# *STAT3* Gain-of-Function Disease



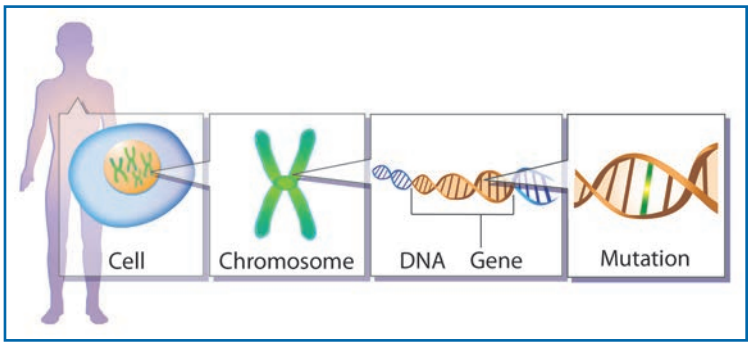
*STAT3* gain-of-function disease (also called *STAT3* GOF disease) is a rare genetic disorder of the immune system. *STAT3* GOF disease is named after the gene that causes it, *STAT3* (signal transducer and activator of transcription 3), and the effect caused by mutations in *STAT3*—gain-of-function, meaning that the gene's protein becomes overactive.

*STAT3* GOF disease is an early-onset autoimmune and lymphoproliferative disease (see Glossary). The symptoms of this disease vary and can include swelling of the lymph nodes (lymphadenopathy), reductions in the number of blood cells (autoimmune cytopenias), autoimmunity that affects multiple organs and tissues, infections, eczema, and in some cases, short stature. Sarah Flanagan and Mark Russell of University of Exeter Medical School and Joshua Milner of NIAID originally described this condition in 19 patients in 2014 and 2015. Since then, dozens of additional patients have been identified.

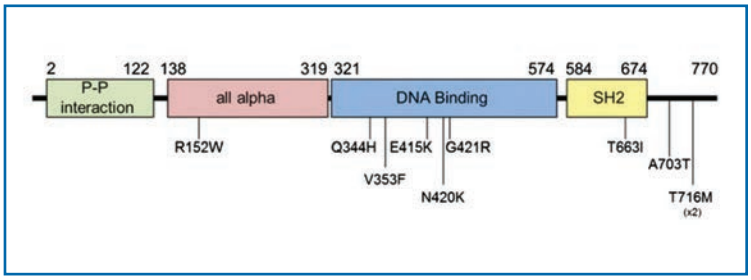
## Genetics and Function

*STAT3* GOF disease is caused by gain-of-function mutations in the *STAT3* gene. This gene provides instructions for production of the STAT3 protein, part of the STAT family of proteins. Various mutations have been identified across the length of the STAT3 protein.

STAT proteins play an essential role in chemical signaling pathways within cells. STAT3 is a transcription factor, a type of protein that regulates when other genes are turned on. Once activated, STAT3 moves into the nucleus of the cell and binds to specific areas of DNA. By binding to regulatory DNA regions near genes, STAT3 controls the activity of a variety of genes. It is necessary for many cellular processes, including cell proliferation, inflammation, differentiation, and cell survival.




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 *STAT3* GOF disease. Credit: NIAID




Schematic of the STAT3 protein showing the location of different mutations and the resulting amino acid changes. Credit: NIAID

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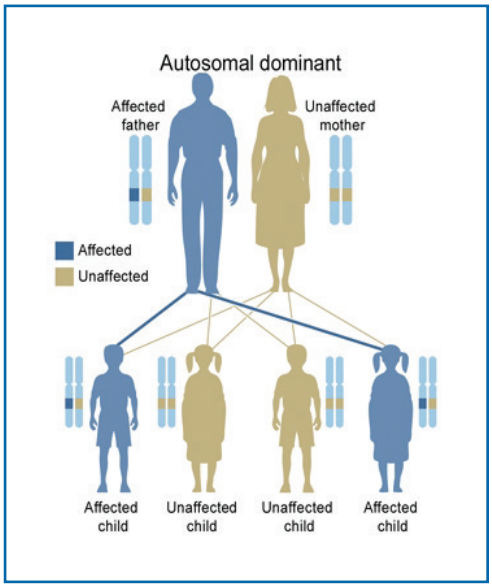
## Inheritance

*STAT3* GOF disease is inherited in an autosomal dominant manner, which means that a person needs an abnormal gene from only one parent to have the disease. The abnormal *STAT3* gene dominates the normal *STAT3* gene from the other parent. Dominant inheritance also means that most families with *STAT3* GOF disease have affected relatives in each generation on the side of the family with the mutation. However, researchers have found that, in some families, relatives carrying a *STAT3* mutation do not have symptoms of the disease. This is called incomplete penetrance.




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

Unlike mutations that run in a family, some *STAT3* 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 similar symptoms. *De novo* mutations can be passed on to children.

Children of a parent who carries a *STAT3* mutation have a 50 percent chance of inheriting the mutation. This means that, within a given family, each child's risk of inheriting the mutated gene is independent of whether or not siblings have the mutation. For example, 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 *STAT3* GOF disease or pass on the mutation.

## Clinical Symptoms

Clinically, *STAT3* GOF disease is diverse. It is characterized by a buildup of immune cells called lymphocytes (lymphoproliferation) and early-onset autoimmunity affecting multiple organs and tissues. Exactly when, where, and to what extent these problems will develop in any one person cannot be predicted.

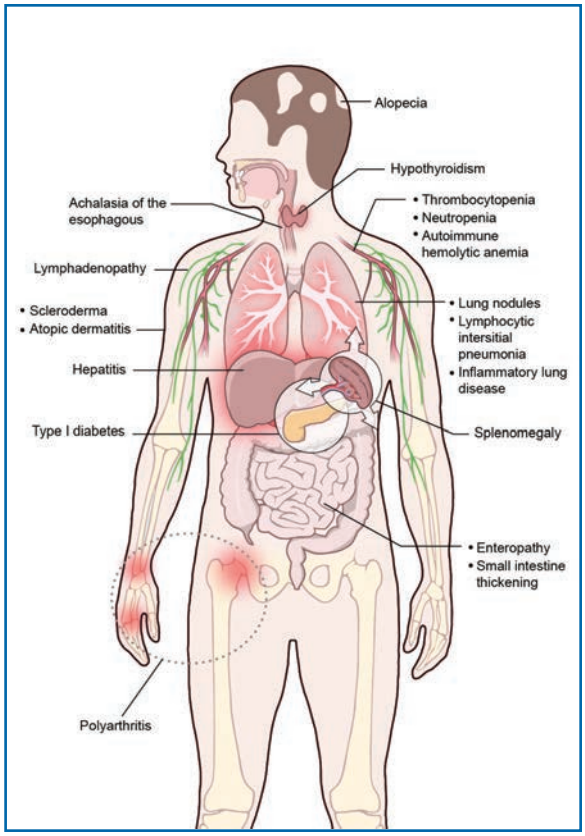
**Lymphoproliferation:** The main signs or symptoms of lymphoproliferation are lymphadenopathy (enlarged or swollen lymph nodes that wax and wane over time) and/or splenomegaly (an enlarged spleen) and sometimes hepatomegaly (an enlarged liver).

**Autoimmunity:** Hematologic autoimmunity is the most common type of autoimmunity in *STAT3* GOF disease. This includes autoimmune hemolytic anemia (attacks against red blood cells), neutropenia (attacks against white blood cells), and/or thrombocytopenia (attacks against platelets). Autoimmunity also can develop against other organs and tissues. Examples of such autoimmune problems include arthritis (attacks against joints), lung disease (attacks against lungs), hepatitis

(attacks against liver), eczema (attacks against skin), alopecia (attacks against hair follicles), type 1 diabetes (attacks against part of the pancreas), and/or scleroderma (attacks against skin and connective tissue).

Some patients also have recurrent, severe infections and fungal infections with low antibody levels (hypogammaglobulinemia). Some patients have short stature, with some exhibiting profound growth failure. In rare cases, patients with *STAT3* GOF develop cancers, such as lymphoma.

Notably, the clinical symptoms of *STAT3* GOF patients differ distinctly from those associated with *STAT3 loss-of-function* mutations. *STAT3* loss-of-function mutations are responsible for hyper-immunoglobulin E syndrome, also called Job's syndrome, which is characterized by recurrent skin infections, unusual eczema-like skin rashes, and susceptibility to severe lung infections.




Clinical features of *STAT3* GOF disease. Credit: NIAID

## Laboratory Findings

*STAT3* GOF patients have moderately low levels of T cells, hypogammaglobulinemia, and elevated levels of immune cells called double negative CD4/CD8 T cells. More studies are required to better understand the connection between these laboratory findings and the type and severity of clinical symptoms.

## Treatment

Treatment is based on a person's clinical condition and may include standard therapies for autoimmune problems. In one reported case, a patient with severe autoimmune hemolytic anemia responded well to the drug rituximab. In another case, use of the drug tocilizumab resulted in a dramatic improvement in one patient's arthritis. Some patients with short stature have responded well to growth hormone treatment. Bone marrow transplant is a possible treatment for this condition and has been used with mixed results in a small number of patients with severe disease.

More research with larger numbers of patients is required to further assess these therapeutic approaches.

## *STAT3* GOF Disease and Your Family

Living with *STAT3* GOF disease 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 *STAT3* GOF disease and

about how the family is dealing with it so misconceptions can be corrected and children can learn to cope with their reactions. Some children with *STAT3* GOF disease 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 *STAT3* GOF disease 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. Patient organizations such as the Immune Deficiency Foundation (www.primaryimmune.org) also are great resources for providing useful information and support. Counseling also can help families cope with the challenges of living with a chronic condition.

At the same time, many families say that *STAT3* GOF disease has brought them closer together. 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 *STAT3* GOF disease. Children also learn who they can turn to for support and how to solve problems. Acknowledging both the challenges and opportunities that *STAT3* GOF disease presents helps children develop resilience.

# Glossary

**Achalasia**—A rare disorder that makes it difficult for food and liquid to pass from the esophagus into the stomach.

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

**Autosomal dominant**—A pattern of inheritance in which an affected person has one mutated copy of a gene and one normal copy.

**Cytopenias**—Reductions in the number of blood cells. Cytopenias can take several forms: a low red blood cell count results in anemia, a low white blood cell count results in leukopenia or neutropenia, and a low platelet count is called thrombocytopenia.

***De novo* mutation**—An alteration in a gene that is present for the first time in one family member as a result of a mutation in the egg or sperm of one of the parents or in the fertilized egg itself.

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

**Double negative CD4/CD8 T cells**—Specific type of T cell without the markers of a CD4 T cell or a CD8 T cell.

**Eczema**—A medical condition in which patches of skin become rough and inflamed, with blisters that cause itching and bleeding. Sometimes also called atopic dermatitis.

**Gain-of-function**—The overactivation of a gene or gene product caused by a genetic mutation.

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

**Gene expression**—The extent to which various genes are "turned on," causing their protein products to be produced.

**Heterozygous**—For a gene present in two copies (one inherited from each parent), heterozygous refers to having a mutation or change in only one of the two copies. This is in contrast to homozygous, in which both copies have mutations or changes.

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

**Hypothyroidism**—A condition in which the thyroid does not produce enough thyroid hormone. The thyroid is a small gland at the base on the neck, below the Adam's apple.

**Incomplete penetrance**—Penetrance refers to the degree to which a particular variant of a gene is expressed in a population. Incomplete penetrance means that not everyone who carries the variant expresses the trait.

**Inflammation**—A localized physical condition in which part of the body becomes reddened, swollen, hot, and often painful, typically as a reaction to injury or infection.

**Lymphadenopathy**—Enlarged lymph nodes.

**Lymphoproliferative**—Referring to the proliferation or overproliferation of immune cells or lymphocytes.

**Nucleus**—The control center of a cell, which houses DNA.

**Signaling pathways**—A set or cascade of chemical reactions inside a cell that occurs when a molecule attaches to a receptor on the cell membrane to cause a change within the cell.

**T-cell lymphopenia**—Having too few T cells.

**Transcription factor**—A protein that binds to specific DNA sequences, thereby controlling which genes are "turned on."

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