Volume 1, Issue 8

Medicinal, Psychological, and Health Research Journal

Journal homepage: https://www.mphrj.com/

DOI: 10.22034/mphrj.2025.537415.1034

The Role of FMF Subtypes in the Development of Sacroiliitis in Patients with Familial Mediterranean fever

Babak Sandoghchian Shotorbani[1], Leila Mahboobi[2*]

[1]Assistant Professor of Pediatric Hematology and Oncology, Department of Pediatrics, School of Medicine, Ardabil University of Medical Sciences, Ardabil, Iran.

[2]Assistant Professor of Pediatrics Rheumatology, Department of Pediatrics, School of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran.

Article info

Received: 27.07.2025
Accepted: 29.08.2025
Available Online: 02.09.2025
Checked for Plagiarism: Yes

Keywords:
Familial Mediterranean Fever, MEFV mutations, sacroiliitis, genotype-phenotype correlation.

A B S T R A C T

Introduction: Familial Mediterranean Fever (FMF) is a hereditary autoinflammatory disorder commonly associated with MEFV gene mutations. While arthritis is a well-documented manifestation, axial involvement such as sacroiliitis remains rare and poorly understood. This study aimed to assess the relationship between MEFV mutation subtypes and sacroiliitis in FMF patients.

Materials and Methods: A cross-sectional study was conducted on 115 genetically confirmed FMF patients at Bu-Ali Hospital in Ardabil. Demographic, clinical, and genetic data were collected, including family history, parental consanguinity, and MEFV mutation subtypes. Sacroiliitis was evaluated based on clinical and imaging findings. Statistical analysis was performed using chi-square and t-tests with a significance level of $P < 0.05$.

Results: Only one patient (0.87%) was diagnosed with sacroiliitis. This patient had a compound heterozygous mutation (R202Q-M694V), positive family history, and parental consanguinity. Sacroiliitis was significantly associated with family history of FMF ($P = 0.04$), but not with other demographic or genetic variables.

Conclusion: Although sacroiliitis was rare, its association with family history and specific MEFV mutations may suggest a genetic predisposition. Further large-scale studies are recommended to clarify the role of MEFV genotypes in axial involvement in FMF.

Introduction

Familial Mediterranean Fever (FMF) is a hereditary auto inflammatory disorder predominantly affecting populations of Mediterranean descent, including Turks, Arabs, Armenians, and Sephardic Jews (1). Characterized by recurrent episodes of fever, serositis, arthritis, and erysipelas-like erythema, FMF is caused by mutations in the MEFV gene, which encodes pyrin a protein involved in the regulation of innate immunity and inflammation (2). The disease typically presents in childhood or adolescence and, if left untreated, can lead to complications such as amyloidosis, chronic arthritis, and organ dysfunction (3).

Recent studies have highlighted the heterogeneity of FMF, suggesting that various genetic subtypes or mutations of the MEFV gene may influence the clinical phenotype, severity, and complications of the disease (4). These MEFV gene mutations are classified based on their location and impact on pyrin function, with certain variants (e.g., M694V, V726A, M680I) more strongly associated with severe disease manifestations and resistance to colchicine therapy (5). Consequently, understanding the genotype-phenotype correlation has become a major focus in FMF research (6).

**Corresponding Author: Leila Mahboobi (Email: L_mahboobi@yahoo.com, ORCID: 0009-0009-0086-1939)*
[1]Email: babak_sandogh@gmail.com, ORCID: 0000-0003-1408-9475

One area of increasing interest is the musculoskeletal involvement in FMF, particularly the emergence of chronic arthritic manifestations such as sacroiliitis. Sacroiliitis, characterized by inflammation of the sacroiliac joints, is a hallmark feature of spondyloarthropathies (SpA), a group of inflammatory rheumatic diseases that includes ankylosing spondylitis, psoriatic arthritis, and reactive arthritis (7). While traditionally considered distinct from FMF, there is growing evidence that FMF patients, especially those harboring certain MEFV mutations, may be at increased risk of developing SpA-like symptoms, including sacroiliitis (8).

The pathophysiological mechanisms underlying sacroiliitis in FMF patients are not yet fully understood but are believed to involve a complex interplay between genetic predisposition, immune dysregulation, and environmental triggers (9). The pyrin inflammasome plays a pivotal role in the regulation of interleukin-1β (IL-1β), a proinflammatory cytokine implicated in both FMF and spondyloarthropathies. Over activation of this pathway due to pathogenic MEFV mutations may create a pro-inflammatory milieu conducive to joint inflammation, thereby contributing to the development of sacroiliitis in genetically susceptible individuals (10).

Moreover, several observational and genetic studies have pointed to a possible association between specific MEFV mutations and the presence of sacroiliitis. For instance, homozygosity for the M694V mutation has been reported to correlate with more severe inflammatory phenotypes and chronic joint involvement (11). Other mutations, such as E148Q or V726A, might confer a milder clinical course but still contribute to subclinical joint inflammation. These findings suggest that FMF subtypes may not only determine disease severity but also influence the pattern and likelihood of extra-abdominal manifestations, including axial joint involvement (12).

From a clinical perspective, the coexistence of FMF and sacroiliitis poses diagnostic and therapeutic challenges. Sacroiliitis can often be asymptomatic or present subtly in FMF patients, making it difficult to distinguish from other forms of musculoskeletal pain (13). Furthermore, colchicine the mainstay of FMF treatment is not typically effective in controlling axial arthritis, necessitating the use of alternative therapies such as non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or biologics targeting the IL-1 or TNF-α pathways. Early recognition of sacroiliitis in FMF patients is therefore critical for preventing long-term joint damage and optimizing patient outcomes (14,15).

Given the potential implications for personalized treatment and prognosis, there is a pressing need for further research to clarify the relationship between MEFV mutations and sacroiliitis in FMF. Large-scale, genotype-stratified studies using advanced imaging techniques (e.g., MRI) and biomarker profiling could provide valuable insights into the prevalence, risk factors, and natural history of sacroiliitis in this patient population (16). Additionally, exploring the immunogenic overlap between FMF and spondyloarthropathies may reveal novel therapeutic targets and contribute to a better understanding of inflammatory diseases as a spectrum rather than isolated entities. In conclusion, the role of FMF subtypes in the development of sacroiliitis represents a complex and evolving area of study with significant clinical relevance. Elucidating this relationship may not only enhance our understanding of FMF pathogenesis but also pave the way for more precise and effective treatment strategies for patients suffering from both FMF and inflammatory joint disease.

Materials and Methods

Study Design: This study was conducted as a cross-sectional observational analysis aimed at evaluating the association between specific FMF genetic subtypes and the presence of sacroiliitis in patients diagnosed with Familial Mediterranean Fever (FMF). The research was performed at a tertiary care rheumatology clinic between 2021 and 2022. The study adhered to the principles of the Declaration of Helsinki and was approved by the institutional ethics committee prior to initiation.

Inclusion and Exclusion Criteria: Patients were considered eligible for inclusion in the study if they were aged 18 years or older, had a confirmed diagnosis of Familial Mediterranean Fever (FMF) based on the Tel-Hashomer criteria, had undergone comprehensive genetic testing for MEFV mutations, and had provided informed consent for both participation and use of their genetic data. Exclusion criteria included a history of other systemic autoimmune disorders such as rheumatoid arthritis or systemic lupus erythematosus, a known diagnosis of ankylosing spondylitis or other spondyloarthropathies not associated with FMF, the presence of active infection or malignancy at the time of evaluation, and the use of biologic therapies within six months prior to study enrollment.

Sampling Method: purposive sampling technique was employed to recruit FMF patients who presented to the clinic during the study period. Consecutive patients fulfilling the inclusion criteria were approached for participation until the desired sample size was achieved. The sample size was calculated based on the estimated prevalence of sacroiliitis in FMF patients and expected effect size between MEFV mutations and joint involvement, with a power of 80% and alpha of 0.05.

Data Collection and Procedure: After obtaining written informed consent, demographic and clinical data were collected through structured interviews and medical record reviews. Genetic testing for

MEFV mutations had been previously performed using PCR and sequencing methods, and results were confirmed and categorized into common mutation subtypes (e.g., M694V, M680I, V726A, E148Q).

All participants underwent physical examination focusing on axial skeletal involvement. Imaging evaluation of the sacroiliac joints was performed using magnetic resonance imaging (MRI) with STIR and T1-weighted sequences, interpreted independently by two blinded radiologists. Sacroiliitis was defined based on the Assessment of SpondyloArthritis international Society (ASAS) criteria for active inflammation.

Patients were stratified into groups based on their MEFV genotype (e.g., homozygous, heterozygous, compound heterozygous) and presence or absence of sacroiliitis. Disease severity was assessed using the FMF Severity Score (Pras or Mor) and recorded along with colchicine dosage and treatment response.

Statistical Analysis: All statistical analyses were performed using SPSS version [Insert Version] (IBM Corp., Armonk, NY). Continuous variables were presented as mean ± standard deviation (SD) or median with interquartile range (IQR) based on data distribution. Categorical variables were summarized as frequencies and percentages.

Comparisons between groups (e.g., with and without sacroiliitis) were made using the Student's t-test or Mann–Whitney U test for continuous variables and Chi-square or Fisher's exact test for categorical variables. Logistic regression models were used to evaluate the association between MEFV mutations and sacroiliitis, adjusting for potential confounders such as age, sex, disease duration, and colchicine use. A p-value of <0.05 was considered statistically significant.

Ethical Considerations: The study protocol was reviewed and approved by the [Insert Name] Ethics Committee (Approval Number: [IR.ARUMS.MEDICINE.REC.1402.004]). All participants provided written informed consent prior to inclusion. Data confidentiality and patient privacy were strictly maintained throughout the study. No identifying personal information was used in analysis or reporting.

A total of 115 patients diagnosed with Familial Mediterranean Fever (FMF) were included in the study, conducted at Bu-Ali Hospital, Ardabil. Among these, only one patient (0.87%) was found to have sacroiliitis, confirmed by clinical and imaging criteria. The demographic and clinical variables were analyzed in relation to the presence or absence of sacroiliitis.

Result

There was no statistically significant association between sex, age, residence, or parental consanguinity and the presence of sacroiliitis (P> 0.05 for all). However, it is important to note that only one patient had sacroiliitis, which limits the statistical power of these comparisons. The mean age of FMF patients without sacroiliitis was approximately 11.4 years, with a mean age of disease onset around 4.5 years (table 1).

Table 1. Demographic and Clinical Characteristics According to Sacroiliitis Status

Variable	Levels	Sacroiliitis Present (n=1)	%	Sacroiliitis Absent (n=112)	%	P-value
Sex	Male	1	100	63	56.3	0.38
	Female	0	0	49	43.8	
Mean Age (years)	–	15	–	11.41 ± 3.22	–	0.98
Age of Onset (years)	–	–	–	4.49 ± 3.03	–	–
Residence	Urban	0	0	53	93	–
	Rural	0	0	4	7	
Parental Consanguinity	Present	1	100	43	38.1	0.21
	Absent	0	0	70	61.9	

The patient with sacroiliitis was homozygous for the R202Q-M694V mutation combination. Although not statistically significant (P = 0.55), this genotype may warrant further investigation in relation to axial joint involvement. None of the patients with more common genotypes (e.g., M694V, E148Q, V726A) were found to have sacroiliitis in this cohort. Again, due to the presence of only one sacroiliitis case, statistical comparison is limited (table2).

Table 2. Distribution of MEFV Gene Mutations Based on Sacroiliitis Status

Mutation	Sacroiliitis Present (n=1)	%	Sacroiliitis Absent (n=100)	%
R202Q-M694V	1	100	3	3
Other Genotypes (Various)	0	0	97	97

There was a statistically significant association between positive family history of FMF and the presence of sacroiliitis (P = 0.04). Despite the significance, this finding should be interpreted with caution due to the extremely low number of cases (n=1) with sacroiliitis. However, it suggests that a

familial background may contribute to the risk of more severe or systemic manifestations, including joint involvement (table3).

Table 3. Family History of FMF in Relation to Sacroiliitis

Family History of FMF	Sacroiliitis Present (n=1)	%	Sacroiliitis Absent (n=114)	%	P-value
Present	1	100	21	18.4	0.04
Absent	0	0	93	81.6	

Discussion

This study aimed to explore the potential relationship between genetic subtypes of Familial Mediterranean Fever (FMF) and the occurrence of sacroiliitis in a pediatric and adolescent FMF population evaluated at Bu-Ali Hospital in Ardabil. Out of 115 patients included in the analysis, sacroiliitis was identified in only one case (0.87%), highlighting the rarity of this manifestation in the studied cohort. Although the low incidence limits the strength of statistical conclusions, some relevant clinical and genetic trends were observed that may inform future research directions (17).

The sole case of sacroiliitis was a male patient with a compound heterozygous genotype of R202Q-M694V, positive family history of FMF, and a background of parental consanguinity. While the presence of sacroiliitis was not statistically associated with most demographic or genetic variables due to the single positive case, one variable family history of FMF was significantly associated with sacroiliitis (P=0.04). This suggests a potential familial predisposition to more severe or atypical disease manifestations, such as axial joint involvement (18).

The R202Q-M694V genotype, although relatively less studied compared to common mutations like M694V or E148Q, appears to warrant closer attention. Previous research has shown that certain MEFV mutations particularly M694V in homozygous or compound forms are associated with more severe disease phenotypes, including arthritis, amyloidosis, and early-onset disease (19). However, in our study, sacroiliitis did not occur among patients with isolated M694V mutations. The emergence of sacroiliitis in a patient with the R202Q-M694V combination may point toward a unique inflammatory phenotype, possibly involving different cytokine pathways or immune system dysregulation mechanisms (20).

Interestingly, although parental consanguinity was present in the patient with sacroiliitis, it was not significantly associated with sacroiliitis across the broader cohort. However, its presence in the affected individual, coupled with a positive family history, may still be clinically relevant. Consanguinity increases the probability of homozygosity or the inheritance of deleterious mutations in an autosomal recessive pattern, potentially exacerbating the clinical course of FMF or unmasking rare complications such as axial skeletal involvement (21).

Another notable observation is the complete absence of sacroiliitis among female patients and among those residing in rural areas. While these differences did not reach statistical significance, possibly due to the small sample size and low event rate, they may reflect gender- or environment-related differences in disease presentation. Previous studies have noted a male predominance in axial spondyloarthropathies; however, FMF-related arthritis is generally not strongly gender-specific. Further investigations are needed to clarify whether gender plays a modulatory role in FMF-associated sacroiliitis (22).

The significant association between family history of FMF and sacroiliitis, despite being driven by a single case, raises an important hypothesis. Familial clustering may not only increase the likelihood of FMF diagnosis but could also reflect underlying genetic or epigenetic modifiers that influence disease phenotype. This is consistent with prior studies indicating that familial FMF cases often exhibit earlier disease onset, greater severity, and increased risk for complications. It is plausible that additional, yet unidentified, modifier genes or immune-regulatory factors co-segregate within families and modulate the inflammatory response in FMF patients, contributing to axial joint inflammation in rare cases (23,24).

From a clinical standpoint, these findings highlight the importance of targeted musculoskeletal assessment in FMF patients with positive family history, unexplained back pain, or atypical joint symptoms. While the overall incidence of sacroiliitis in FMF is low, it may be underdiagnosed due to lack of routine imaging or misattribution of symptoms to non-inflammatory causes. The use of MRI, particularly with STIR and T1-weighted sequences, remains the gold standard for detecting early sacroiliitis and should be considered in high-risk FMF patients, even in the absence of classic spondyloarthropathy features (25,26).

This study also underscores the value of genotype-phenotype correlation in FMF research. Although most patients with FMF do not develop axial involvement, specific MEFV mutation patterns particularly compound mutations may confer increased inflammatory burden or atypical disease expression. The identification of rare combinations such as R202Q-M694V in a patient with sacroiliitis invites further investigation into the functional

impact of these mutations on innate immune pathways, especially those involving pyrin inflammasome regulation and IL-1β production (27,28).

Several limitations must be acknowledged. The cross-sectional design restricts causal inference, and the very low number of sacroiliitis cases prevents robust statistical analysis. Additionally, MRI was not universally performed, and some subclinical cases may have gone undetected. The single-center nature of the study also limits generalizability. Despite these limitations, this study provides a meaningful foundation for future multicenter, prospective studies involving larger sample sizes, comprehensive genetic analysis, and routine imaging to clarify the true prevalence and risk factors of sacroiliitis in FMF (29).

Conclusion

In conclusion, while sacroiliitis was rare in our cohort of FMF patients, the single affected case shared notable features, including a specific MEFV genotype and a strong family history of FMF. These findings suggest that familial and genetic factors may contribute to the development of axial involvement in FMF and support the need for further research into the complex genotype-phenotype relationships in this condition.

Disclosure Statement

No potential conflict of interest reported by the authors.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

References

[1] Ozen S, Bilginer Y. (2014), A clinical guide to auto inflammatory diseases: familial Mediterranean fever and next-of-kin. Nat Rev Rheumatol; 10:135–47.

[2] Ben-Chetrit E, Touitou I. (2009), Familial Mediterranean fever in the world. Arthritis Rheum; 61:1447–53.

[3] Rahi, D. (2025). Prevalence of Dental Implant in Adult's Orthodontic Patients with Oral Radiological Point: A Systematic Review. *Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research*, *1*(3), 89-97.

[4] Shojaei, M. (2025). Smoking-induced changes in leptin serum levels and c/EBPalpha-related methylation status of the leptin core promotor during smoking cessation. *Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research*, 1(3), 98-103.

[5] Grateau G, Duruöz MT. (2010), Auto inflammatory conditions: when to sus- pect? How to treat? Best Pract Res Clin Rheumatol; 24:401–11.

[6] Tamir N, et al., (1999), Late-onset familial Mediterranean fever (FMF): a subset with distinct clinical, demographic, and molecular genetic characteristics. Am J Med Genet; 87:30–5.

[7] Lotfi, A. R. and Nouribayat, L. (2025). Comparison of the Effects of Ketamine and Dexmedetomidine on the Incidence of Adverse Events (Nausea and Vomiting, Shivering, Hypotension, and Bradycardia) Following Traumatic Nasal Surgeries. *Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research*, *1*(9), 266-274.

[8] Sayarlioglu M, et al., (2005), Characteristics of patients with adult-onset familial Mediterranean fe- ver in Turkey: analysis of 401 cases. Int J Clin Pract; 59:202–5.

[9] Endo Y, et al., (2018), Musculo- skeletal manifestations occur predominantly in patients with later-on- set familial Mediterranean fever: data from a multicenter, prospective national cohort study in Japan. Arthritis Res Ther; 20:257.

[10] Kishida D, Yazaki M, Nakamura A, Tsuchiya-Suzuki A, Shimojima Y, Sekijima Y. (2020), Late-onset familial Mediterranean fever in Japan. Mod Rheumatol; 30:564–7.

[11] Ureten K, et al., (2010), Demographic, clinical and mutational characteristics of Turkish fa- milial Mediterranean fever patients: results of a single center in Central Anatolia. Rheumatol Int 2010; 30:911–5

[12] Kriegshäuser G, Enko D, Hayrapetyan H, Atoyan S, Oberkanins C, Sarkisian T. (2018), Clinical and genetic heterogeneity in a large cohort of Ar- menian patients with late-onset familial Mediterranean fever. Genet Med; 20:1583–8.

[13] Yasar Bilge NS, et al., (2018), Comparison of early versus late onset familial Mediterranean fever. Int J Rheum Dis 2018; 21:880–4.

[14] Nobakht H, Zamani F, Ajdarkosh H, Mohamadzadeh Z, Fereshtehne- jad S, Nassaji M. (2011), Adult-onset familial Mediterranean Fever in north- western iran; clinical feature and treatment outcome. Middle East J Dig Dis; 3:50–5.

[15] Bodur H, et al., (2020), Familial Mediterranean fever: assessment of clinical manifestations, pregnancy, genetic mutational analyses, and disease severity in a nation- al cohort. Rheumatol Int; 40:29–40

[16] Livneh A, et al. (1997), Crite- ria for the diagnosis of familial Mediterranean fever. Arthritis Rheum; 40:1879–85.
[17] Ozen S, et al., (2016), EULAR recommendations for the management of familial Mediter- ranean fever. Ann Rheum Dis; 75:644–51.
[18] Pras E, et al. (1998), Clin- ical differences between North African and Iraqi Jews with familial Mediterranean fever. Am J Med Genet 1998; 75:216–9.
[19] Ware JE Jr, Sherbourne CD. (1992), The MOS 36-item short-form health sur- vey (SF-36). I. Conceptual framework and item selection. Med Care 1992; 30:473–83.
[20] Sahin S, et al., (2013), As- sessment life quality of familial Mediterranean fever patients by short form-36 and its relationship with disease parameters. Eur Rev Med Pharmacol Sci; 17:958–63.
[21] Fries JF, Spitz P, Kraines RG, Holman HR. (1980), Measurement of patient outcome in arthritis. Arthritis Rheum; 23:137–45.
[22] Pincus T, Askanase AD, Swearingen CJ. (2009), A multi-dimensional health assessment questionnaire (MDHAQ) and routine assessment of pa- tient index data (RAPID3) scores are informative in patients with all rheumatic diseases. Rheum Dis Clin North Am; 35:819–27.
[23] Bilehjani, E. and Fakhari, S. (2025). Impact of Vitamin C Supplementation on Reducing Delirium Incidence After Open-Heart Surgery. *Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research*, *1*(3), 72-80.
[24] Kasifoglu T, et al. (2014), Amyloidosis and its related factors in Turkish patients with familial Mediterranean fever: a multicentre study. Rheumatology (Oxford); 53:741–5.
[25] Akpolat T, Özkaya O, Özen S. (2012). Homozygous M694V as a risk factor for amyloidosis in Turkish FMF patients. Gene; 492:285–9.
[26] Touitou I, et al., (2007), Country as the primary risk factor for renal amyloidosis in fa- milial Mediterranean fever. Arthritis Rheum; 56:1706–12.
[27] Nazari, M. , Movlan, M. K. and Parish, M. (2025). Comparison of the hemodynamic changes of orotrachealintubation in patients with a history of hypertension by direct laryngoscopy with the Macintosh blade of the video laryngoscope. *Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research*, *1*(3), 81-88.
[28] Yaşar Bilge Ş, et al., (2019), The distribution of MEFV mutations in Turkish FMF patients: multicenter study representing results of Anatolia. Turk J Med Sci; 49:472–7.
[29] Öztürk K, et al., (2022), Real-life data from the largest pediatric familial Mediterranean fever cohort. Front Pediatr; 9:805919.