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Case Report

# A Heterozygous Mutation M694V in the MEFV Gene and HLA-B27 Negative Spondyloarthritis: The Chicken Egg Paradox?

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## 2. Key words

Spondyloarthritis; Corticosteroids; Familial Mediterranean gen

## 1. Abstract

There is evidence that the familial Mediterranean gene (MEFV) M694V mutation plays a role in the susceptibility to Spondyloarthritis (SpA). There is an increased prevalence of SpA among Familial Mediterranean fever (FMF) patients, especially in human leukocyte antigen (HLA) B27 negative patients carrying the MEFV M694V mutation.

We report the case of a 53 years old woman who presented with chronic inflammatory low back pain and oligoarthritis. The patient had no significant comorbidity and personal medical history except for her son diagnosed with FMF and carrying the homozygous mutation M694V in the MEFV gene. She was herself tested few years ago and the genetic testing revealed the same M694V mutation in the MEFV gene at heterozygous state. When asking about episode of recurrent fever, the patient recalled having such episode associated with abdominal pain, vomiting and diarrhea, especially while pregnant. A comprehensive analysis of her medical report confirmed recurrent episodes of fever and abdominal pain leading to emergency department visits and even hospitalizations, respectively in 1988, 1996, 1997, 1999 and 2019. The diagnosis work-up was always inconclusive showing mild elevation of inflammatory parameters without any microbiological findings. The endoscopic digestive investigation showed no specific signs of inflammation. The episodes were always self-limiting. Since September 2000, she reported recurrent episodes of inflammatory low back pain and polyarthralgia.

The diagnostic work up showed an elevated white blood cells count (WBC: 9,680/mm$^3$) with neutrophilic leukocytosis (7,980/mm$^3$), the C-reactive protein (CRP) level was 46 mg/L. She was negative for HLA-B27, rheumatoid factor and anti-citrullinated peptide antibodies. A magnetic resonance imaging (MRI) of the sacroiliac (SI) joints showed severe bilateral sacroiliitis with large area of bone marrow edema and sclerosis of the sacroiliac joints. An ultrasound of the hands confirmed synovitis of both wrists, 2$^{nd}$ and 3$^{rd}$ proximal interphalangeal joints of the left hand and 3$^{rd}$ and 4$^{th}$ metacarpophalangeal joints of the right hand. A diagnosis of axial and peripheral spondyloarthritis was established. The patient was treated with rapidly tapering dose of corticosteroids and Salazopyrine (Pfizer, New-York, USA) was initiated.

Whether this patient suffers either from spondyloarthritis with heterozygous MEFV M694V mutation conferring a genetic risk for SpA or from FMF with SpA associated disease can be argued. Indeed, the patient could be considered as having FMF with a compound heterozygous of MEFV M694V mutation and another rare variant that is not routinely tested. A multifactorial form of FMF associating a heterozygous MEFV mutation with environmental factors and other potential molecular defects could also be hypothesized.

## 3. Introduction

Familial Mediterranean fever (FMF) and spondyloarthritis (SpA) are two conditions that lie at both ends of the spectrum of auto-inflammatory diseases [1]. FMF is the prototype of auto-inflammatory diseases and is characterized by recurrent short episodes of fever associated with peritonitis, pleuritis, arthritis and skin rash [2]. It is an hereditary autosomal recessive disorder due to mutation in the familial Mediterranean gene (MEFV) that encodes a protein called pyrin that regulates the inflammatory response through its action on interleukin 1 beta (IL-1b) signalling pathway [3].

SpA is characterized by sacroiliitis, spondylitis, peripheral arthritis and enthesitis. It is considered as a mixed-pattern disease, sharing

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aspects of both auto-immune and auto-inflammatory diseases [1]. Unlike FMF, SpA is a complex multigenic disease with a strong association with the human leukocyte antigen (HLA)-B27 allele that accounts for 40% of the genetic risk for SpA [4]. Recently, many other polymorphisms located in non-HLA genes and involving innate immune recognition and cytokine signalling pathway have been linked with SpA. There is evidence that MEFV M694V mutation plays a role in the susceptibility to SpA [5]. Conversely, there is an increased prevalence of SpA among Familial Mediterranean fever (FMF) patients, especially in HLA-B27 negative patients carrying the MEFV M694V mutation [6]. It raises the question of a potential pathogenic link between the two disorders and suggests a shared inflammatory pathway of interleukin 1 (IL-1) in the pathogenesis of these diseases. We report hereby a case that illustrates this question.

## 4. Case Presentation

We report the case of a 53 years old woman who presented with chronic inflammatory low back pain and oligoarthritis. The patient was from North African origin, was married and had 6 children. She never smoked or drank alcohol. The patient had no significant comorbidity and personal medical history. Her son was diagnosed with FMF at the age of 32 and carrying the homozygous mutation M694V in the MEFV gene. She was been tested a few years ago and the genetic testing revealed the same M694V mutation in the MEFV gene at heterozygous state. When inquiring about episodes of recurrent fever, the patient recalled having such fever associated with abdominal pain, vomiting and diarrhea, especially while pregnant. A comprehensive analysis of her medical report confirmed recurrent episodes of fever and abdominal pain leading to emergency department visits and even hospitalizations, respectively in 1988, 1996, 1997, 1999 and 2019. The diagnosis work-up was always inconclusive showing mild elevation of inflammatory parameters without any microbiological findings. The endoscopic digestive investigation showed no specific signs of inflammation. The episodes were always self-limiting. Since September 2000, she reported recurrent episodes of inflammatory low back pain and polyarthralgia. Since February 2020, she reported worsening of low back pain and the onset of symmetrical arthralgia, joint swelling and fatigue. She also complained of morning stiffness in the joints and in the back improving after one to two hours. She reported no fever, no weight loss, no diarrhea or abdominal pain, no skin rash or psoriasis, no uveitis, no sicca symptoms, no Raynaud phenomenon. On examination, she had 6 swollen joints (both wrists, 2$^{nd}$ and 3$^{rd}$ proximal interphalangeal joints of the left hand and 3$^{rd}$ and 4$^{th}$ metacarpophalangeal joints of the right hand) and exhibited 10 tender joints.

The diagnostic work up showed an elevated white blood cells count (WBC: 9,680/mm$^3$) with neutrophilic leukocytosis (7,980/mm$^3$), the C-reactive protein (CRP) level was 46 mg/L. She was negative for HLA-B27, rheumatoid factor and anti-citrullinated peptide antibodies. X-Ray of hands and feet showed no erosion. X-Ray of sacroiliac joints showed sacroiliitis. A magnetic resonance imaging (MRI) of the sacroiliac (SI) joints showed severe bilateral sacroilliitis with a large area of bone marrow edema and sclerosis of the sacroiliac joints. An ultrasound of the hands confirmed synovitis of both wrists, 2nd and 3rd proximal interphalangeal joints of the left hand and 3rd and 4th metacarpophalangeal joints of the right hand. A diagnosis of axial and peripheral spondyloarthritis was established. The patient was treated with rapidly tapering dose of corticosteroids and Salazopyrine (Pfizer, New-York, USA) was initiated. Two weeks after initiation of treatment, she reported a marked improvement in term of back pain, joint swelling and morning stiffness. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score was 3, 9 coming from an initial BASDAI score > 6.

## 5. Discussion

Whether this patient suffers either from spondyloarthritis with heterozygous MEFV M694V mutation conferring a genetic risk for SpA or from FMF with SpA associated disease can be argued.

The MEFV gene is located on the short arm of chromosome 16 at position 13.3 and encodes a protein called pyrin that activates inflammasome complexes in response to pathogen infections. This leads to activation of caspase-1, a pro-inflammatory protease, that ultimately results in the production of pro-inflammatory cytokines such as interleukin 1 beta (IL-1b) and interleukin 18 (IL-18) [7]. MEFV gene mutations have been linked to FMF, a hereditary autoinflammatory disease. Multiple associations have also been reported between MEFV gene mutations and other autoinflammatory conditions such as spondyloarthritis [8], Behçet [9] and inflammatory bowel disease [10]. Recently, a meta-analysis confirmed a positive association between SpA and the MEFV M694V mutation. The frequency of M694V mutation was statistically significantly higher in SpA patients without clinical features of FMF (5,06%) compared to controls (1.59%) and the pooled odds-ratio (OR) was 3.33 (95% CI, 2.13–5.21) [5]. Another study reported that M694V mutation is also more frequent in HLA-B27 negative patients with SpA [11]. These findings corroborate the fact that HLA-B27 is not the only factor playing a role in the pathogenesis of AS. Recently, several studies have pointed associations between IL-1 polymorphisms and SpA [12]. We could therefore postulate that M694V mutation may increase the risk of SpA through the IL-1b–mediated inflammatory pathway.

Spondyloarthritis have been reported in up to 7.5% of FMF patients [13]. The M694V mutation in particular was more frequently reported in FMF patients with sacroiliitis than without sacroiliitis. A study of 256 FMF patients reported a frequency of 93.7% of M694V mutations in FMF patients with sacroiliitis compared to 44.5% in patients without sacroiliitis ($p < 0.001$) [14]. We could

therefore also argue that our patient suffers of FMF with SpA associated disease. Indeed, the patient could be considered as having FMF as she fulfils the Tel-Hashomer criteria that are exclusively clinical [15]. From a molecular point of view, the patient could be considered as compound heterozygous of MEFV M694V mutation and another rare variant that is not routinely tested. A multifactorial form of FMF associating a heterozygous MEFV mutation with environmental factors and other potential molecular defects could also be hypothesized. The study of Jéru et al. supports that theory and even provides the first statistical demonstration that heterozygosity was not responsible for classical FMF, but constitutes a susceptibility factor for clinically similar multifactorial forms of the disease [16].

## 6. Conclusion

Whether this patient suffers either from spondyloarthritis with heterozygous MEFV M694V mutation conferring a genetic risk for SpA or from FMF with SpA associated disease can be argued. Indeed, the patient could be considered as having FMF with a compound heterozygous of MEFV M694V mutation and another rare variant that is not routinely tested. A multifactorial form of FMF associating a heterozygous MEFV mutation with environmental factors and other potential molecular defects could also be hypothesized.

## 7. Main Points

- This case report raises the question of a potential pathogenic link between FMF and SpA and suggests a shared inflammatory pathway of interleukin 1 (IL-1) in the pathogenesis of these diseases.
- This article discusses the role of heterozygous MEFV M694V mutation as a genetic risk for SpA.
- This article discusses the association of SpA in FMF patients.
- This article discusses the role heterozygous MEFV M694V mutation as susceptibility factor for clinical forms of FMF (but with a polygenic inheritance).

## Reference


1. Generali E, Bose T, Selmi C, Voncken JW, Damoiseaux JGMC. Nature versus nurture in the spectrum of rheumatic diseases: Classification of spondyloarthritis as autoimmune or autoinflammatory. Autoimmun Rev. 2018; 17(9): 935-41.
2. Ben-Chetrit E, Levy M. Familial Mediterranean fever. Lancet Lond Engl. 1998; 351(9103): 659-64.
3. Schnappauf O, Chae JJ, Kastner DL, Aksentijevich I. The Pyrin Inflammasome in Health and Disease. Immunology. 2019; 1745.
4. Vitulano C, Tedeschi V, Paladini F, Sorrentino R, Fiorillo MT. The interplay between HLA-B27 and ERAP1/ERAP2 aminopeptidases: from anti-viral protection to spondyloarthritis. Clin Exp Immunol. 2017; 190(3): 281-90.
5. Zhong L, Song H, Wang W, Li J, Ma M. MEFV M694V mutation has a role in susceptibility to ankylosing spondylitis: A meta-analysis. PloS One. 2017; 12(8): e0182967.
6. Watad A, Bragazzi NL, Adawi M, Shoenfeld Y, Comaneshter D, Cohen AD, et al. FMF Is Associated With a Wide Spectrum of MHC Class I- and Allied SpA Disorders but Not With Classical MHC Class II-Associated Autoimmune Disease: Insights From a Large Cohort Study. Front Immunol. 2019; 10: 2733.
7. Heilig R, Broz P. Function and mechanism of the pyrin inflammasome. Eur J Immunol. 2018; 48(2):v 230-8.
8. Cinar M, Dinc A, Simsek I, Erdem H, Koc B, Pay S, et al. The rate and significance of Mediterranean fever gene mutations in patients with ankylosing spondylitis: a three-month, longitudinal clinical study. Rheumatol Int. 2008 Nov; 29(1): 37-42.
9. Wu Z, Zhang S, Li J, Chen S, Li P, Sun F, et al. Association between MEFV Mutations M694V and M680I and Behçet's Disease: A Meta-Analysis. Wallace GR, editor. PLOS ONE. 2015; 10(7): e0132704.
10. Akyuz F, Besisik F, Ustek D, Ekmekçi C, Uyar A, Pinarbasi B, et al. Association of the MEFV gene variations with inflammatory bowel disease in Turkey. J Clin Gastroenterol. 2013; 47(3): e23-7.
11. Cosan F, Ustek D, Oku B, Duymaz-Tozkir J, Cakiris A, Abaci N, et al. Association of familial Mediterranean fever-related MEFV variations with ankylosing spondylitis. Arthritis Rheum. 2010; 62(11): 3232-6.
12. Sims A-M, Timms AE, Bruges-Armas J, Burgos-Vargas R, Chou C-T, Doan T, et al. Prospective meta-analysis of interleukin 1 gene complex polymorphisms confirms associations with ankylosing spondylitis. Ann Rheum Dis. 2008; 67(9): 1305-9.
13. Akar S, Soysal O, Balci A, Solmaz D, Gerdan V, Onen F, et al. High prevalence of spondyloarthritis and ankylosing spondylitis among familial Mediterranean fever patients and their first-degree relatives: further evidence for the connection. Arthritis Res Ther. 2013; 15(1): R21.
14. Kaşifoğlu T, Calişir C, Cansu DU, Korkmaz C. The frequency of sacroiliitis in familial Mediterranean fever and the role of HLA-B27 and MEFV mutations in the development of sacroiliitis. Clin Rheumatol. 2009; 28(1): 41-6.
15. Sohar E, Gafni J, Pras M, Heller H. Familial Mediterranean fever. A survey of 470 cases and review of the literature. Am J Med. 1967; 43(2): 227-53.
16. Jéru I, Hentgen V, Cochet E, Duquesnoy P, Le Borgne G, Grimprel E, et al. The risk of familial Mediterranean fever in MEFV heterozygotes: a statistical approach. PloS One. 2013; 8(7): e68431.
17. Duvan Cİ, Turhan NÖ, Onaran Y, Gümüş İİ, Gözdemir E. Familial mediterranean fever: a diagnostic challenge in pregnancy. J Turk Ger Gynecol Assoc. 2009; 10(4): 235-7.