PLCG2-associated antibody deficiency and immune dysregulation

Description

PLCG2-associated antibody deficiency and immune dysregulation (PLAID) is an immune system disorder characterized by an allergic reaction to cold temperatures. Other immune system problems can also occur. The hallmark feature of PLAID is the development of a red, itchy rash (hives) when the skin is exposed to cool temperatures, which is known as cold urticaria. In PLAID, the hives typically develop in response to evaporative cooling, such as when a cool breeze or air conditioning blows on damp or sweaty skin. Being in a cold swimming pool can also trigger hives. In contrast, people with PLAID do not have a reaction when they touch a cold object, like an ice cube. (The ice cube test is a common test for a cold allergy; it triggers a reaction in people with other forms of cold urticaria, which usually begin later in life than PLAID.) However, some people with PLAID do experience a burning sensation in their throats when they eat cold foods, like ice cream. In PLAID, the hives go away once the skin warms up. Prolonged exposure to cold can lead to loss of consciousness or a serious allergic reaction known as anaphylaxis.

Other skin problems can also occur in PLAID. A small number of affected individuals develop a blistering rash on the tip of their nose, ears, and fingers shortly after birth. The rash usually heals on its own in infancy, although in rare cases, it worsens over time. After the initial rash goes away, a different rash sometimes develops on the torso and limbs later in life. This rash, called a granuloma, can affect small patches of skin or be widespread. In people with PLAID, the granulomas do not occur in warm regions of the body, such as the armpits and other skin folds.

In many people with PLAID, immune system function is reduced, leading to recurrent infections such as frequent colds, ear infections, or bouts of pneumonia. The infections are likely related to lower-than-normal levels of special proteins called antibodies or immunoglobulins, particularly immunoglobulin M (IgM) or immunoglobulin G (IgG). Antibodies attach to specific foreign particles and germs, marking them for destruction. The number of immune system cells called natural killer (NK) cells may also be reduced.

Autoimmune disorders, which occur when the immune system malfunctions and attacks the body's own tissues and organs, can also occur. Autoimmune disorders associated with PLAID include autoimmune thyroiditis and vitiligo. Autoimmune thyroiditis results

from damage to the butterfly-shaped, hormone-producing gland in the lower neck (the thyroid). Vitiligo is caused by attacks on the pigment cells in the skin, resulting in a patchy loss of skin coloration. Most people with PLAID have abnormal antibodies called autoantibodies in their blood. One such antibody common in people with PLAID is known as antinuclear antibody (ANA). Autoantibodies attach to normal proteins and can trigger an immune attack against the body's own tissues. However, not everyone with these abnormal antibodies has an autoimmune disease.

Frequency

PLAID is a rare disorder whose prevalence is unknown. Only a few affected families have been reported in the medical literature.

Causes

PLAID is caused by mutations in the *PLCG2* gene, which provides instructions for making an enzyme called phospholipase C gamma 2 (PLCγ2). This enzyme is found predominantly in immune system cells and is critical for the cells' roles in preventing infection by recognizing and attacking foreign invaders, such as bacteria and viruses.

The *PLCG2* gene mutations that cause PLAID remove (delete) segments of DNA from the gene. These changes alter a region of the PLCγ2 enzyme that controls whether it is turned on or off. The altered enzyme does not function properly. At lower temperatures, the enzyme is constantly active, rather than being turned on only when needed. It is thought that when the skin is cooled, the PLCγ2 enzyme is turned on, and the abnormal activity triggers an immune reaction, resulting in hives and skin rashes. Researchers are unsure if a similar mechanism underlies autoimmune disease in people with PLAID. Researchers speculate that the abnormal activity of the enzyme occurs in only a small range of cool temperatures. Direct contact with a cold object, such as an ice cube, may be too cold to turn on the enzyme, which might explain why people with PLAID do not react to the ice cube test.

In contrast, at normal body temperature, the PLCγ2 enzyme's activity is reduced. The resulting impairment of immune cell function prevents the body from effectively fighting foreign invaders, leading to recurrent infections.

Learn more about the gene associated with PLCG2-associated antibody deficiency and immune dysregulation

- PLCG2

Inheritance

This condition is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder.

In most cases, an affected person has one parent with the condition.

Other Names for This Condition

- Antibody deficiency and immune dysregulation, PLCG2-associated
- FACU
- Familial atypical cold urticaria
- Familial cold autoinflammatory syndrome 3
- Familial cold urticaria with common variable immunodeficiency
- FCAS3
- PLAID
- PLCG2 associated antibody deficiency and immune dysregulation

Additional Information & Resources

Genetic Testing Information

- Genetic Testing Registry: Familial cold autoinflammatory syndrome 3 (https://www.ncbi.nlm.nih.gov/gtr/conditions/C3280914/)

Genetic and Rare Diseases Information Center

- Cold urticaria (https://rarediseases.info.nih.gov/diseases/6131/index)

Patient Support and Advocacy Resources

- National Organization for Rare Disorders (NORD) (https://rarediseases.org/)

Catalog of Genes and Diseases from OMIM

- FAMILIAL COLD AUTOINFLAMMATORY SYNDROME 3; FCAS3 (https://omim.org/entry/614468)

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28Immune+System+Diseases%5BMAJR%5D%29+AND+%28%28PLCG2+associated+antibody+deficiency+and+immune+dysregulation%5BTIAB%5D%29+OR+%28PLAID%5BTIAB%5D%29%29+OR+%28%28PLCG2%5BTIAB%5D%29+AND+%28cold+urticaria%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D)

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