NIAID

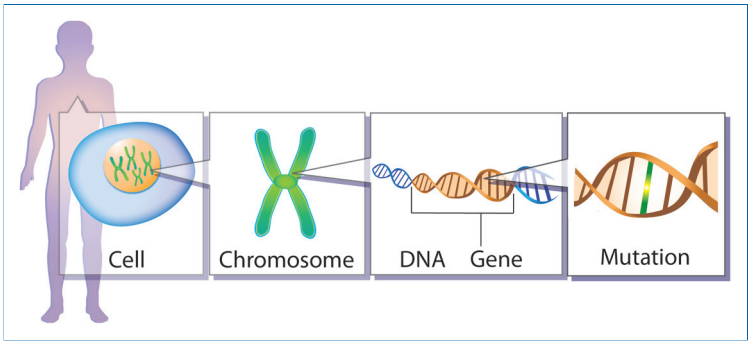
Wiskott-Aldrich Syndrome

Introduction

Wiskott-Aldrich syndrome is a rare genetic disorder of the immune system that primarily affects boys. It is characterized by abnormal immune function and a reduced ability to form blood clots.

Genetics

Wiskott-Aldrich syndrome is caused by mutations in the *WAS* gene, which provides instructions for production of a protein called WASp. This protein plays an essential role in relaying signals from the surface of the blood cell to the cell's actin cytoskeleton, the network of fibers that make up the cell's structural framework. Immune cells that lack the WASp protein have a decreased ability to respond to their environment, fight invaders, and form functional platelets.



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 Wiskott-Aldrich syndrome. Credit: NIAID

Inheritance

Wiskott-Aldrich syndrome follows an X-linked inheritance pattern. Each person has 23 pairs of chromosomes—one pair of sex chromosomes (XX for girls and XY for boys) and 22 pairs of numbered chromosomes, called autosomes. *WAS* is located on the X chromosome. Boys who inherit a disease-causing gene on their X chromosome are affected by the disease. Girls who inherit an X-linked mutation are "carriers"—meaning that they have one mutated copy of the gene and one normal copy.

All children of a carrier mother have a 50 percent chance of inheriting the mutation. This means that about half of the boys will be affected by the disease and about half of the girls will be carriers. Female carriers of a mutated *WAS* gene do not experience symptoms of the disease. This means that boys with Wiskott-Aldrich syndrome do not have other affected female relatives, but they may have brothers or male relatives on their mother's side, such as uncles, who also have the disease. The disease cannot be passed from father to son.

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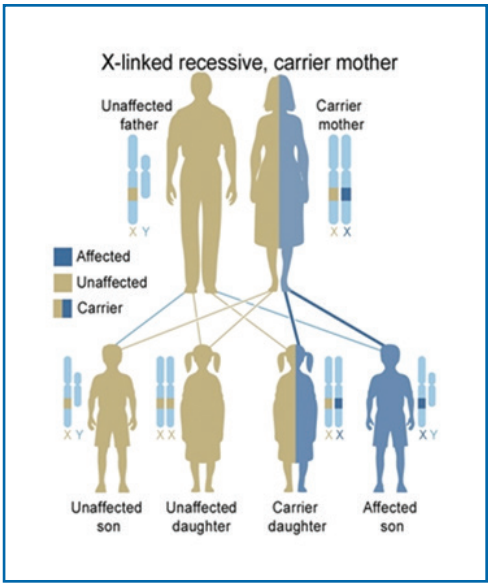
Some *WAS* mutations occur as a result of a mutation in the egg or sperm of one of the parents or in the fertilized egg itself. These are called *de novo*, which means "new," mutations. In these cases, the patient does not have a family history of the disease. Approximately one-third of boys with Wiskott-Aldrich syndrome have *de novo* mutations.



In this example, an unaffected woman carries one copy of a gene mutation for an X-linked recessive disorder. She has an affected son, an unaffected daughter who carries one copy of the mutation, and two unaffected children who do not have the mutation. Credit: U.S. National Library of Medicine

Clinical Symptoms

Wiskott-Aldrich syndrome typically is characterized by three major features:

- Low number of platelets and small platelet size, which can lead to an increased tendency to bleed
- Recurrent bacterial, viral, and fungal infections
- Eczema (an inflammatory skin disease)

In addition, some patients with Wiskott-Aldrich syndrome have autoimmune diseases, such as autoimmune hemolytic anemia (destruction of one's own red blood cells) or vasculitis (destruction and inflammation of blood vessels). Additionally, a minority of people with Wiskott-Aldrich syndrome develop lymphoma or leukemia. Occasionally these cancers occur in young children, but they are more likely to develop as people age.

It is important to note that the severity of this disease can vary remarkably, even within the same family. This is known as variable expressivity.

Laboratory Findings

The key laboratory findings for Wiskott-Aldrich syndrome relate to platelets. In addition to being low in number, the platelets themselves are small and dysfunctional. Determining platelet size and shape is the most rapid test for diagnosis of Wiskott-Aldrich when it is suspected in a boy with thrombocytopenia (a low level of platelets). In addition, people with Wiskott-Aldrich syndrome typically have elevated levels of IgE and IgA, sometimes with low levels of IgM. Additionally, the function of the immune T cells is often abnormal.

Treatment

Once a diagnosis is made, treatment for Wiskott-Aldrich syndrome is based on a person's clinical condition. Possible treatment options for some people with Wiskott-Aldrich syndrome include immunoglobulin (antibody) infusions, platelet transfusions, topical creams for eczema, and steroids or similar medications to control autoimmunity. Because of their abnormal immune function, people

with Wiskott-Aldrich syndrome may be advised to avoid live-virus vaccines. In severe cases, bone marrow transplantation or gene therapy may be considered.

A few decades ago, options for managing Wiskott-Aldrich syndrome were poor, and many patients died of the disease as children. Today, improvements in immunoglobulin supplementation, antibiotics, and other care have greatly improved the quality of life enjoyed by most patients. Improvements in bone marrow transplantation and new medications to treat infectious complications also have helped considerably.

Wiskott-Aldrich Syndrome and Your Family

Living with Wiskott-Aldrich syndrome can be difficult not only for the person who has it but also for their family members. It is important for families to talk openly about Wiskott-Aldrich syndrome 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 boys with Wiskott-Aldrich syndrome have to work hard to develop their self-confidence and sense of security. All children need to be reminded that they have many positive characteristics, especially when their illness requires special attention.

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

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

Glossary

Actin cytoskeleton—Part of the structures within a cell that give the cell its shape, help organize it, and help the cell move.

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

Autosome—A chromosome that is not a sex chromosome. Humans have 22 pairs of autosomes.

Bone marrow transplant—A procedure to replace the bone marrow of a sick person with the bone marrow stem cells of a healthy person. Bone marrow is the soft, fatty tissue inside bones. Stem cells are immature cells in the bone marrow that give rise to all types of blood and immune system cells. Bone marrow transplants are sometimes called hematopoietic stem cell transplants.

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.

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.

Gene—A unit of heredity that is transferred from parent to child. Genes are made up of DNA.

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

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 E (IgE)—A subtype of antibody produced by the immune system. In people with an allergy, the immune system overreacts to an allergen by producing IgE. These antibodies interact with certain immune cells, triggering the release of inflammatory chemicals that cause the symptoms of an allergic reaction.

Immunoglobulins—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 falls under a general subtype. Examples of the subtypes include IgG, IgA, and IgM.

Inheritance—The passing of genetic traits to offspring.

Leukemia—Cancer that starts in blood-forming tissue, such as the bone marrow, and causes large numbers of abnormal blood cells to be produced and enter the bloodstream.

Lymphocytes—A class of white blood cells that are part of the immune system.

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

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

Platelet—A small, disk-shaped cell fragment that helps blood clot.

T cell—A lymphocyte produced or processed by the thymus gland (a small organ located in the upper chest under the breastbone) that is actively involved in the immune response.

Thrombocytopenia—An abnormally low amount of clot-forming platelets in the blood.

Vasculitis—Inflammation of the blood vessels that causes changes in the blood vessel walls.

X-linked inheritance—A mode of inheritance in which an alteration in a gene on the X chromosome causes a condition or trait.

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