CARD11 Gene

Subjects: Genetics & Heredity

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caspase recruitment domain family member 11

genes

1. Normal Function

The *CARD11* gene provides instructions for making a protein involved in the function of immune system cells called lymphocytes, particularly certain types called T cells and B cells. These cells identify foreign substances such as bacteria, viruses, and fungi and defend the body against infection. When T or B cells recognize a foreign substance, the CARD11 protein is turned on (activated) and attaches (binds) to two other proteins, BCL10 and MALT1, to form the CBM signalosome complex. This complex in turn activates other protein complexes called nuclear factor-kappa-B (NF-κB) and mTOR complex 1 (mTORC1), which are important for cellular signaling. NF-κB and mTORC1 signaling direct the development and function of T and B cells so they can support an immune response against foreign invaders.

2. Health Conditions Related to Genetic Changes

2.1. Atopic Dermatitis

At least five *CARD11* gene mutations have been identified in people with a skin disorder called atopic dermatitis (also known as atopic eczema). This condition is characterized by dry, itchy skin and red rashes. The word "atopic" indicates an association with allergies. While atopic dermatitis is not always due to an allergic reaction, it is commonly associated with other allergic disorders. People with atopic dermatitis caused by *CARD11* gene mutations often have additional allergic disorders, such as asthma and environmental (such as pollen) or food allergies. Many of these individuals also have recurrent infections due to problems with the immune system (immunodeficiency).

Atopic dermatitis is generally thought of as a complex condition that is influenced by multiple genetic and environmental factors, which each contribute only a small amount to the overall risk of developing the condition. However, *CARD11* gene mutations appear to cause atopic dermatitis without other factors. These mutations likely account for only a small percentage of cases of the condition.

A mutation in one of the two copies of the *CARD11* gene in each cell is sufficient to cause atopic dermatitis. These mutations result in the production of an altered protein that does not function normally. The altered protein produced from the mutated copy of the gene interferes with the normal protein produced from the non-mutated copy of the gene (such mutations are described as "dominant-negative"), so the amount of functioning CARD11 protein in cells is reduced. These genetic changes are thought to prevent formation of the CBM signalosome complex, impairing signaling by NF-κB and mTORC1. Without these signals, T cells do not develop or function properly. The number of these cells is normal, but their response to foreign invaders is diminished, leading to recurrent infections.

It is not clear how the immune dysfunction caused by *CARD11* gene mutations leads to atopic dermatitis and allergic disorders. Atopic dermatitis is not initially caused by an allergic reaction, although sometimes substances that can cause allergic reactions (allergens) are thought to contribute to flare-ups of the rashes.

2.2. Omenn Syndrome

Omenn syndrome

2.3. Other Disorders

CARD11 gene mutations can cause other immune system disorders. At least 3 mutations in the gene have been found to cause a type of severe combined immunodeficiency (SCID) known as immunodeficiency 11. SCID is a group of disorders characterized by an almost total lack of immune protection from foreign invaders. Immunodeficiency 11 is characterized by recurrent severe infections in the respiratory tract, particularly pneumonia caused by a fungus known as *Pneumocystis jirovecii*. Immunodeficiency 11 occurs when both copies of the *CARD11* gene are mutated. The mutations are described as "loss of function" because they lead to production of an abnormally short, nonfunctional CARD11 protein. The lack of CARD11 function diminishes T cells' ability to fight foreign invaders, despite normal numbers of the cells, leading to recurrent infections. Individuals with immunodeficiency 11 do not appear to have an increased risk of atopic dermatitis (described above) or allergies.

At least four mutations in the *CARD11* gene cause another immune cell disorder called B-cell expansion with NF-κB and T-cell anergy (BENTA). This condition is characterized by an excess of immune system cells called B cells (B-cell lymphocytosis), an increased risk of B-cell lymphoma, and susceptibility to infection. The mutations that cause BENTA are inherited and occur in one copy of the *CARD11* gene. Like those involved in B-cell and T-cell cancers (described above), the genetic changes that cause BENTA are "gain-of-function" mutations; they lead to production of an altered CARD11 protein that is always turned on, resulting in constant NF-κB signaling. Overactive NF-κB promotes the proliferation of B cells, which can lead to B-cell lymphoma. These abnormal cells, however, cannot respond to infections. T cells are also abnormal and unable to fight foreign invaders (a phenomenon known as anergy). These immune cell problems lead to the increased risk of infection in people with BENTA.

2.4. Cancers

Mutations in the *CARD11* gene are also associated with cancers of B cells (primarily diffuse large B-cell lymphoma) and T cells (adult T-cell leukemia/lymphoma). These mutations are not inherited; instead, they arise during a person's lifetime and are found only in B or T cells that give rise to cancer. These genetic changes are called "gain-of-function" mutations because they lead to production of an altered CARD11 protein that is always turned on, even without recognition of foreign substances by the B or T cell. As a result, NF-κB is constantly activated. Unregulated NF-κB signaling allows these cells to grow and divide without control, contributing to the development of cancer.

3. Other Names for This Gene

- bcl10-interacting maguk protein 3
- BENTA
- BIMP3
- CARD-containing MAGUK protein 1
- carma 1
- CARMA1
- caspase recruitment domain-containing protein 11
- IMD11
- IMD11A
- PPBL

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