Familial cold autoinflammatory syndrome type 2

Description

Familial cold autoinflammatory syndrome type 2 is a condition that causes episodes of fever, skin rash, and joint pain. These episodes can be triggered by exposure to cold temperatures, or they may arise without warning, and they can last a few hours to several days. These episodes typically begin in childhood and persist throughout life.

Episodes typically occur after an hour or more of cold exposure in affected individuals who are sensitive to cold; however only a few minutes of cold exposure is required in some individuals.

In people with familial cold autoinflammatory syndrome type 2, the most common symptom that occurs during an episode is a fever. Other common features are an itchy rash and joint and muscle pain.

Additional features of familial cold autoinflammatory syndrome type 2 include abdominal pain, diarrhea, headache, and nausea. Some affected individuals develop hearing loss (sensorineural deafness) due to chronic inflammation.

Frequency

Familial cold autoinflammatory syndrome type 2 is a very rare condition. More than 60 cases of this condition have been reported in the scientific literature.

Causes

Familial cold autoinflammatory syndrome type 2 is caused by variants (also known as mutations) in the *NLRP12* gene. The NLRP12 gene provides instructions for making the protein monarch-1. Monarch-1 belongs to a family of proteins called intracellular "NOD-like" receptor (NLR) proteins. These proteins are involved in the immune system, helping to regulate the process of inflammation. Inflammation occurs when the immune system sends signaling molecules and white blood cells to a site of injury or disease to fight microbial invaders and facilitate tissue repair. When this has been accomplished, the body stops (inhibits) the inflammatory response to prevent damage to its own cells and tissues. The monarch-1 protein is primarily involved in stopping the inflammatory response, but it can trigger inflammation in certain situations.

Most variants in the *NLRP12* gene appear to reduce the ability of the monarch-1 protein

to stop inflammation, resulting in an unusually long inflammatory response. Research shows that other variants increase the protein's ability to trigger inflammatory responses, even when there is no injury or disease.

Impairment of the body's mechanisms for controlling inflammation results in the episodes of skin rash, fever, and joint pain seen in familial cold autoinflammatory syndrome type 2. It is unclear why episodes can be triggered by cold exposure in this disorder.

Additional changes in the *NLRP12* gene or changes in other genes may influence the severity of familial cold autoinflammatory syndrome type 2, but little is known about how these changes contribute to the condition.

Learn more about the gene associated with Familial cold autoinflammatory syndrome type 2

- NLRP12

Inheritance

In most cases, familial cold autoinflammatory syndrome type 2 is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder. Most affected individuals have one parent with the condition.

In some families, individuals with an *NLRP12* gene variant may develop familial cold autoinflammatory syndrome type 2 but others with the variant do not, which is a situation known as reduced penetrance.

In rare cases, familial cold autoinflammatory syndrome type 2 is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have variants. The parents of an individual with an autosomal recessive condition each carry one copy of the altered gene, but they typically do not show signs and symptoms of the condition.

Other Names for This Condition

- Familial cold-induced autoinflammatory syndrome type 2
- FCAS2

Additional Information & Resources

Genetic Testing Information

- Genetic Testing Registry: Familial cold autoinflammatory syndrome 2 (https://www.ncbi.nlm.nih.gov/gtr/conditions/C2673198/)

Genetic and Rare Diseases Information Center

- Familial cold urticaria (https://rarediseases.info.nih.gov/diseases/9535/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 2; FCAS2 (https://omim.org/entry/611762)

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=familial+cold+autoinflammatory+syndrome+AND+NLRP12)

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