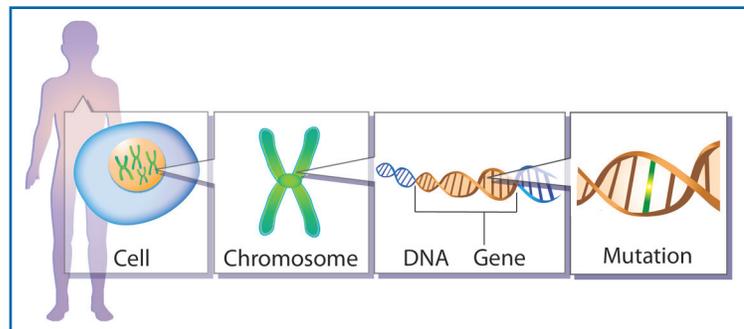
CTLA4 haploinsufficiency is a rare genetic disorder of the immune system caused by mutations in the *CTLA4* gene. This disease impairs normal regulation of the immune system and results in excessive numbers of immune cells called lymphocytes (lymphoproliferation), autoimmunity, low levels of antibodies (hypogammaglobulinemia), and recurrent infections. Sometimes the excess lymphocytes enter and accumulate in organs where lymphocytes typically are not present in large numbers, which can cause a variety of symptoms. *CTLA4* haploinsufficiency also may slightly increase a person's risk of lymphoma, a type of cancer. *CTLA4* haploinsufficiency is also sometimes called *CTLA4* deficiency or CHAI disease (*CTLA4* haploinsufficiency with autoimmune infiltration). *CTLA4* haploinsufficiency is diagnosed based on clinical symptoms, laboratory findings, and genetic testing.

Genetics and Function

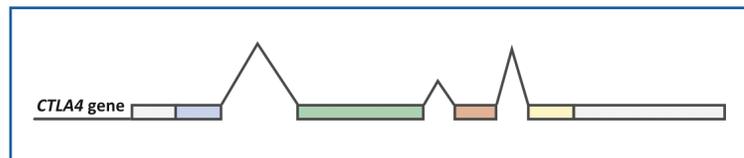
CTLA4 haploinsufficiency is caused by mutations in the gene *CTLA4*, which stands for cytotoxic T lymphocyte antigen 4. *CTLA4* provides instructions for production of a protein called CTLA4. The CTLA4 protein functions as a “brake” to slow down or decrease the action of the immune system. The action of a healthy immune system needs to be able to both ramp up and slow down, much like a car controlled by gas and brake pedals. *CTLA4* mutations affect multiple immune cell types and can lead to both autoimmunity and immunodeficiency.

Haploinsufficiency is the genetic mechanism underlying the disease. Each person has two copies of the *CTLA4* gene—one from each parent.

Haploinsufficiency means that having a single working copy of *CTLA4* is not sufficient to produce enough CTLA4 protein to have a normal immune system.



Genetics primer: All the cells in the body contain instructions on how to do their job. These instructions are packaged into chromosomes, each of which contains many genes, which are made up of DNA. Errors, or mutations, in the genes can cause diseases such as *CTLA4* haploinsufficiency. Credit: NIAID



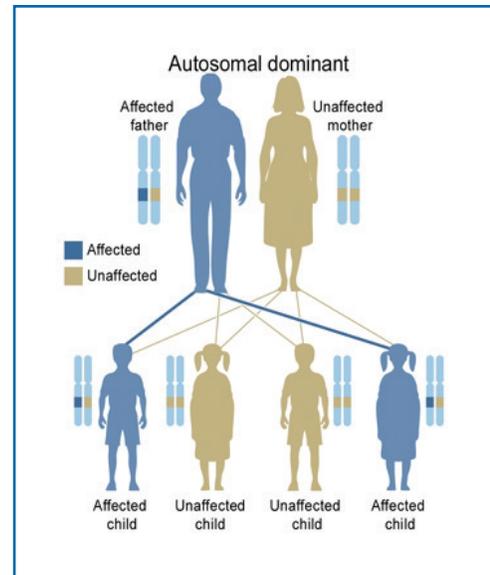
The *CTLA4* gene provides instructions for production of the CTLA4 protein. The gene has four protein-coding regions (exons), which are shown in blue, green, red, and yellow. Credit: NIAID



Inheritance

CTLA4 haploinsufficiency is inherited in an autosomal dominant manner, which means that a person only needs an abnormal gene from one parent to have the disease. One normal copy of the gene is not enough to compensate for the abnormal copy. Dominant inheritance also means that most families with *CTLA4* haploinsufficiency have affected relatives in each generation on the side of the family with the mutation.

Children with a parent who carries a *CTLA4* mutation have a 50 percent chance of inheriting the mutation. Within a family, each child's risk of inheriting the mutated *CTLA4* gene is independent of whether other siblings have the mutation. In other words, if the first three children in a family have the mutation, the fourth child has the same 50 percent risk of inheriting the mutation. Children who do not inherit the abnormal gene will not develop *CTLA4* haploinsufficiency or pass on the mutation.



In this example, a man with an autosomal dominant disorder has two affected children and two unaffected children. Women also can pass on the mutation. Credit: U.S. National Library of Medicine

Clinical Symptoms

CTLA4 haploinsufficiency is characterized by infiltration of T cells into the gut, lungs, bone marrow, central nervous system, kidneys, and possibly other organs. Most people with *CTLA4* haploinsufficiency have diarrhea or intestinal disease (enteropathy). Enlargement of the lymph nodes (lymphadenopathy) and liver and spleen (hepatosplenomegaly), as well as respiratory infections, also are common. People with *CTLA4* haploinsufficiency often experience autoimmune problems that can affect various organs and tissues, including

- **Blood:** Blood problems may include thrombocytopenia and hemolytic anemia (see the Glossary). Thrombocytopenia causes poor blood clotting, and bleeding cannot be stopped following minor injuries. Anemia may cause a feeling of weakness or fatigue.
- **Thyroid:** Autoimmune thyroiditis is an inflammation of the thyroid, a small gland at the base of the neck.
- **Skin:** The autoimmune skin disease psoriasis is characterized by red, itchy patches of skin.
- **Joints:** Autoimmune arthritis causes joint pain and stiffness.

Importantly, the symptoms and course of this disease vary widely. Some people are severely affected, whereas others show few symptoms of disease. This “variable expressivity” can be striking, even within the same family, and may be explained by differences in lifestyle, exposure to pathogens, effectiveness of treatment, or other genetic factors.

Laboratory Findings

The clinical symptoms of *CTLA4* haploinsufficiency are caused by immune system abnormalities. Most people with *CTLA4* haploinsufficiency develop reduced levels of at least one type of immunoglobulin. People with *CTLA4* haploinsufficiency also may have low *CTLA4* protein expression in regulatory T cells, overactivation of effector T cells, low levels of a certain type of B cell called a switched memory B cell, and progressive loss of circulating B cells (see the Glossary for more information about these cell types).

Treatment

Once a diagnosis is made, treatment is based on a person's clinical condition and may include standard therapies for autoimmune problems and immunoglobulin deficiencies. Additionally, treatment with a drug called CTLA4-Ig, which mimics the action of CTLA4 and reduces immune activity, is a potential therapy for people with *CTLA4* haploinsufficiency.

CTLA4 Haploinsufficiency and Your Family

Living with *CTLA4* haploinsufficiency can be difficult not only for the person who has it, but for their family members as well. It is important for families to talk openly about *CTLA4* haploinsufficiency and about how the family is dealing with it so misconceptions can be identified and corrected and children can learn to identify and cope with their reactions. Some people with *CTLA4* haploinsufficiency have to work hard to develop their self-confidence and sense of security. Everyone needs to be reminded that they have many positive characteristics, especially when their appearance attracts attention (for example, due to large lymph nodes).

Some children who have siblings with *CTLA4* haploinsufficiency worry about their brother or sister being in pain or dying from the disease. Some think that they may develop symptoms because they look or act like a sibling who has the disease or that the disease is contagious. Some children struggle with how much time their parents spend with their sick sibling. Many families benefit from meeting or talking to other families affected by the same rare disease. Counseling can also help families cope with the challenges of *CTLA4* haploinsufficiency.

At the same time, many families say that *CTLA4* haploinsufficiency has brought them closer together. Through their experiences with the disease and its treatment, family members learn about controllable and uncontrollable aspects of life. Although certain aspects of the disease cannot be controlled, how a family responds to the stress of any illness is controllable and an important aspect of managing *CTLA4* haploinsufficiency. Children also learn who they can turn to for support and how to solve problems. Acknowledging both the challenges and opportunities that *CTLA4* haploinsufficiency presents helps children develop resilience.

Glossary

Arthritis—Painful inflammation and stiffness of the joints.

Autoimmune—Describes a process during which a person's immune system attacks healthy cells, organs, and tissues.

B cells—Immune cells that present antigens to T cells and produce antibodies, or immunoglobulins.

Cell—The basic unit of living organisms. Human cells consist of a nucleus (control center) and cellular organs, called organelles, enclosed by a membrane. Groups of cells with similar structure and function form tissues.

Central nervous system—The complex of nerve tissues that controls the activities of the body. The central nervous system comprises the brain and spinal cord.

Chromosome—A thread-like structure made up of DNA that is tightly coiled around supporting proteins. Chromosomes reside in the control center, or nucleus, of a cell.

DNA (deoxyribonucleic acid)—A self-replicating material present in nearly all living organisms. It is the carrier of genetic information.

Effector T cell—A type of immune cell that performs the functions of an immune response such as cell killing and cell activation.

Enteropathy—Disease of the intestines.

Exon—A segment of DNA that contains information coding for a protein.

Haploinsufficiency—Indicates that having a single working copy of a gene is not sufficient to produce enough protein to be free from the gene-associated disease.

Hemolytic anemia—A condition in which red blood cells are destroyed and removed from the bloodstream before their normal lifespan is over.

Hypogammaglobulinemia—A type of immune deficiency that is characterized by a reduction in all types of gamma globulins, or infection-fighting antibodies.

Immune system—A system of biological structures and processes within the body that protects it against “foreign” threats such as bacteria or viruses.

Immunodeficiency—A state in which the immune system's ability to fight disease is compromised or entirely absent.

Immunoglobulin—Large Y-shaped proteins, also known as antibodies, produced by immune cells called B cells. The immune system uses immunoglobulins to identify and neutralize foreign objects such as bacteria. Each immunoglobulin is unique, but they fall under general subtypes. Examples of the subtypes include IgG, IgA, and IgM.

Lymphoma—A type of blood cancer that occurs when certain immune cells start dividing uncontrollably and no longer behave like normal immune cells.

Lymphoproliferation—The excessive production or buildup of immune cells called lymphocytes.

Mimetic—Relating to something that stimulates the action or effect of that which is being mimicked.

Mutation—A change in the DNA sequence that is associated with disease or susceptibility to disease.

Pathogen—A bacterium, virus, or other microorganism that can cause disease.

Psoriasis—A skin disease marked by red, itchy, scaly patches.

Regulatory T cell—A type of immune T cell that monitors and regulates the activity of other T cells.

Thrombocytopenia—An abnormally low number of platelets in the blood.

Thyroiditis—A condition in which the thyroid is inflamed, often due to being attacked by a person's own immune system. The thyroid is a small gland at the base of the neck, below the Adam's apple.

