PLCG2 gene

phospholipase C gamma 2

Normal Function

The *PLCG2* gene provides instructions for making an enzyme called phospholipase C gamma 2 (PLCγ2). This enzyme performs a chemical reaction that enables molecules to relay signals from outside the cell to the inside. These signals direct cellular functions, including growth, maturation, and movement (migration). The PLCγ2 enzyme is particularly important in immune system cells, including B cells, natural killer (NK) cells, and mast cells. The enzyme is critical for the cells' roles in preventing infection by recognizing and attacking foreign invaders, such as bacteria and viruses.

When foreign invaders are detected, the PLCγ2 enzyme relays signals for B cells to produce specialized proteins called antibodies (or immunoglobulins) that attach to foreign particles and mark them for destruction. Signaling through the enzyme is also involved in the destruction of foreign invaders by NK cells. PLCγ2 enzyme signaling in mast cells and other immune cells triggers inflammation, which helps clear infections or other irritants. Mast cells also play a role in allergic reactions, which occur when the immune system overreacts to stimuli that are not harmful.

Health Conditions Related to Genetic Changes

PLCG2-associated antibody deficiency and immune dysregulation

At least three mutations in the *PLCG2* gene have been found to cause PLCG2-associated antibody deficiency and immune dysregulation (PLAID). This condition is characterized by the development of a red, itchy rash (known as hives or urticaria) when exposed to cool temperatures, in particular cooling caused by evaporation, such as when a cool breeze blows on damp skin. Other skin rashes, recurrent infections, and autoimmune diseases, which occur when the immune system malfunctions and attacks the body's own tissues, can also occur in PLAID.

The mutations associated with PLAID are classified as germline, which means they are present in essentially all of the body's cells. They remove (delete) small pieces of DNA from the *PLCG2* gene. These changes alter a region of the PLCγ2 enzyme that controls whether the enzyme is turned on (activated) or turned off (inactivated).

The altered PLCγ2 enzyme does not function normally. At low temperatures, the

enzyme is constantly turned on, even when it is not needed. Signals triggered by PLCγ2 in response to cold, particularly in mast cells in the skin, likely result in hives and other skin rashes. Researchers are unsure if a similar mechanism underlies autoimmune disease in people with PLAID.

In contrast, at normal body temperature the altered enzyme's activity is reduced. The resulting impairment of B-cell and NK-cell function prevents the body from effectively fighting foreign invaders, leading to recurrent infections in people with PLAID.

Other disorders

At least two mutations in the *PLCG2* gene cause a condition called autoinflammation and PLCG2-associated antibody deficiency and immune dysregulation (APLAID). The condition is characterized by episodes of abnormal inflammation throughout the body and recurrent infections. Inflammation is a normal immune system response to injury and foreign invaders. However, in APLAID the uncontrolled inflammation occurs even without infection and can damage many of the body's tissues and organs, including the skin, eyes, lungs, gastrointestinal system, and joints. Individuals with APLAID can also have reduced immune function leading to recurrent infections, similar to those in PLAID (described above). Unlike PLAID, APLAID is not associated with an allergic reaction to cold.

The *PLCG2* gene mutations involved in APLAID change single protein building blocks (amino acids) in the PLCγ2 enzyme. The changes occur in the same region of the enzyme that is affected in PLAID. In APLAID, the altered enzyme is constantly turned on at normal body temperature. The overactivity abnormally increases inflammation, causing the characteristic features of APLAID. For unknown reasons, the function of B cells is impaired in people with APLAID, resulting in recurrent infections.

Several *PLCG2* gene mutations have been associated with ibrutinib resistance, which is a condition in which the drug ibrutinib becomes ineffective in people with these mutations. Ibrutinib is used to treat a blood cell cancer called chronic lymphocytic leukemia (CLL). The drug normally prevents a protein called BTK from sending signals for cells to grow and divide, which blocks the growth of cancer cells. The *PLCG2* gene mutations associated with ibrutinib resistance increase the activity of the PLCγ2 protein. Overactive PLCγ2 enzymes relay signals for cancerous cells to multiply despite the blockage of BTK signaling. Often two or more *PLCγ2* gene mutations are found in affected individuals. Mutations in other genes can also be involved. Unlike mutations that cause APLAID and PLAID (described above), *PLCG2* gene mutations associated with ibrutinib resistance arise during a person's lifetime (somatic mutations) and are present only in cancer cells.

Other Names for This Gene

- *1-Phosphatidylinositol 4,5-Bisphosphate Phosphodiesterase Gamma-2*
- *Phosphatidylinositol-Specific Phospholipase C-Gamma*
- *PLC-gamma 2*

- *PLCgamma2*

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- *Tests of PLCG2 (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=5336[geneid])*

Scientific Articles on PubMed

- *PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28%28PLCG2%5BTIAB%5D%29+OR+%28phospholipase+C+gamma+2%5BTIAB%5D%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D)*

Catalog of Genes and Diseases from OMIM

- *PHOSPHOLIPASE C, GAMMA-2; PLCG2 (https://omim.org/entry/600220)*
- *AUTOINFLAMMATION, ANTIBODY DEFICIENCY, AND IMMUNE DYSREGULATION; APLAID (https://omim.org/entry/614878)*

Gene and Variant Databases

- *NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/5336)*
- *ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=PLCG2[gene])*

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Genomic Location

The *PLCG2* gene is found on chromosome 16 (https://medlineplus.gov/genetics/chromosome/16/).

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