DOCK8 Immunodeficiency Syndrome

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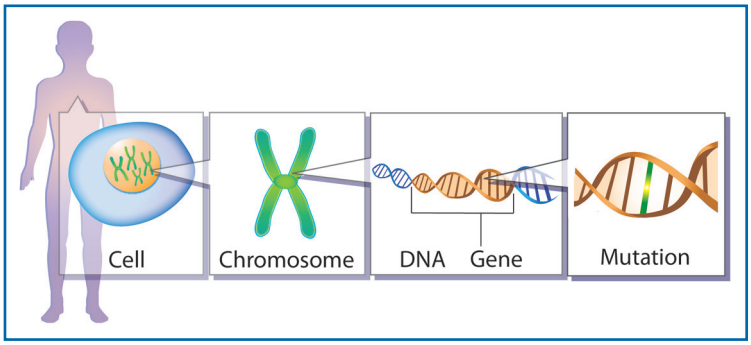
What Is DOCK8 Immunodeficiency Syndrome?

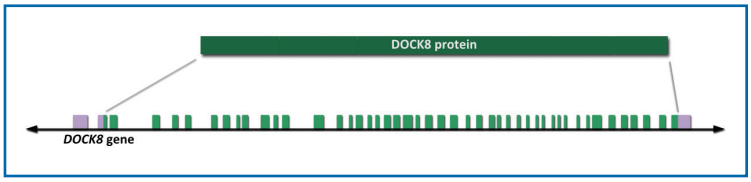
DOCK8 immunodeficiency syndrome is a rare genetic disorder of the immune system characterized by recurrent viral infections of the skin and respiratory system. People with DOCK8 immunodeficiency syndrome typically have allergies, asthma, and an increased risk of some types of cancer. DOCK8 immunodeficiency syndrome is diagnosed based on clinical symptoms, laboratory findings, and genetic testing. Bone marrow transplant, a therapy that restores normal function to the immune system and is used to treat many genetic immunodeficiencies, can cure DOCK8 immunodeficiency syndrome.

Genetics

DOCK8 immunodeficiency syndrome is caused by mutations in the gene *DOCK8*. *DOCK8* stands for "dedicator of cytokinesis 8" and is involved in regulating the cytoskeleton—the proteins inside a cell that support its shape and movement. Many *DOCK8* mutations are large deletions, but point mutations also are common (see the Glossary for more information about these mutation types).



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 DOCK8 immunodeficiency syndrome. Credit: NIAID



The *DOCK8* gene provides instructions for producing the DOCK8 protein. Mutations in the *DOCK8* gene can lead to a DOCK8 protein that does not function properly or a DOCK8 protein that is not produced at all. Credit: NIAID

The *DOCK8* mutations that cause the disease are present in every cell of the body. For some people with DOCK8 immunodeficiency syndrome, additional *DOCK8* mutations develop in immune cells as the body attempts to fix the *DOCK8* gene. These extra mutations, known as somatic reversions, can help to correct some problems with the immune system. Somatic reversions partially explain differences in disease severity among people with DOCK8 immunodeficiency syndrome. However, somatic reversions do not cure the disease.

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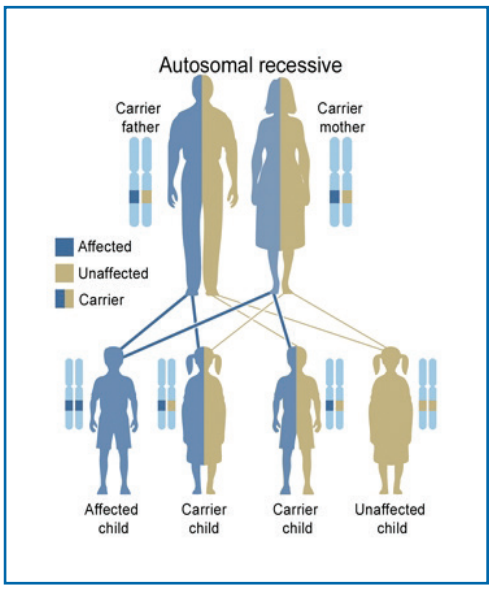
Inheritance

DOCK8 immunodeficiency syndrome is inherited in an autosomal recessive manner, which means that a person needs two copies of the abnormal gene—one copy from each parent—to develop DOCK8 immunodeficiency syndrome. Typically, both parents of an affected child carry one abnormal gene and are unaffected by the disease. When both parents have one abnormal copy of the *DOCK8* gene, each child has a 25 percent, or one in four, chance of being affected by the disease.

Sometimes the two copies of the *DOCK8* gene that a child inherits have identical, or homozygous, mutations. This is common if the child's parents are related to each other. Many patients have different mutations on the two copies of *DOCK8*, and their mutations are called compound heterozygous mutations. In either case, the patient is not able to produce a functional DOCK8 protein.



In this example, two unaffected parents each carry one copy of a gene mutation for an autosomal recessive disorder. They have one affected child and three unaffected children, two of which carry one copy of the gene mutation. Credit: U.S. National Library of Medicine

Clinical Symptoms

DOCK8 immunodeficiency syndrome is characterized by recurrent infections, allergies, and certain cancers. Nearly all patients have recurrent or chronic upper and lower respiratory tract infections. Recurrent lung infections may lead to destruction and widening of the large airways called bronchiectasis. In addition, many patients need sinus surgery or placement of ear tubes (myringotomy tubes) to help with their sinus and ear infections.

Cutaneous, or skin, infections in people with DOCK8 immunodeficiency syndrome are distinctive and may include the following:

- Severe and difficult-to-treat infections with viruses such as herpes simplex virus, human papillomavirus, and molluscum contagiosum virus
- Infections with bacteria such as *Staphylococcus aureus*
- Fungal infections of the mouth or skin, which are often caused by the fungus *Candida*

Eczema, a condition that causes the skin to become inflamed or irritated, also is common in people with DOCK8 immunodeficiency syndrome. Eczema can be quite severe and may be further complicated by bacterial infections. In some cases, the skin problems present in people with DOCK8 immunodeficiency syndrome can become disfiguring.

People with DOCK8 immunodeficiency syndrome frequently have food allergies, environmental allergies, and asthma. Some patients also may experience autoimmune problems, such as autoimmune

hemolytic anemia (the body destroys its own red blood cells), vasculitis (blood vessel inflammation), or vasculopathy (blood vessel damage).

Patients also are at increased risk for developing squamous cell carcinoma, a type of skin cancer, and lymphoma, a cancer of the lymphatic system. Some, but not all, of these lymphomas are associated with infections with Epstein-Barr virus, a cancer-causing virus. The cancer risks in people with DOCK8 immunodeficiency syndrome are significant, and patients should be monitored closely for signs of cancer.

Laboratory Findings

DOCK8 immunodeficiency syndrome is considered a combined immunodeficiency because it includes both decreased numbers of immune cells and defective immune cell function. It also can be classified as a type of autosomal recessive hyperimmunoglobulinemia E syndrome, which means that people with the disease have too much of a type of immunoglobulin, or antibody, called IgE.

Laboratory findings in people with DOCK8 immunodeficiency syndrome show progressive decreases in the number of lymphocytes (a type of immune cell), which is referred to as lymphopenia. Lymphopenia primarily affects certain T cell subsets and can reduce B cell and/or natural killer cell numbers in some patients (see the Glossary for more information about these cell types). Other common laboratory findings include an increase in immune cells called eosinophils (eosinophilia) and a variety of immunoglobulin abnormalities. People with DOCK8 immunodeficiency syndrome frequently have poor antibody responses to vaccines. Production of the DOCK8 protein can be measured using a technique called flow cytometry testing (see the Glossary). Loss of production of the DOCK8 protein indicates a problem with the *DOCK8* gene and suggests DOCK8 immunodeficiency syndrome.

Treatment

Once a diagnosis is made, treatment for DOCK8 immunodeficiency syndrome is based on a person's clinical condition and may include medications and other strategies for managing specific infections, allergies, and asthma. Doctors may recommend the prophylactic, or preventive, use of antimicrobial drugs to prevent infections. Doctors also may consider using immunoglobulin replacement therapy if immunoglobulin levels are low. In some patients, a drug called interferon alpha has been used to control serious viral infections, such as widespread warts or herpes.

Bone marrow transplants, also called hematopoietic stem cell transplants, can cure many genetic immunodeficiency diseases. This therapy has been used to cure patients with DOCK8 immunodeficiency syndrome and resolve most of their clinical symptoms and laboratory abnormalities. Families must carefully consider the risks and benefits before pursuing bone marrow transplant or other treatment options.

DOCK8 Immunodeficiency Syndrome and Your Family

DOCK8 immunodeficiency syndrome is a difficult disease to have for many reasons. It is important for families to talk openly about DOCK8 immunodeficiency 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 children with DOCK8 immunodeficiency syndrome have to work hard to develop their self-confidence and sense of security. Everyone benefits from being reminded that they have many positive characteristics, but this is especially important when a child's appearance attracts attention (for example, due to warts or severe eczema).

Some children who have siblings with the disease feel anxious about their brother or sister being in pain or even 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. The Koch family blog (www.kjkdancingthroughtherain.blogspot.com) chronicles one family's experiences with DOCK8 immunodeficiency syndrome. Patient organizations such as the Immune Deficiency Foundation (www.primaryimmune.org) or Be The Match (www.bethematch.org), operated by the National Marrow Donor Program, are also great resources for providing useful information and support. Counseling can also help families cope with the challenges of DOCK8 immunodeficiency syndrome.

At the same time, many families say that the disease 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 DOCK8 immunodeficiency syndrome. Children also learn who they can turn to for support and how to solve problems. Acknowledging both the challenges and opportunities that DOCK8 immunodeficiency syndrome presents helps children develop resilience.

NIH Research Opportunities for People With DOCK8 Immunodeficiency Syndrome

These research protocols are open to patients with DOCK8 immunodeficiency syndrome. Please ask your care team for more information.

- 08-HG-0059: Studies of Skin Microflora in Healthy Individuals and Atopic Dermatitis Patients
- 09-I-0133: Establishing Fibroblast-derived Cell Lines from Skin Biopsies of Patients with Immunodeficiency or Immunodysregulation Disorders
- 94-I-0073: Recruitment and Apheresis Collection of Peripheral Blood Hematopoietic Stem Cells, Mononuclear Cells, and Granulocytes
- 10-I-0148: Natural History of Atopic Dermatitis and Other Genetic/Congenital Diseases Associated with Allergic Inflammation

Glossary

Antigen—Any substance that causes the immune system to produce antibodies against it. An antigen may be a foreign substance from the environment. Examples of antigens include chemicals, bacteria, viruses, and pollen.

B cell—A type of immune system cell that produces antibodies against antigens.

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.

Bronchiectasis—A condition in which damage to the airways of the lungs causes them to become widened and scarred.

Cancer-causing virus—Any virus that can cause cancer, such as Epstein-Barr virus or human papillomavirus. Also known as "oncovirus."

Candida—A type of yeast that is the most common cause of fungal infections.

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.

Cutaneous—Of, relating to, or affecting the skin.

Deletion mutation—A type of mutation in which part of the DNA sequence is missing. This results in a loss of genetic material.

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

Eczema—A condition in which patches of skin become rough and inflamed, with blisters that cause itching and bleeding.

Eosinophilia—A higher than normal number of eosinophils, a type of white blood cell, in the blood.

Epstein-Barr virus—A ubiquitous, usually harmless, virus that sometimes is associated with lymphoma and other cancers.

Flow cytometry testing—A laser-based technology used for cell counting, cell sorting, and detection of biomarkers, which are molecules that indicate the effect or progress of a disease.

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.

Herpes simplex virus—The virus that causes herpes.

Human papillomavirus (HPV)—The virus that causes warts.

Immunodeficiency—A state in which the immune system's ability to fight infectious 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 they fall under general subtypes. Examples of the subtypes include IgG, IgA, and IgE.

Inheritance—The passing of genetic traits to offspring.

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.

Lymphopenia—A condition in which the level of lymphocytes in the blood is abnormally low.

Molluscum contagiosum—A chronic viral skin disease characterized by groups of small, smooth, painless pinkish bumps on the skin with central depressions that yield a milk-like fluid when squeezed.

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

Myringotomy tube—A small tube inserted into the eardrum that helps to allow air into the middle ear and to prevent accumulation of fluid in the middle ear. Also known as a tympanostomy tube or ear tube.

Natural killer (NK) cells—Small lymphocytes that are part of the first line of immune defense.

Phenotype—A person's observable characteristics.

Point mutation—A mutation that affects only one or very few nucleotides or base pairs in a gene sequence.

Prophylactic—A medicine or course of action used to prevent disease.

Somatic reversions—Mutations acquired after conception and present in select groups of cells, such as the cells of the immune system. In the context of DOCK8 immunodeficiency syndrome, these are additional acquired DNA changes that sometimes correct parts of the immunodeficiency.

Squamous cell carcinoma of the skin—A common form of skin cancer that develops in the thin, flat squamous cells that make up the outer layer of the skin.

Staphylococcus aureus—A common bacterium that can cause infections.

Syndrome—An association of several clinically recognizable features, signs, or symptoms that often occur together.

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.

Vasculitis—Inflammation of a blood vessel or blood vessels.

Vasculopathy—Damage to a blood vessel caused by disease.

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