

# Cryopyrin-Associated Periodic Syndrome

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**C**ryopyrin-associated periodic syndrome (CAPS) includes three overlapping disorders: familial cold autoinflammatory syndrome (FCAS, also known as familial cold urticaria [FCU]), Muckle-Wells syndrome (MWS), and neonatal onset multisystem inflammatory disorder (NOMID, also known as chronic infantile neurological cutaneous and articular [CINCA] syndrome). Once considered separate entities, these hereditary autoinflammatory disorders have been found to share a common genetic basis, pathogenesis and treatment and are therefore now considered a continuous clinical spectrum of a single entity [1].

## PREVALENCE

No formal studies have been conducted to assess the prevalence of CAPS, but it is estimated to be 1–10 cases per million in different countries, with the clinical severity reported to vary greatly. Caucasians seem to be affected more than other races, and there is no male/female preponderance. In Israel there are approximately 30 known CAPS patients, with no particular ethnic predilection. However, since the separate clinical features are common (urticaria, arthralgia) and most physicians are unaware of the syndrome, misdiagnoses and delays in diagnosis occur frequently in CAPS. The assumed prevalence is therefore far greater.

## GENETICS AND PATHOGENESIS

All cryopyrinopathies are caused by dominantly inherited or de novo gain-of-function mutations in the *NLRP3* (also known as *CIAS1*) gene, located on chromosome 1q44, with a variable penetrance [2]. The *NLRP3* gene encodes the NALP3 protein (also known as cryopyrin), which is a family member of the intracellular nucleotide-binding oligomerization

domain (NOD)-like receptors (NLRs). NLRs are pattern recognition receptors (PRPs) that can recognize different danger-associated molecular pattern molecules (DAMPs) and pathogen-associated molecular pattern molecules (PAMPs). All NLRs contain a NACHT domain that enables them to aggregate and to oligomerize. Upon activation, NALP3 oligomerizes and recruits other proteins such as ASC and caspase-1, creating a multi-protein assembly called the inflammasome. The inflammasome induces inflammation through the activation and secretion of interleukin (IL)-18 and IL-1 $\beta$ . IL-1 $\beta$  is a potent inflammatory cytokine that causes fever, vasodilation and systemic inflammation through other inflammatory cytokines. Mutations in the NACHT domain of the *NLRP3* lead to increased activation of the inflammasome and to increased inflammation [3]. Overall, the different mutations display a strong genotype-phenotype correlation, although a specific mutation may be associated with different phenotypes of varying severity. In a small subset of patients no mutation is found, despite a definitive clinical picture of CAPS. In some of these cases further tests have revealed somatic mosaicism, suggesting a role for somatic mutations.

## CLINICAL MANIFESTATIONS

CAPS is characterized by chronic or recurrent systemic inflammation, involving the skin, muscles, skeleton, joints, eyes and central nervous system (CNS), as well as by progressive hearing loss. Historically, three different syndromes were separately described: FCAS [4], MWS [5] and NOMID [6].

FCAS is the mildest CAPS disorder, in which exposure to cold results in a systemic inflammatory response including fever, an urticarial rash, conjunctival infection and arthralgia. Urticaria followed by fever and leukocytosis can appear from 30 minutes [4] up to 48 hours [7] following cold exposure. Symptoms develop in the first year of life, specifically in the newborn period in over 90% of cases. The severity and length of attacks vary widely depending on the duration of cold exposure, and tend to relent after a few hours, usually resolving within 24 hours. Affected individuals may experience daily rashes, fatigue, headache, myalgias and conjunctivitis even in the absence of any clear challenge. In contrast to other CAPS phenotypes, secondary amyloidosis is uncommon in FCAS.

**Table 1.** *NLRP3* mutations and phenotype correlation

Mutation	Prevalence	Phenotype
R260W	25%	<ul style="list-style-type: none"> <li>Late age of onset (median &gt; 2 yr)</li> <li>Positive family history</li> <li>Cold-triggered attacks</li> <li>40% undergo a chronic course</li> </ul>
T348M	15%	<ul style="list-style-type: none"> <li>Early age at onset (median &lt; 2 mo)</li> <li>85% undergo a chronic course</li> <li>Hearing loss (70%)</li> </ul>
V198M	10%	<ul style="list-style-type: none"> <li>Low penetrance</li> <li>Median age of onset ~ 1.5 yr</li> <li>Neurological involvement uncommon</li> </ul>
A439 V	10%	<ul style="list-style-type: none"> <li>Median age of onset ~ 4 yr</li> <li>Neurological involvement uncommon</li> <li>Positive family history</li> </ul>
E311 K	7%	<ul style="list-style-type: none"> <li>Median age of onset ~ 2 yr</li> <li>High rate of hearing loss</li> <li>Neurological involvement uncommon</li> </ul>
Q703 K	7%	<ul style="list-style-type: none"> <li>Considered a polymorphism (5% of healthy Caucasians)</li> <li>Median age of onset ~ 6 yr (rarely before 12 mo)</li> <li>Very mild disease</li> <li>No arthritis or neurological involvement (with the exception of morning headaches)</li> <li>No hearing loss</li> </ul>
Rarer mutations or no mutation	25%	<ul style="list-style-type: none"> <li>Severe disease</li> <li>Early age of onset</li> <li>Severe neurological manifestations</li> <li>Severe musculoskeletal involvement</li> <li>Hearing loss</li> </ul>

Based on European registry data, Levy et al. [9]

MWS is an intermediate phenotype characterized by chronic or intermittent episodes of fever, headache, urticarial rash, arthralgias or arthritis in the absence of a specific trigger. The febrile attacks commence in early childhood and patients also develop progressive sensorineural hearing loss as well as secondary amyloidosis leading to proteinuria and renal failure.

NOMID, the most severe phenotype of CAPS, is characterized by chronic inflammation with numerous flare-ups involving the skin, joints and the CNS. Mortality is high, sometimes before adulthood. Chronic urticaria-like rash is the presenting symptom, appearing shortly after birth. Musculoskeletal involvement includes cartilaginous proliferation at growth plates and epiphyses and arthritis of knees, ankles and feet, elbows, wrists and hands. CNS symptoms include chronic meningitis, headaches, seizures, spasticity of legs, as well as cognitive and mental deficits. Progressive sensorineural deafness develops earlier than in MWS. Ocular involvement includes uveitis, papillary involvement, conjunctivitis and optic neuritis. Typical morphological features of NOMID neonates are short stature, head enlargement, saddle-back nose and short and thick extremities with clubbing of fingers [8].

Due to the considerable overlap, CAPS is considered today as a single clinical entity. Few studies have been conducted on all CAPS patients. A recent survey of a large European registry [9] confirmed earlier reports of CAPS symptoms and provides

new data on European CAPS patients. In this cohort, median age at onset was 0.8 years (interquartile range 0.1–5), while age at diagnosis was 15 years (IQR 5–36), reflecting a considerable diagnosis delay. These results confirm earlier studies in 30 FCAS patients from the United States, where 44% were reported to have another diagnosis prior to the identification of CAPS. Forty percent of patients experience a recurrent course, 40% a chronic course, and 20% a chronic course with exacerbations. Most attacks resolve within 24 hours (48%), but a substantial portion (36%) last more than 3 days. Similarly, half the patients suffer fewer than 12 attacks a year, but in 40% of the patients the frequency is more than 24 attacks/year. The trigger is usually cold (85%), but some report other triggers such as infection, trauma, food and fatigue.

The skin is the most commonly affected organ in CAPS (97%), but only 90% have the classic urticarial rash. Fever is frequent (84%) as well as other constitutional symptoms (fatigue, malaise, mood disorders, failure to thrive). Musculoskeletal complaints (arthralgia and myalgia) are common (86%), but only 36% suffer from arthritis. Forty percent of CAPS patients suffer from neurological symptoms, such as morning headaches (29%), meningitis (26%) and papilledema (27%). Severe neurological involvement, such as seizure, hydrocephalus or mental retardation is reported in 12% of patients. Ocular involvement is common (70%), mostly in the form of conjunctivitis (66%) and far less commonly uveitis (7%), optic nerve atrophy, cataract, glaucoma and impaired vision. Hearing loss is reported by more than 40% of patients. Amyloidosis, a severe late complication, develops in 4%.

Laboratory results in CAPS are not specific and reflect systemic inflammation. Erythrocyte sedimentation rate and C-reactive protein are elevated, as are levels of serum amyloid A. Acute attacks are characterized by a marked leukocytosis, and meningitis is associated with increased intracranial pressure and cerebrospinal fluid pleocytosis. Anemia and thrombocytosis are common. X-rays may reveal patellar hypertrophy/overgrowth, epiphyseal overgrowth, and complications of arthritis.

Diagnosis is determined by genetic testing for *NLRP3* mutations. Some mutations correlate with phenotypes and can predict outcome [Table 1]. Diagnosis should be suspected in any patient with recurrent episodes of fever, urticaria, unexplained systemic inflammation, a positive family history, and early onset of symptoms. Differential diagnosis includes other periodic inflammatory disorders, such as tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS), hyper-immunoglobulinemia D with periodic fever syndrome (HIDS), juvenile systemic granulomatosis, and other common rheumatological disorders such as juvenile idiopathic arthritis. In Israel, familial Mediterranean fever (FMF) is the most common periodic fever syndrome, especially among certain ethnic groups. Behçet's disease, another autoinflammatory disorder common in Mediterranean populations, can also mimic CAPS.

Shinar et al. [10] report the diagnosis of CAPS in a three-generation Jewish Turkish family, previously diagnosed with Behçet's disease due to mucosal ulcers and human leukocyte antigen-B51 carriage. This case emphasizes the importance of physician awareness of the possible diagnosis of CAPS in all periodic inflammatory disorders.

## TREATMENT

In the past, different anti-inflammatory drugs were used in CAPS with limited success. With the introduction of anti-IL-1 agents, therapy has become more effective with a marked improvement in patients' quality of life. The three commercially available anti-IL-1 drugs today are anakinra, rilonacept and canakinumab.

Anakinra (Kinneret<sup>®</sup>, SOBI, Sweden), an IL-1 receptor antagonist, is given subcutaneously on a daily basis. Anakinra prevents cold-induced attacks, markedly reduces daily symptoms, and ameliorates proteinuria caused by renal amyloidosis. Some have also reported a partial recovery in hearing loss. Unfortunately, some severe cases of NOMID do not always respond to anakinra. Similarly, bone and joint abnormalities do not adequately respond to anakinra.

Rilonacept (Acralyst<sup>®</sup>, Regeneron, USA) is an IL-1 trap given by weekly subcutaneous injections and has been shown to be effective in CAPS. This drug has been studied in FCAS and MWS, showing a significant reduction in symptom scores compared with placebo. The drug is well tolerated, and the most common adverse effects were injection site reactions.

Canakinumab (Ilaris<sup>®</sup>, Novartis, Switzerland) is a human anti-IL-1 beta monoclonal antibody given by subcutaneous injections every 8 weeks. Canakinumab has been shown to be a potent therapeutic agent in CAPS, inducing complete remission in 97% of patients, though severe cases may require a dose escalation. Its main side effect was a substantial incidence of infections [1].

Another drug studied in CAPS is a caspase1 inhibitor (VX-765, Vertex Pharmaceuticals, USA) [1], but despite initial success in a small open-label trial no further studies have been conducted. Other drugs such as thalidomide and an anti-IL-6 receptor antibody were found to be beneficial in CAPS but have never been tested in larger studies.

## SUMMARY

CAPS is a rare autoinflammatory disease associated with mutations in the *NLRP3* gene that result in over-activation of the inflammasome, increased secretion of IL-1 $\beta$  and IL-18, and systemic inflammation. Genetic testing has allowed for grouping of the three, previously distinct clinical syndromes of FCAS, MWS and NOMID, into a single syndrome termed CAPS. The clinical features include urticarial rash and fever, CNS and musculoskeletal involvement, ocular disorders and progressive deafness. Onset, severity and complications (mainly retardation, seizures, destructive arthropathy and amyloidosis) depend on the specific mutation. Diagnosis is determined by genetic tests but is often delayed due to lack of awareness. In Israel, the relative abundance of other autoinflammatory disorders (FMF, Behçet's disease) may result in misdiagnosis. Treatment is based on IL-1 antagonism, which usually results in prompt clinical response and may prevent amyloidosis.

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## “Don't judge each day by the harvest you reap but by the seeds that you plant”

Robert Louis Stevenson (1850-1894), Scottish novelist, poet, essayist, and travel writer. His most famous works are *Treasure Island*, *Kidnapped*, and *The Strange Case of Dr Jekyll and Mr Hyde*

## “Please all, and you will please none”

Aesop (620–564 BCE), ancient Greek fabulist or storyteller credited with a number of fables now collectively known as *Aesop's Fables*. Although his existence remains uncertain and no writings by him survive, numerous tales credited to him were gathered across the centuries and in many languages in a storytelling tradition that continues to this day. Many of the tales are characterized by animals and inanimate objects that speak, solve problems, and generally have human characteristics