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CASE REPORT | INFLAMMATORY BOWEL DISEASE

# Atypical Autosomal-Dominant Inheritance of Familial Mediterranean Fever

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## ABSTRACT

Familial Mediterranean fever (FMF) was previously believed to be an autosomal recessive disease. We present a patient with only one pathogenic variation of the *MEFV* gene due to the c.2177T>C mutation. The patient had clinical features of recurrent fevers and abdominal pain, serositis, and a history of multiple abdominal surgeries for pain. He was eventually diagnosed with FMF. This case report demonstrates an example of the rare autosomal-dominant phenotype of FMF.

## INTRODUCTION

Siegal[1] first described familial Mediterranean fever (FMF) in 1945 as "benign paroxysmal peritonitis." FMF is characterized by paroxysmal abdominal pain, joint and chest pains, and fevers of unknown origin. It is typically categorized as an autosomal recessive disorder and occurs in patients of Turkish, Armenian, Iranian, Jewish, Spanish, and Mediterranean ethnic groups.[2–4] The disease occurs by mutations in the *MEFV* gene on chromosome 16, which encodes pyrin.[5,6] Pyrin seems to be responsible for the regulation of inflammation, apoptosis, and cytokines on mononuclear cells. Mutations cause multiprotein complexes are known as inflammasomes to malfunction, resulting in caspase-1 activation and interleukin (IL)-1β release, which ultimately contributes to the presenting symptoms.[7–9] It seems to bind to interferon and normally suppresses excessive inflammasome activation and IL-1β activation. In FMF, this interaction seems to be blunted.[6,10] Overall, FMF's impaired pyrin inflammasomes cause excessive and extended inflammatory responses with blunting of normal autophagy and apoptosis.[6,10,11] As a primarily autosomal recessive disorder, autosomal dominant inheritance of FMF is rare. There are 9 recognized mutations of autosomal-dominant mutations.[12] The mutation presented in this patient, c.2177T>C, causes Val726Ala. This modification of the *MEFV*'s 10th exon has been associated with FMF.[13] We present one copy of a the p.Val726Ala mutation was found. This case represents an atypical (autosomal dominant) inheritance of a common FMF mutation.[14,15]

## CASE REPORT

The patient is a 34-year-old man of Irish, German, and Spanish descent who presents to the clinic with recurrent attacks of generalized abdominal pain, nausea, vomiting, fever, arthralgia, and fatigue for the past 4 years. His symptoms were chronic and intermittent, with increasing frequency for the past 2 years. His abdominal pain is described as sharp, radiating to the back, and associated with multiple episodes of fasting diarrhea. Pertinent family history includes fibromyalgia and rheumatoid arthritis in his mother and ulcerative colitis in his maternal aunt.

He was hospitalized multiple times for severe dehydration secondary to the above symptoms. During his most recent hospitalization, he complained of right lower quadrant abdominal pain, fevers, and subacute worsening diarrhea. A computed tomography scan of his abdomen showed findings concerning for acute appendicitis and small bowel obstruction. He underwent a diagnostic laparoscopy with appendectomy and a 20-cm small bowel resection. Pathology revealed an inflamed jejunum with fibrous obliteration, serosal adhesions, and enteritis with cryptitis, but a normal appendix. His postoperative course was complicated by a high-grade

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bowel obstruction requiring another diagnostic laparoscopy, resulting in further lysis of adhesions and an additional 50-cm small bowel resection.

Laboratory workup was remarkable for antinuclear antibody test 1:160 (homogenous pattern), elevated C-reactive protein to 5.7 mg/dL, erythrocyte sedimentation rate of 23 mm/hr, and thyroid-stimulating hormone of 10 IU/mL. Inflammatory bowel disease was effectively ruled out with negative biopsies, endoscopy, video capsule endoscopy, and magnetic resonance enterography.

Because of the specific constellation of fevers, abdominal pain, and arthralgias, the patient was sent for autoimmune workup and was found to have positive *MEFV* gene analysis for FMF. A single gene pathogenic variation, c.2177T>C (p.Val726Ala), was found. He received a short trial of 3 months of colchicine and steroids, without significant improvement in his symptoms. The patient was referred to rheumatology and had symptomatic improvement in the severity of diarrhea and abdominal pain after a trial of amitriptyline and canakinumab. The canakinumab response, an IL-1 beta antibody, is observed in many inflammatory diseases, including FMF.

## DISCUSSION

Symptomatic FMF from a single *MEFV* mutation suggests an autosomal dominant inheritance. Although FMF is viewed as an autosomal recessive disorder, recent evidence suggests additional complexity, supported by the work of Marek-Yagel et al. The study postulated that FMF may be represented as an autosomal dominant disorder with low penetrance rather than an autosomal recessive disorder.[16] In a 2009 study by Booty et al, with phenotypical FMF secondary to a single identified *MEFV* mutation, the *MEFV* reverse transcription-polymerase chain reaction levels and pyrin expression levels were found to be similar in patients with one mutation vs those with 2 mutations. Ancestry of this population was more likely atypical, had a more mixed heritage, and was commonly of Spanish heritage, as in our patient.[17]

Evidence shows that asymptomatic carriers of one FMF mutation have subclinical inflammation.[18] In nearly 30% of individuals with an FMF phenotype, no second allele is found.[17,19,20] Variation in expression of the severity of the FMF phenotype and the susceptibility to amyloidosis is associated with specific *MEFV* mutations and its modifying alleles. Additional theories to explain the absence of a second mutation in an autosomal disease includes epigenetic mechanisms, genetic variations in the inflammatory cascade, and environmental factors.[21,22]

This case is notable for autosomal dominant diagnosis of FMF. He had "attacks" roughly monthly consisting of abdominal pain, joint pains, symptom-free intervals, transient inflammatory response, and repeated laparotomies. The patient did not tolerate a 3-month course of colchicine with prednisone because of continued attacks of abdominal pain and worsening diarrhea. The patient meets a diagnosis of FMF based on the Livneh et al criteria.[23] Thus far, the patient has had no evidence of renal amyloid, no protein found in urine, and no elevation in creatinine. This case illustrates the importance of including clinical data in the interpretation of a genetic test, in this case, for an unusual genotype of FMF.

## DISCLOSURES

Author contributions: NS Evans and J. Ray wrote and revised the manuscript for intellectual content. C. Prather approved the final manuscript. J. Ray is the article guarantor.

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