Tumor necrosis factor receptor-associated periodic syndrome

Tumor necrosis factor receptor-associated periodic syndrome (commonly known as TRAPS) is a condition characterized by recurrent episodes of fever. These fevers typically last about 3 weeks but can last from a few days to a few months. The frequency of the episodes varies greatly among affected individuals; fevers can occur anywhere between every 6 weeks to every few years. Some individuals can go many years without having a fever episode. Fever episodes usually occur spontaneously, but sometimes they can be brought on by a variety of triggers, such as minor injury, infection, stress, exercise, or hormonal changes.

During episodes of fever, people with TRAPS can have additional signs and symptoms. These include abdominal and muscle pain and a spreading skin rash, typically found on the limbs. Affected individuals may also experience puffiness or swelling in the skin around the eyes (periorbital edema); joint pain; and inflammation in various areas of the body including the eyes, heart muscle, certain joints, throat, or mucous membranes such as the moist lining of the mouth and digestive tract. Occasionally, people with TRAPS develop amyloidosis, an abnormal buildup of a protein called amyloid in the kidneys that can lead to kidney failure. It is estimated that 15 to 20 percent of people with TRAPS develop amyloidosis, typically in mid-adulthood.

The fever episodes characteristic of TRAPS can begin at any age, from infancy to late adulthood, but most people have their first episode in childhood.

Frequency

TRAPS has an estimated prevalence of one per million individuals; it is the second most common inherited recurrent fever syndrome, following a similar condition called familial Mediterranean fever. More than 1,000 people worldwide have been diagnosed with TRAPS.

Genetic Changes

TRAPS is caused by mutations in the *TNFRSF1A* gene. This gene provides instructions for making a protein called tumor necrosis factor receptor 1 (TNFR1). This protein is found within the membrane of cells, where it attaches (binds) to another protein called tumor necrosis factor (TNF). This binding sends signals that can trigger the cell either to initiate inflammation or to self-destruct. Signaling within the cell initiates a pathway that turns on a protein called nuclear factor kappa B that triggers inflammation and leads to the production of immune system proteins called cytokines. The self-destruction of the cell (apoptosis) is initiated when the TNFR1 protein, bound to the TNF protein, is brought into the cell and triggers a process known as the caspase cascade.
Most TNFRSF1A gene mutations that cause TRAPS result in a TNFR1 protein that is folded into an incorrect 3-dimensional shape. These misfolded proteins are trapped within the cell and are not able to get to the cell surface to interact with TNF. Inside the cell, these proteins clump together and are thought to trigger alternative pathways that initiate inflammation. The clumps of protein constantly activate these alternative inflammation pathways, leading to excess inflammation in people with TRAPS. Additionally, because only one copy of the TNFRSF1A gene has a mutation, some normal TNFR1 proteins are produced and can bind to the TNF protein, leading to additional inflammation. It is unclear if disruption of the apoptosis pathway plays a role in the signs and symptoms of TRAPS.

Inheritance Pattern
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. However, some people who inherit the altered gene never develop features of TRAPS. (This situation is known as reduced penetrance.) It is unclear why some people with a mutated gene develop the disease and other people with the mutated gene do not. In most cases, an affected person inherits the mutation from one affected parent. Other cases result from new mutations in the gene and occur in people with no history of the disorder in their family.

Other Names for This Condition
• autosomal dominant familial periodic fever
• familial Hibernian fever
• FPF
• TNF receptor-associated periodic fever syndrome
• TRAPS

Diagnosis & Management
Genetic Testing
• Genetic Testing Registry: TNF receptor-associated periodic fever syndrome (TRAPS)

Other Diagnosis and Management Resources
• University College London: National Amyloidosis Center (UK)
General Information from MedlinePlus

- Diagnostic Tests
  https://medlineplus.gov/diagnostictests.html
- Drug Therapy
  https://medlineplus.gov/drugtherapy.html
- Genetic Counseling
  https://medlineplus.gov/geneticcounseling.html
- Palliative Care
  https://medlineplus.gov/palliativecare.html
- Surgery and Rehabilitation
  https://medlineplus.gov/surgeryandrehabilitation.html

Additional Information & Resources

MedlinePlus

- Health Topic: Amyloidosis
  https://medlineplus.gov/amyloidosis.html
- Health Topic: Fever
  https://medlineplus.gov/fever.html
- Health Topic: Rashes
  https://medlineplus.gov/rashes.html

Genetic and Rare Diseases Information Center

- Tumor necrosis factor receptor-associated periodic syndrome

Educational Resources

- American College of Rheumatology
- Cleveland Clinic: Periodic Fever Syndrome
  https://my.clevelandclinic.org/health/diseases/17354-periodic-fever-syndrome
- Disease InfoSearch: Periodic fever, familial, autosomal dominant
  http://www.diseaseinfosearch.org/Periodic+fever%2C+familial%2C+autosomal+dominant/5672
• NHS Foundation Trust (UK)
  https://www.ucl.ac.uk/amyloidosis/pdfs/traps

• Orphanet: Tumor necrosis factor receptor 1 associated periodic syndrome
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=32960

Patient Support and Advocacy Resources
• Autoinflammatory Alliance
  http://autoinflammatory.org/traps.php

• National Organization for Rare Disorders (NORD)
  https://rarediseases.org/rare-diseases/tumor-necrosis-factor-receptor-associated-
  periodic-syndrome/

• RareConnect
  https://www.rareconnect.org/en/community/tnf-receptor-associated-periodic-fever-
  syndrome

ClinicalTrials.gov
• ClinicalTrials.gov
  https://clinicaltrials.gov/ct2/results?cond=%22tumor+necrosis+factor+receptor-associated+
  periodic+syndrome%22+OR+%22autosomal+dominant+familial+
  periodic+fever%22

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  %29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last
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OMIM
• PERIODIC FEVER, FAMILIAL, AUTOSOMAL DOMINANT
  http://omim.org/entry/142680
Sources for This Summary

  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/13130484

  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/25888769
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4416318/

  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17666110
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