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Novel Gene Deletion in NLRC4 Expanding the Familial Cold Inflammatory Syndrome Phenotype

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Abstract

Familial cold inflammatory syndrome (FCAS) is a rare, inherited inflammatory disease characterized by episodes of fever, rash, and arthralgias after exposure to cold stimuli. Previous literature has established FCAS linked to autosomal dominant mutations in the NLRP3 (CIAS1) and NLRP12 genes. Moreover, there has been recent evidence of NLRC4-inflammasomopathies. Although there have been cases of FCAS secondary to missense mutations in NLRC4, we report the first symptomatic case associated with a 93-base-pair in-frame deletion within Exon 5 of the leucine rich repeat domain.

Keywords

NLRC4, familial cold inflammatory syndrome, familial cold urticaria, autoinflammatory disorder, gene deletion

Case Presentation

A 41-year-old woman nonsmoker presented with facial rash and rheumatologic concerns. The patient demonstrated recurrent episodes of low-grade fever, fatigue, facial skin rash and right knee joint effusion that lasted 3 to 6 days most commonly occurring during the winter. She denied any ocular or abdominal symptoms during the episodes.

The symptoms first started when she was 5 to 6 years of age with attacks of fever and myalgia. Her symptoms occurred throughout the winter months and were often related to outdoor activities (sledding). The episodes have since occurred 3 to 4 times per year and have been increasing in frequency and severity in the last 5 years. She now has attacks that occur 7 to 8 times per year, most notably during the winter. The facial rash has persisted for the past 4 years and has become more pronounced during attacks.

Her joint swelling during each recent episode has become severe enough to impede her ability to ambulate and is accompanied by arthralgia, myalgia, and hypotension. Her attacks have further evolved to include chest pain requiring numerous visits to the hospital for her symptoms. Electrocardiogram and laboratory studies during the hospital visits were unremarkable and her chest pain was thought to be musculoskeletal in etiology. Steroids during her hospital course provided only minimal relief and have not prevented or reduced the frequency of occurrences.

Her past medical history is significant for Rosacea and Ménière's disease. Of note, she has a history of bilateral chronic sensorineural hearing loss unrelated to Ménière's disease. She also has a history of chronic oral ulcers that are exacerbated by the episodes.

The laboratory studies prior to her referral revealed an ANA titer of 1:40 with homogenous pattern. A genetic autoinflammatory panel was performed (Invitae™). The genetic testing revealed a variant mutation in the NLRC4 gene of uncertain significance. This variant was a 93-base-pair in-frame deletion of the genomic region of Exon 5 of the leucine rich repeat (LRR) domain that preserved the integrity of the reading

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Table 1. Comparison of the Classic FCAS Symptoms Versus Clinical Presentation of Patient Described.[2–4]

	Familial Cold Inflammatory Syndrome	Case Presentation
Skin rash	Urticarial skin rash may be present daily	Facial skin rash daily for 4 years, worsened by acute attacks; history of Rosacea
Fever	Low-grade fever	Low-grade fever
Joint swelling/arthralgia	Present during episode	Present during episode
Fatigue	May be present	Present during episode
Conjunctivitis	May be present	No reported ocular symptoms
Myalgia	May be present	Present during episode
Sensorineural hearing loss	Rare	Present bilaterally
Oral ulcers	Not present	History of chronic oral ulcers that are worsened during episodes
Onset after cold exposure	Rash onset 1 to 2 h with fever and arthralgia 4 to 6 h later	Rash always present accompanied by fever, joint swelling, and myalgia
Duration of episodes	Hours to days	Lasts 3 to 6 days
Age of onset	<6 months	5 to 6 years of age based on patients memory of episodes, but may have occurred earlier

frame (Exon 5 starting at c.2258 [5′ end] and ending at c.2350 [3′ end]). This same in-frame deletion was observed in her father who shares a similar clinical phenotype.

A clinical diagnosis of familial cold inflammatory-like syndrome secondary to a NLRC4 gene deletion was concluded based on cold-induced onset of symptoms and genetic testing (Invitae™). The patient has obtained insurance approval for interleukin-1 receptor antagonist (Anakinra), but has not received first dose.

Discussion

Familial cold inflammatory syndrome (FCAS), also known as Familial Cold Urticaria, is an autosomal dominant autoinflammatory disorder characterized by aberrant activation of the innate immune response after exposure to cold stimuli.[1] FCAS usually presents within the first 6 months of life with recurrent attacks of urticarial rash and low-grade fever. The attack onset occurs within 1 to 2 hours of exposure to cold temperatures with resolution of symptoms within 24 hours on average.[2] Further symptoms can include conjunctivitis, arthralgias, myalgias, nausea, headache, or fatigue.[2,3] Sensorineural hearing loss can also occur although uncommon.[4]

FCAS and other hereditary autoinflammatory diseases including Muckle–Wells Syndrome and neonatal onset multisystemic inflammatory disease (NOMID) have been previously associated with autosomal dominant gain of function mutations within the NLRP3 and related NLRP12 genes.[3,5] This in turn leads to inappropriate activation of the inflammasome and subsequent elevation of interleukin (IL)-1 cytokine activity.[1] However, mutations within the NLRC4 gene have recently emerged as a novel cause of autoinflammatory diseases.

NLRC4 mutations have been associated with hereditary autoinflammatory diseases including FCAS, NOMID, and autoinflammation with infantile enterocolitis (AIFEC).[1,6] NLRC4 is a cytoplasmic inflammasome that is involved in innate host responses against gram negative organisms and cellular damage. NLRC4 activates Caspase-1, a primary protease that cleaves the precursors of key inflammatory cytokines IL-18 and IL-1B, thus initiating a pro-inflammatory response.[7] Inappropriate activation of NLRC4 leads to the overexpression of pro-inflammatory cytokines and inflammatory-mediated cell death.

The NLRC4 protein is comprised of an N-terminal CARD domain, a NBD domain, 2 hinge domains (HD1 and HD2), a winged helix domain and a C-terminal LRR domain.[8,9] The LRR terminal domain consists of 15 repeating units and serves as a negative regulator of NLRC4.[7,10] We suggest that the deletion in Exon 5 disrupts the regulatory effects of the LRR domain with subsequent constitutional activation of the NLCR4 inflammasome mediating tissue injury.

There have only been 2 reported mutations within the LRR domain of NLRC4, both of which are missense mutations upstream of Exon 5.[8,9] Moghaddas et al. reported a p.Trp655Cys in 2 unrelated patients with macrophage activated syndrome.[8] The cysteine mutation was discovered to provide an LRR–LRR interface for spontaneous oligomerization and activation of the NLRC4 inflammasome complex.[8] Through a similar mechanism, Chear et al. reported a 12-year-old with recurrent fever, skin erythema, and arthritis that carried a p.Gln657Leu mutation in the LRR domain.[9]

NLRC4 gain of function mutations can present with a spectrum of clinical phenotypes. Although the majority of NLRC4 gain of function mutations reported have been linked to AIFEC, there have been 2 reports of NLRC4-associated FCAS. Kitamura et al. described a H443P missense mutation of the NLRC4 gene in a Japanese family with history of FCAS.[11] Volker-Touw et al. reported a family with a history of FCAS carrying a S445P missense mutation.[12] It is also important to note a French systematic review on NLRC4 inflammasomopathies that may have reported additional genotypes, but is unavailable for English translation.[13]

Our patient presents with recurrent episodes of low-grade fever, fatigue, facial rash, and joint effusions of which the onset has been attributed to exposure to cold conditions. Furthermore, the patient experiences recurrent myalgias during episodes and has a history of sensorineural hearing loss of unknown origin. Although the patient has an atypical presentation compared to classic FCAS (Table 1), the cold-induced symptomology and NLRC4 mutation is compatible with a FCAS-like syndrome. The patient shares the same mutation with her father who is similarly symptomatic. Although mutations in this gene have been reported previously, we report the first case of a familial cold inflammatory-like syndrome caused by a 93-base-pair deletion within Exon 5 (LRR domain) of the NLRC4 gene discovered by genetic testing (Invitae^{TM}).

Conclusion

FCAS is a rare, inherited autoinflammatory disorder characterized by episodes of fever, rash, and arthralgias after exposure to cold stimuli. FCAS has been previously linked to NLRC4 mutations. We report the first case linked to a 93-base-pair deletion within Exon 5 of the LRR domain.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

This study was approved by our institutional review board.

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Statement of Human and Animal Rights

This article does not contain any studies with human or animal subjects.

Statement of Informed Consent

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