

BENTA Disease

What Is BENTA Disease?

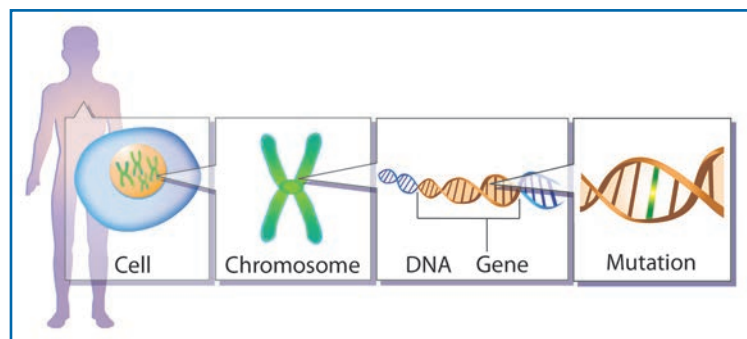
BENTA disease is a rare genetic disorder of the immune system caused by mutations in the gene *CARD11*. BENTA stands for “**B**-cell **e**xpansion with **NF-κB** and **T**-cell **a**nergy.” The disease is characterized by high levels of certain immune cells starting in infancy, an enlarged spleen, enlarged lymph nodes, immunodeficiency, and an increased risk of lymphoma, a type of cancer. Breaking down the name, BENTA, helps explain the syndrome.

- A *B cell* is a type of immune cell from the bone marrow.
- *Expansion* means that the number of B cells is greater than normal.
- *NF-κB* is a protein complex involved in gene expression, or the degree to which certain genes are turned on or off.
- A *T cell* is a type of immune cell that matures in the thymus, a small organ located in the upper chest under the breastbone.
- *Anergy* refers to a “less-than-normal” (T cell) immune reaction to foreign substances.

BENTA disease is diagnosed based on clinical and laboratory findings as well as genetic testing.

Genetics and Function

BENTA disease is caused by “gain-of-function” mutations in the gene *CARD11*, which provides instructions for production of the *CARD11* protein. These gain-of-function mutations cause the *CARD11* protein to be overactive. The *CARD11* protein is required for activation of NF-κB in both B and T cells, which is essential for a healthy immune response. The development and differentiation of B cells might also be partially impaired in BENTA disease.



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 BENTA disease. Credit: NIAID



The gain-of-function *CARD11* mutations associated with BENTA disease may also predispose patients to B-cell cancers. Importantly, overactivation of the NF-κB pathway, as occurs in BENTA disease, is frequently associated with B-cell cancers. Specifically, somatic (present only in some cells, such as cancer cells) gain-of-function *CARD11* mutations are seen frequently in a type of cancer called diffuse large B-cell lymphoma. These mutations do not appear to be associated with T-cell cancers.

Inheritance

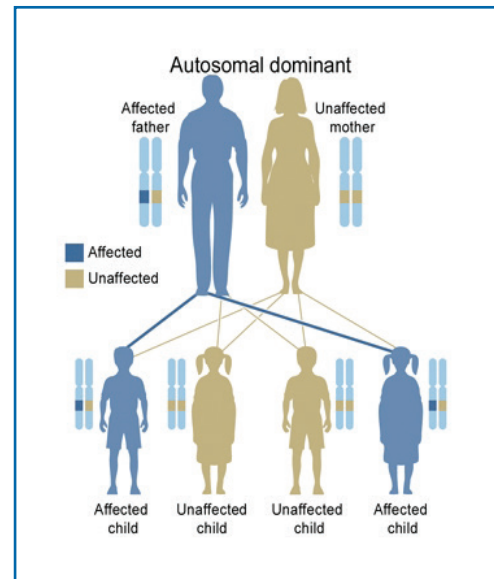
BENTA disease is inherited in an autosomal dominant manner. “Autosomal” refers to the fact that every person has two copies of the *CARD11* gene, one inherited from each parent. Only one of the two copies of *CARD11* needs to be abnormal for a person to have BENTA disease. “Dominant” indicates that the abnormal copy of the gene from one parent dominates the matching, normal gene copy from the other parent. Autosomal dominant inheritance means that most families with BENTA disease have affected relatives on the side of the family with the mutation.

Children of a parent who carries a *CARD11* mutation have a 50 percent chance of inheriting the mutation. In a family, each child’s risk of inheriting a mutated copy of the *CARD11* gene is independent of whether his or her siblings inherited the mutation. For example, if the first four children in a family have the mutation, the next child has the same 50 percent risk of inheriting the mutation. Children who do not inherit the mutation will not develop BENTA disease or pass on the mutation to their children.

BENTA disease can also arise spontaneously in a patient as the result of a *de novo* mutation in *CARD11*. *De novo* mutations are not inherited but occur as a result of a mutation in the egg or sperm of one of the parents or in the fertilized egg itself. A patient with a *de novo* mutation can pass on the mutation to his or her children.

Clinical Symptoms

People with BENTA disease have polyclonal B-cell lymphocytosis (elevated levels of certain types of B cells) that develops in infancy, splenomegaly (enlarged spleen), and lymphadenopathy (enlarged lymph nodes). These features, as well as laboratory findings characteristic of BENTA disease, likely contribute to the mild immunodeficiency seen in people with BENTA disease. People with BENTA disease are susceptible to recurrent sinus and lung infections, as well as infections with viruses such as molluscum contagiosum virus, Epstein-Barr virus, or BK virus.



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

People with BENTA disease must be closely monitored for any signs of a B-cell cancer. A diagnosis of leukemia can generally be ruled out in people with BENTA disease based on the unremarkable appearance of their resting lymphocytes, or white blood cells. However, at least one patient with BENTA disease developed B-cell chronic lymphocytic leukemia as an adult. Cancer symptoms may include fatigue, loss of appetite, weight loss, or night sweats.

Laboratory Findings

There are a few notable patterns that doctors can observe in the blood of a person with BENTA disease. The majority of BENTA patient blood cells are naïve, mature B cells, with elevated levels of a subtype of B cells called transitional B cells. Laboratory studies also have shown poor B-cell differentiation and immunoglobulin, or antibody, secretion. Serum IgM, a type of antibody, is low in most patients, and total IgG and IgA are typically on the low end of normal. Some patients have poor immune responses to certain vaccines. T-cell counts in people with BENTA disease are within or just above the normal range, although the T cells may be poorly responsive to certain foreign pathogens, hence inclusion of the word “anergy” as part of the BENTA acronym.

Treatment

Currently, minimal treatment options are available for people with BENTA disease. Doctors closely monitor BENTA patients for infections and for signs of development of B-cell cancers. Splenectomy, or spleen removal, potentially could help reduce the B-cell burden in patients with BENTA disease. However, according to two published reports, B-cell counts increased dramatically in two patients who underwent the procedure. It remains to be determined whether immunosuppressive drugs, including B-cell-depleting drugs such as rituximab, are effective for treating BENTA disease.

BENTA Disease and Your Family

Living with BENTA disease 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 BENTA 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 BENTA 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 spleen and lymph nodes). Some children with BENTA disease are asked to wear special “spleen guards,” which can be cumbersome, to protect against serious injuries when playing sports.

Some children who have siblings with BENTA 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) are great resources for providing useful information and support. The BENTA disease Wikipedia page (en.wikipedia.org/wiki/BENTA_disease) also provides simple information about the disease. Counseling can also help families cope with the challenges of BENTA disease.

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

Glossary

Anergy—A lacking or weak immune system response.

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

B cell—A type of immune cell that comes from the bone marrow. B cells present antigens, or foreign substances, to T cells and produce antibodies, or immunoglobulins.

BK virus—A common virus that typically only causes problems for those with immune deficiency.

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.

De novo mutation—A gene mutation that occurs in the egg or sperm of one of the parents or in the fertilized egg itself.

Differentiation—The process by which a cell changes from one cell type to another or acquires a different set of functions.

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

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

Gain-of-function mutation—A type of gene mutation that causes the protein produced from the gene to be overactive.

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

Germline—Part of a person's genetic makeup that is present in every cell of the body and can be transmitted to offspring.

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

Immunosuppressive medications—Medications that are used to suppress an overactive immune system.

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.

Lymphadenopathy—Enlarged lymph nodes.

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

Lymphocytosis—A disorder involving abnormally high lymphocyte counts.

Lymphoma—Cancer that begins in cells of the immune system.

Molluscum contagiosum—A viral skin infection that results in round, firm, painless bumps.

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

NF- κ B—A protein complex involved in gene expression, or the degree to which certain genes are turned on or off. NF- κ B controls many genes required for cell growth, survival, and cell function in the immune system.

Rituximab—An antibody-based drug that destroys B cells and is used to treat diseases characterized by excessive numbers of B cells, overactive B cells, or B cells that do not function properly.

Splenectomy—Removal of the spleen, a fist-sized organ that sits above the stomach and is part of the lymphatic system.

Splenomegaly—Enlargement of the spleen.

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

