GATA2 deficiency is a rare disorder of the immune system with wide-ranging effects. First identified in 2011, the disorder is characterized by immunodeficiency, myelodysplastic syndrome (a condition characterized by ineffective blood cell production), lung disease, and problems of the vascular/lymphatic system. GATA2 deficiency is diagnosed based on clinical findings, laboratory tests, and genetic testing. Early diagnosis is critical for optimal disease management, prevention of severe complications, treatment, and evaluation of at-risk relatives.

Genetics and Function

GATA2 deficiency is caused by germline mutations in the GATA2 gene. Germline means that the mutation is present in every cell in the body, not just the immune system cells.

The GATA2 gene produces a protein called a transcription factor. Transcription factors regulate when other genes are turned on. The GATA2 transcription factor helps regulate blood cell differentiation, the process by which blood stem cells give rise to specialized types of blood cells. When this process does not work properly, people are at risk of developing a wide range of symptoms.

Everyone has two copies of the GATA2 gene—one inherited from the mother and
one from the father. The mechanism underlying GATA2 deficiency is called “haploinsufficiency.” This means that having one mutated copy of GATA2 and one working copy of GATA2 is insufficient for normal functioning of the hematopoietic, or blood-making, system.

Many different germline GATA2 mutations have been reported. These can broadly be categorized as missense, null, and regulator mutations (see Glossary). Approximately 5 percent of people with the clinical symptoms of GATA2 deficiency have no detectable GATA2 mutations, suggesting an important role for undiscovered regulatory regions.

**Inheritance**

GATA2 deficiency is inherited in an autosomal dominant manner, which means that a person needs only one abnormal GATA2 gene copy to have GATA2 deficiency. Dominant inheritance usually means that relatives from the side of the family with the mutation also have symptoms of GATA2 deficiency. These symptoms are typically not present at birth but develop over time. By age 20, about 50 percent of people with a GATA2 mutation have symptoms. By age 60, however, only about 5 percent of people remain symptom-free. This phenomenon is called “incomplete penetrance.”

In a family with a parent who has a GATA2 mutation, each child has a 50 percent, or 1 in 2, chance of inheriting the mutated GATA2 gene. Importantly, the chance of one child inheriting the mutation is independent of whether his or her siblings have the mutation. In other words, if the first three children in a family have the mutation, the fourth child still has a 50 percent chance of inheriting it. Children who do not inherit the abnormal gene will not develop GATA2 deficiency or pass on the mutation. Often, the initial diagnosis in a family will initiate a cascade of genetic testing in relatives who are at risk for having inherited the mutation.
Some GATA2 mutations are not inherited but rather arise spontaneously, or de novo, in the patient. De novo mutations are the result of a mutation in the parent’s sperm or egg or in the fertilized egg itself. Everyone is born with de novo mutations throughout their genomes, but people usually only find out about mutations that occur in important genes such as GATA2.

**Clinical Features**

The clinical features of GATA2 deficiency are wide-ranging both in type and severity. For example, one person may have severe viral infections causing recalcitrant warts; another may develop acute myeloid leukemia; and another’s only symptom may be hearing loss. This variation in how GATA2 deficiency manifests in each person, called “variable expressivity,” can be striking, even in the same family. Generally, the disease has a progressive course. The main clinical features of GATA2 deficiency include the following:

- **Hematologic:** Cytopenias, or reductions in the number of blood cells (cyto meaning cell, penia meaning too few), are common and can affect several cell types, including B cells, natural killer cells, monocytes, and T cells. The results of this can be profound. Sometimes the problems with these cells progress to the point that they are formally called “myelodysplastic syndrome.” In a subset of patients, this can evolve into cancers of the blood, such as acute myeloid leukemia (AML) or chronic myelomonocytic leukemia (CMML). Progressively worsening cytopenias are associated with other major complications of GATA2 deficiency, including lung problems and infections.

- **Infectious:** The majority of patients with GATA2 deficiency eventually develop major viral, bacterial, or fungal infections. Viral infections are the most common and may include human papillomavirus (HPV), which causes warts; severe herpesvirus; persistent Epstein-Barr virus (EBV) viremia; or molluscum contagiosum (see Glossary for more details about these infections).

- **Pulmonary:** The main pulmonary feature of GATA2 is the development of pulmonary alveolar proteinosis (PAP). This is a rare lung disease in which a type of protein builds up in the air sacs (alveoli) of the lungs, making breathing difficult. A subset of patients with PAP go on to develop a serious type of high blood pressure that affects the arteries in the lungs and heart, called pulmonary arterial hypertension.
• **Dermatologic:** The main dermatologic symptoms are caused by the underlying immunodeficiency or hematologic problems. Persistent warts are the most common skin issue in people with GATA2 deficiency, and typically these warts are not helped by cauterization, cryotherapy, topical treatments, or laser treatments (see Glossary for more details). Chronic skin infections increase the risk of skin cancers, including squamous cell carcinoma. Skin problems due to bacteria, fungus, or lymph problems also have been reported in people with GATA2 deficiency.

• **Neoplastic:** In addition to blood cancers, solid tumors—most commonly skin cancers—also may occur in people with GATA2 deficiency. A number of other types of tumors have been seen, although their occurrence is rare and their association with the underlying GATA2 deficiency is unclear.

• **Vascular/lymphatic:** A minority of patients with GATA2 deficiency may experience chronic lymphedema, swelling in an arm or leg caused by a lymphatic system blockage.

• **Other:** Hearing loss, increased risk of miscarriage, and hypothyroidism also may be part of the clinical spectrum of GATA2 deficiency.

Because GATA2 deficiency is a rare disorder, current knowledge is based on the careful study of several dozen families affected by GATA2 deficiency. As research continues, understanding of the clinical spectrum, disease course, and underlying biology will be refined.

**Laboratory Findings**

Laboratory findings can vary widely in this disease, although they typically include low levels of certain blood cells, especially B cells, natural killer cells, monocytes, and dendritic cells.

**Management and Treatment**

Treatment for GATA2 deficiency is based on a person’s clinical condition and may include medications and other strategies for managing specific infections, cytopenias, and pulmonary or vascular issues. Doctors may recommend the prophylactic, or preventive, use of antimicrobial drugs to prevent infections.

A bone marrow transplant, also called a hematopoietic stem cell transplant, is the best long-term treatment option for many serious genetic immunodeficiency diseases. This therapy has been used to manage patients with GATA2 deficiency, and it can resolve most of their clinical symptoms and laboratory abnormalities. In this procedure, stem cells are removed from a donor, the patient receives treatment to destroy his or her own blood-forming cells, and then the patient receives the donor's
stem cells. The transplanted stem cells form a new, healthy immune system. Unfortunately, bone marrow transplantation poses substantial risks. These include graft-versus-host disease, in which the transplanted cells recognize the recipient’s cells as “foreign” and attack them; graft failure, in which the recipient’s immune system rejects the transplant; and complications from the chemotherapy prior to transplant, such as infertility. Families must carefully consider the risks and benefits before pursuing bone marrow transplant or other treatment options.

**GATA2 Deficiency and Your Family**

Living with GATA2 deficiency 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 GATA2 deficiency 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 GATA2 deficiency 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.

Some children who have siblings with GATA2 deficiency 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) or Be The Match (www.bethematch.org), operated by the National Marrow Donor Program, are great resources for providing useful information and support. Counseling also can help families cope with the challenges of GATA2 deficiency.

At the same time, many families say that GATA2 deficiency has brought them closer together. Through their experiences with the disease and its treatment, family members learn about controllable and uncontrollable aspects of life. How a family responds to the stress of any illness is controllable and an important aspect of managing GATA2 deficiency. Children also learn who they can turn to for support and how to solve problems. Acknowledging both the challenges and opportunities that GATA2 deficiency presents helps everyone develop resilience.
Glossary

Acute myeloid leukemia (AML)—A type of cancer of the blood and bone marrow that affects immature blood cell growth.

Bone marrow transplant—A procedure to replace unhealthy or defective bone marrow with healthy bone marrow stem cells. Bone marrow is the soft, fatty tissue inside bones. Also called hematopoietic stem cell transplant.

Cauterization—A procedure in which warts are destroyed by burning them in a controlled way.

Chronic lymphedema—Swelling in an arm or leg caused by a lymphatic system blockage.

Chronic myelomonocytic leukemia (CMML)—A type of cancer of the blood that tends to progress more slowly than acute forms of leukemia.

Cryotherapy—A procedure in which warts are destroyed by freezing them in a controlled way.

Cytopenia—A reduction in the number of blood cells, which can take many forms depending on the population of cells affected.

De novo mutations—Mutations that are not inherited but new in the patient as a result of a mutation in their parent’s sperm or egg or in the fertilized egg itself.

Dermatologic—Related to conditions of the skin.

Differentiation—The process by which cells become progressively more specialized.

Epstein-Barr virus (EBV) viremia—EBV is a very common virus that can remain in the body indefinitely in its latent form. Viremia is the presence of the virus in the blood. EBV viremia can signal broader problems with the immune system.

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

Germline mutations—A mutation that is present in every cell in a person’s body, not just the immune system cells.

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.

Hematologic—Related to the blood system.

Hematopoietic system—The system of organs and tissues, primarily the bone marrow, spleen, tonsils, and lymph nodes, that are involved in the production of blood and immune cells.

Herpesvirus—A large family of viruses that can cause disease.

Human papillomavirus (HPV)—A common virus that can cause warts.

Hypothyroidism—A condition in which the thyroid gland, an endocrine gland at the base of the neck that helps regulate metabolism, does not produce enough thyroid hormone.

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.

Incomplete penetrance—Penetration 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.

Lymphatic system—The network of vessels through which lymph drains from the tissues into the blood.

Missense mutation—A type of mutation in which a single nucleotide change results in a change in an amino acid. Amino acids are the building blocks of proteins.

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.

Myelodysplastic syndrome—A diagnostic term that refers to a group of disorders caused by poorly formed or dysfunctional blood cells.

Neoplastic—Related to an abnormal growth of tissue, benign or malignant.

Null mutation—A type of mutation that results in the complete lack of the normal function of the gene.

Pulmonary—Related to the lungs.

Pulmonary alveolar proteinosis (PAP)—A rare lung disease in which a type of protein builds up in the air sacs (alveoli) of the lungs, making breathing difficult.

Regulatory mutations—A type of mutation that affects the regulation of the gene.

Squamous cell carcinoma (SCC)—A type of cancer caused by an uncontrolled growth of an abnormal squamous cell. SCC can develop from many organs but is often a skin cancer.

Stem cells—Cells that are capable of giving rise to several different cell types.

Transcription factor—A protein that regulates when other genes are turned on.

Vascular system—A system of vessels that carry blood and lymph through the body, delivering oxygen and nutrients and taking away waste. Also called the circulatory system.