JEIMP
E-ISSN: 2980-0617

The Journal of
European Internal Medicine Professionals

JEIMP
The Science

Review

Genetic and Epigenetic Features of Familial Mediterranean Fever: What is New?

Author(s) ORCID Edip Erkuş

Affiliation(s) Erzurum City Hospital, Department of Nephrology, Erzurum, Turkiye

Corresponding Author Edip Erkuş, M.D., Erzurum City Hospital, Department of Nephrology, Erzurum, Turkiye
E-mail: dr.ediperkus@gmail.com

doi 10.5281/zenodo.11215800

J Eur Int Prof. Year; 2024, Volume: 2, Issue: 2 *Submitted at*: 24.03.2024, *Accepted at*: 07.05.2024, *Published at*: 15.05.2024

JEIMP belongs to "*The Foundation for the Management of Chronic Diseases***" and is supervised by the MKD Digital Publishing.** *www.jeimp.com and digitalmkd.com*

Abstract

Familial Mediterranean Fever (FMF) is a hereditary autoinflammatory disorder characterized by recurrent fever episodes and systemic inflammation, primarily attributed to mutations in the Mediterranean Fever (*MEFV*) gene.

Genetic studies have identified various mutations in the *MEFV* gene, with notable variants such as *V726A*, *M694V*, *M694I*, *M680I*, and *E148Q* predominating in affected populations. The *MEFV* gene encodes the pyrin protein, crucial for inflammasome assembly and subsequent inflammatory responses. While biallelic mutations are typical in FMF, monoallelic carriers also exhibit phenotypic variability, suggesting the involvement of additional genetic and environmental factors. Epigenetic mechanisms, particularly DNA methylation and histone modifications, play pivotal roles in regulating gene expression and inflammatory pathways in FMF. Studies investigating DNA methylation patterns of the *MEFV* gene have yielded conflicting results regarding their association with disease severity and colchicine responsiveness. Furthermore, histone modifications, including acetylation and methylation, have been implicated in inflammasome activation and FMF pathophysiology, offering potential therapeutic targets

MicroRNAs (miRNAs), crucial regulators of gene expression, have emerged as key players in FMF pathogenesis. Dysregulated miRNA expression profiles in FMF patients, particularly those homozygous for specific mutations, suggest their involvement in immune dysregulation and cytokine modulation. Moreover, miRNAs hold promise as diagnostic biomarkers and therapeutic targets, with potential implications for personalized treatment strategies.

Keywords: Familial Mediterranean Fever, FMF, MEFV gene, epigenetics, miRNAs

INTRODUCTION

Familial Mediterranean Fever (FMF) is an inherited autoinflammatory disease characterized by recurrent fever attacks, arthritis, serositis, and amyloidosis caused kidney involvement. FMF has a frequency of 100-200 per 100,000 people, predominantly affecting those of Eastern Mediterranean origin (1). Initially thought to primarily impact individuals living in the Mediterranean region (Arabs, Armenians, and Turks), it has now become increasingly diagnosed worldwide due to easier transportation and increased migration (2). Notably, individuals from Japan, North America, and Europe have also reported cases of FMF. Among the affected populations.

EPIDEMIOLOGY

FMF is common among communities around the Mediterranean (2). It is most commonly seen in individuals of Armenian, Turkish, North African, Middle Eastern Jewish, and Arab descent. The prevalence of FMF in Turkey is approximately 1/400 - 1/1000, making it likely the country with the highest rate of FMF patients worldwide (3,4). Among Armenian citizens, the carrier rate for FMF mutation is approximately 1/7, with a disease occurrence rate of 1/500 (5). In Israel, the carrier rate among Jewish populations varies, with 1/8 among Ashkenazi Jews, 1/6 among North African Jews, and 1/4 among Iraqi Jews (6). The disease is not limited to these ethnic backgrounds and is also observed in countries with lower rates such as China, Greece, Japan, and Italy (2,7,8). In the Balkans, as countries move away from Turkey, the number of FMF patients and the carrier rate of *MEFV* mutations decrease (9). This could reflect the expansion of the Ottoman Empire in this region. FMF is presumed to have originated more than 3000 years ago

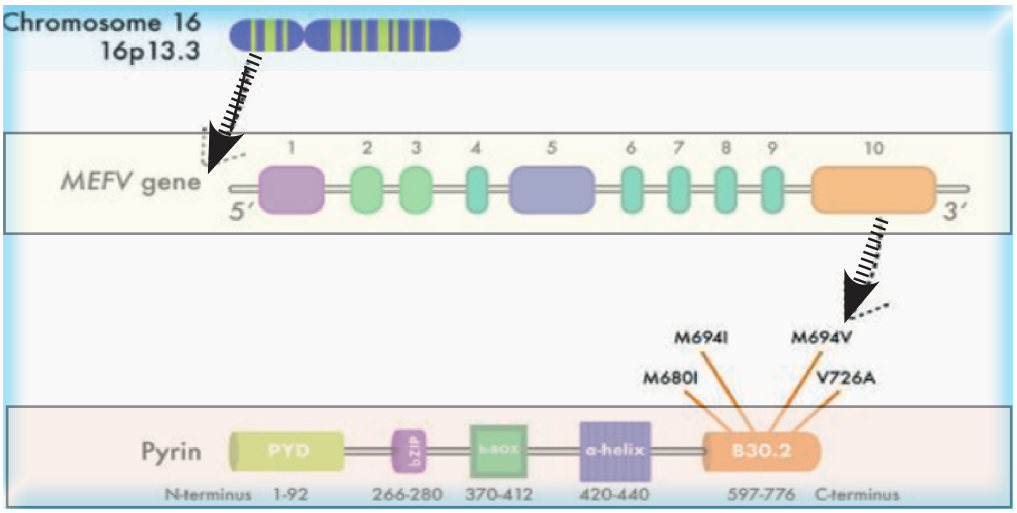

Figure 1. The MEFV gene, situated on chromosome 16's short arm at locus 16p13.3, comprises 10 exons and is responsible for encoding the pyrin protein. Pyrin, a crucial player in the innate immune system, consists of five distinct domains: PYD, bZIP transcription factor, B-box, α-helical coiled-coil, and B30.2. Among these, the C-terminal B30.2 domain holds particular significance, as it serves as the primary site where the most prevalent FMF mutations, including *M680I, M694I, M694V*, and *V726A*, are concentrated. These mutations within the *MEFV* gene lead to the activation of pyrin, triggering its assembly with pro-caspase-1 and ASC into a multiprotein complex known as the inflammasome. This molecular complex plays a pivotal role in initiating the inflammatory response, ultimately contributing to the characteristic symptoms observed in FMF patients. (Adopted from the Reference 16).

in Mesopotamia (10). In the modern world, the spread of the disease from the Mediterranean region to distant countries can be explained by overseas transportation and air travel.

GENETIC MUTATIONS

MEFV Gene Mutation

FMF is generally considered an autosomal recessive disease. Affected individuals carry biallelic pathogenic mutations in the Mediterranean Fever (*MEFV*) gene located on the short arm of chromosome 16 (16p13.3) (**Figure 1**) (11,12). The *MEFV* gene consists of 10 exons, with over 370 variants identified to date (13). The number of variants continues to increase with the use of genome sequencing. Mutations including *V726A, M694V, M694I, M680I,* and *E148Q* constitute approximately 75% of FMF chromosomes in typical cases among Armenian, Arab, Jewish, and Turkish populations (14). Among these mutations, *M694V* is the most common, occurring in 20%-65% of cases across all four populations. Additionally, approximately 10%-20% of individuals meeting the diagnostic criteria for FMF do not have *MEFV* mutations. It is debated whether this represents a FMF-like condition or true FMF with unidentified genetic variations (15).

In FMF endemic countries, approximately 30% of patients carry a single pathogenic variant (monoallelic disease) (16,17). This observation raises the question of whether the disease may also be transmitted as an autosomal dominant trait. Some reports suggest a dominant feature among patients with specific mutations such as the deletion mutation *M694V* and missense mutations *H478Y, T577N*, and *P373L* (18-20). The deletion mutation can lead to a severe defect in the encoded pyrin protein, resulting in the onset of clinical FMF. However, there is no clear explanation for the presence of FMF in individuals carrying other single missense mutations. It is thought that additional genetic and environmental (epigenetic) factors affect the phenotypic characteristics of asymptomatic disease in more than 95% of carriers (heterozygotes) of a single MEFV mutation. In a study aimed at estimating the contribution of heterozygosity to disease prevalence, a genotype comparison was conducted in 63 sibling pairs from familial types and a genotype study in 557 patients from four Mediterranean populations (21). This study demonstrated that heterozygosity alone is not responsible for classic Mendelian inherited FMF, but it constitutes a risk factor for developing FMF with a six- to eight-fold higher risk compared to individuals without *MEFV* mutations.

Although mutations in the entire *MEFV* gene are found in FMF patients, *M694V* and *M680I* are the mutations associated with the most severe forms of the disease, clustered in exon 10, encoding a motif known as the B30.2/SPRY domain at the C-terminal of the protein. Homozygotes for *M694V* exhibit a severe phenotype, with a higher likelihood of early disease onset, arthritis, erysipelas-like skin lesions, high fever, splenomegaly, more frequent attacks, and renal amyloidosis compared to individuals with other *MEFV* mutations (22). Additionally, patients with these mutations require higher doses of colchicine to prevent attacks compared to those with other genotypes. The *M694V* mutation predominantly affects FMF patients of North African Jewish descent, who are known to experience more severe

attacks. Moreover, a high prevalence of amyloidosis was detected before the use of colchicine (23). Ashkenazi Jews and Druze, who have a low frequency of the *M694V* mutation, tend to have milder versions of FMF with a lower prevalence of amyloidosis.

Genetic variants found in Exon 2 (e.g., E148Q, R202Q) and Exon 3 (P369S) typically present with a milder clinical presentation of FMF, often associated only with mild and nonspecific inflammatory symptoms. However, this is not always the case, as reports of more severe or atypical disease with these variants exist. For example, several studies have shown that *E148Q*, *P369S*, and *R408Q* can be found on a single allele (in cis) and may manifest as FMF-like disease or PFAPA (periodic fever, aphthous stomatitis, pharyngitis, adenitis) syndrome (24,25).

Additional studies conducted in Greece and Turkey have reported an association between the *R202Q* mutation and an inflammatory phenotype of FMF (26,27). Therefore, it has been observed that typical clinical features of FMF, especially arthritis, are observed in patients with compound mutations, including *R202Q* (25).

In Japan, where most mutations occur in Exons 2, 3, and 4, FMF tends to be mild and easily controlled with low-dose colchicine (28). Individuals with no or only one pathogenic *MEFV* mutation tend to have a milder disease compared to those with biallelic pathogenic variants (29). These observations indicate an additional role of environmental factors in the FMF phenotype.

Whether the *E148Q* mutation is merely a polymorphism or a sequence alteration causing the disease remains uncertain (30,31). The penetrance of the *E148Q* mutation is reduced, and *E148Q* homozygotes are either asymptomatic or may have mild disease. Additionally, amyloidosis is rare in individuals with these mutations. However, patients carrying the *E148Q* mutation along with an additional different mutation are almost always symptomatic. In one study, the penetrance of *M694V*/*E148Q* was found to be 17 times higher than that of *M694V*/-. This suggests that the *E148Q* mutation plays an active role when combined with the *M694V* mutation (32).

Considering other genetic factors, the incomplete penetrance and variable presentations of FMF suggest the presence of potential genetic factors that could influence the disease's presentation. Evidence that another gene may modulate the clinical features of the *MEFV* gene is demonstrated by the segregation of different alleles of the major histocompatibility class I chain-related gene A (*MICA*) among FMF patients with different clinical features. In a study evaluating 151 affected patients and family members for the presence of five common MICA alleles, the A-9 allele was strongly associated with early disease onset in *M694V* homozygotes, while the A-4 allele was found to impact the frequency of FMF attacks (33). The mechanism by which MICA or another closely linked gene influences the FMF phenotype is not yet clear.

In one study, the presence of the serum amyloid A1 (SAA1) alpha homozygous genotype was associated with a sevenfold increased risk of renal amyloidosis compared to other SAA1 genotypes (34).

EPIGENETIC

For a long time, conventional knowledge held that altering the DNA sequence was the only means to potentially induce phenotypic variation. However, in 1942, Waddington introduced the term "epigenetics", which explains changes in gene functions capable of being transmitted to subsequent generations without direct alterations to the DNA sequence itself (35,36).

The study of epigenetics facilitates the identification of various disease biomarkers, empowering researchers and healthcare experts to detect specific diseases based on associated epigenetic mechanisms at an early stage, before their full manifestation or progression. Such an approach is pivotal in formulating tailored treatment or prevention strategies for prospective patients (37).

Numerous epigenetic mechanisms have been studied, with DNA methylation, histone modification, and noncoding RNAs—particularly microRNAs (miRNAs)—emerging as the most extensively investigated within the spectrum of inflammatory diseases (38).

DNA Methylation

DNA methylation stands as a predominant epigenetic mechanism influencing gene expression and phenotype without altering the underlying DNA sequence. This process, primarily occurring within CpG islands of gene promoters, orchestrates chromatin remodeling, subsequently impacting transcriptional activity and protein levels (39).

In the context of FMF, investigations into the methylation status of the *MEFV* gene, a key player in the disease pathogenesis, have yielded conflicting results. While some studies suggested a potential link between *MEFV* methylation and disease severity, inconsistencies emerged, underscoring the complexity of epigenetic regulation in FMF manifestation (**Table 1**) (16,40-43).

Moreover, emerging evidence implicates epigenetic modifications in the regulation of inflammasome complexes, shedding light on novel pathways contributing to FMF pathophysiology. The epigenetic regulation of NLRP13 and NLRP3 inflammasomes, along with their impact on IL-1β expression, suggests a multifaceted interplay between epigenetics and

Table 1. Studies investigating DNA methylation in FMF

Study	Findings
Ulum et al. (2015) (40)	No correlation found between *MEFV* gene methylation and clinical symptoms in Turkish children diagnosed with FMF.
Kirectepe et al. (2011) (41)	Higher levels of *MEFV* gene methylation observed in FMF patients compared to healthy controls, associated with decreased gene expression.
Doğan et al. (2019) (42)	No correlation found between *MEFV* methylation and *MEFV* expression levels in pediatric FMF patients in Turkey.
Zekry et al. (2023) (43)	No significant difference observed in methylation levels of *MEFV* gene exon 2 between colchicine responders and nonresponders in FMF patients.

FMF; Familial Mediterranean Fever methylation

inflammatory processes in FMF (44).

Furthermore, insights into the potential influence of DNA methylation on colchicine responsiveness among FMF patients highlight the therapeutic implications of epigenetic variability. However, definitive conclusions regarding the efficacy of colchicine in methylation-associated cases await further elucidation through expanded research endeavors. While the results showed that the colchicine nonresponders had a greater methylation level of exon 2 of the *MEFV* gene than did the colchicine responders, these results were deemed to be nonsignificant (43).

Overall, while the role of DNA methylation in FMF etiology and treatment response remains an area of active investigation, it is evident that epigenetic mechanisms contribute significantly to the clinical heterogeneity and pathogenic mechanisms of this complex autoinflammatory disorder. Future studies elucidating the intricate interplay between epigenetic modifications and FMF phenotypes hold promise for advancing both diagnostic and therapeutic strategies in the management of this debilitating condition.

Histone Modification

Histone modification emerges as a pivotal epigenetic mechanism intricately intertwined with DNA methylation, collectively orchestrating chromatin dynamics and gene expression patterns throughout cellular growth and development (45). While histone modifications encompass a diverse array of biochemical alterations, including methylation, acetylation, phosphorylation, ubiquitination, and SUMOylation, their cumulative effects govern transcriptional activity either by directly modulating chromatin structure or via interactions with effector proteins (**Table 2**) (16,46-49).

Of particular interest is the role of histone modifications in the activation of the NLRP3 inflammasome, a central mediator of autoimmune and autoinflammatory disorders such as systemic lupus erythematosus, rheumatoid arthritis, and Behçet disease. Despite the well-established implications of histone modifications in these diseases, their role in FMF remains largely unexplored (**Table 3**) (16,50-52).

Notably, histone acetylation dynamics have been implicated in the regulation of the NLRP3 inflammasome, exemplified by studies demonstrating increased NLRP3 expression levels upon histone acetylation in various inflammatory contexts (48,49,53). Similarly, histone demethylation has been shown to modulate NLRP3 inflammasome activity, underscoring the intricate interplay between histone modifications and inflammatory responses.

The shared genetic and inflammatory features between FMF and Behçet disease warrant investigation into the potential role of histone modifications in FMF manifestation (54). Studies elucidating the impact of histone acetylation, histone demethylation,

Table 2. Histone modifications and their effects

Histone Modification	Effect on Gene Expression
Methylation	Can lead to either gene activation or repression, depending on the specific lysine or arginine residue methylated. Represses gene expression when occurring on H3K9, H3K27, and H4K20. Activates gene expression when occurring on H3K4, H3K36, and H3K79.
Acetylation	Activates gene expression by neutralizing the positive charge of lysine residues, allowing DNA to remain accessible to transcriptional machinery.
Phosphorylation	Generally results in the activation of gene expression.
Ubiquitination	Can lead to either the activation or repression of gene expression. Monoubiquitylation of H2A mainly represses gene expression, while that of H2B activates gene expression.
SUMOylation	Generally associated with transcriptional repression.

Table 3. Role of histone modifications in inflammasome regulation and autoinflammatory diseases

Inflammasome Regulation	Role of Histone Modifications
Activation of NLRP3 Inflammasome	Histone acetylation dynamics, such as increased acetylation of histones H3K9 and H4 in the promoter region of NLRP3, have been shown to increase its expression levels and activate the inflammasome.
Regulation of Behçet's Disease (BD) **Manifestation**	Histone modifications, particularly the regulation of histone acetylation by SIRT1, have been implicated in the manifestation of BD, suggesting potential treatment options targeting histone acetylation.

ubiquitination, and SUMOylation on inflammatory pathways in experimental models of FMF hold promise for expanding our understanding of epigenetic contributions to disease expression and potential therapeutic targets (**Table 4**).

In summary, exploring the role of histone modifications in FMF pathophysiology not only sheds light on the underlying mechanisms driving disease manifestation but also offers novel avenues for therapeutic intervention and personalized treatment strategies aimed at mitigating inflammation and improving patient outcomes. Further research in this area is imperative for unraveling the complex interplay between epigenetics and autoinflammatory disorders, ultimately paving the way for more effective management and targeted therapies.

miRNAs

microRNAs (miRNAs) is as pivotal regulators of gene expression, orchestrating intricate cellular processes through post-transcriptional mechanisms. These small noncoding RNA molecules, encompassing approximately 2600 mature forms in humans, exert their influence by modulating mRNA stability and translation, thereby impacting diverse biological pathways (55).

The role of miRNAs extends beyond intracellular functions, as they are actively secreted into extracellular fluids, serving as intercellular messengers that facilitate communication between cells (56). Through their interactions with target genes, miRNAs play a crucial role in modulating immune responses, with implications in both proinflammatory and anti-inflammatory processes. Several immune response mechanisms, such as the proliferation and differentiation of B and T cells, the amplification of monocytes and neutrophils, the stimulation of antibody production, and the secretion of inflammatory mediators, have been associated with miRNAs (57).

miRNAs have emerged as key players in the pathogenesis of FMF, influencing various mechanisms such as apoptosis, inflammation, and autophagy (58). Studies have identified differential expression patterns of specific miRNAs in FMF patients, particularly those homozygous for the *M694V* mutation, compared to healthy controls. These dysregulated miRNAs, such as miR-144-3p, miR-21-5p, and miR-451, are implicated in immune processes and cytokine regulation, suggesting their potential as biomarkers for disease activity and therapeutic targets (59).

Moreover, investigations into the association between specific miRNAs and FMF genotype have revealed intriguing findings, with miR-107 showing significant downregulation in patients carrying the *M694V* mutation (60). Such insights not only deepen our understanding of the molecular mechanisms underlying FMF but also hold promise for the development of personalized diagnostic and therapeutic strategies.

The studies exploring the therapeutic potential of miRNAs in FMF have identified miR-204-3p as a candidate for modulating the phosphoinositide 3-kinase gamma (PI3Kγ) pathway, a key mediator of inflammatory cytokine release. By targeting this pathway, miR-204-3p offers a potential avenue for mitigating inflammation and ameliorating disease symptoms in FMF patients (61).

The microarray analysis conducted by Latsoudis et al. highlighted elevated expression levels of miR-4520a in FMF patients, suggesting its involvement in FMF pathogenesis through the regulation of autophagy via the mTOR pathway (62). Similarly, investigations by Akkaya-Ulum et al. revealed differential expression of inflammatory pathway-related miRNAs in FMF patients, with distinct profiles observed in homozygous and heterozygous individuals (**Table 5**) (16,63). Notably, miR-197-3p emerged as a potential therapeutic target, with its overexpression demonstrating anti-inflammatory

Table 4. Histone modifications and their effects

Shared Features	Implications and Studies
Genetic Overlap	*MEFV* mutations, particularly *M694V*, have been associated with increased risk of Behçet's Disease (BD) in regions where both FMF and BD are prevalent.
Inflammatory Features	Shared pathophysiological features suggest potential shared mechanisms between FMF and Behçet's Disease, warranting further investigation.

Table 5. Studies Investigating miRNA Expression in FMF Patients

Study	Findings
Latsoudis et al. (2017) (62)	Higher expression of miR-4520a in FMF patients, targeting RHEB involved in autophagy regulation.
Akkaya-Ulum et al. (2017) (63)	Differential expression of miRNAs related to inflammatory pathways in FMF patients with *MEFV* mutations.
Akkaya-Ulum et al. (2021) (58)	Overexpression of miR-197-3p in FMF patients, exhibiting anti-inflammatory effects by targeting IL-1R1.
Karpuzoglu et al. (2021) (73)	Dysregulated expression of miRNAs involved in apoptosis in FMF children.
Abdelkawy et al. (2021) (65)	Evaluation of miR-181a and miR-125a as potential biomarkers of inflammation in FMF patients.

FMF; Familial Mediterranean Fever methylation, RHEB; ras homolog enriched in brain, miRNA; microRNA

effects by targeting IL-1R1 and modulating NF-κB signaling.

Furthermore, studies evaluating miRNA expression in FMF patients undergoing colchicine treatment have identified potential biomarkers associated with treatment response (64). The upregulation of miR-132, miR-15a, and miR-181a in colchicine-treated patients suggests their involvement in mediating the anti-inflammatory effects of colchicine. Additionally, investigations into the role of miRNAs in apoptotic pathways revealed dysregulated expression patterns in FMF children, further implicating miRNAs in disease progression.

Moreover, recent studies have explored the utility of miRNAs as biomarkers of inflammation in FMF, with miR-181a and miR-125a showing promise in this regard (**Table 6**) (16,65). Elevated levels of proinflammatory cytokines and decreased expression of anti-inflammatory miRNAs were observed in FMF patients compared to healthy controls, highlighting the potential of miRNAs as diagnostic and prognostic markers.

In conclusion, the dysregulation of miRNAs in FMF underscores their multifaceted roles in disease pathogenesis, treatment response, and inflammation. Further elucidation of miRNA-mediated mechanisms holds significant promise for the development of novel therapeutic strategies and personalized approaches for managing FMF. Additionally, the utility of miRNAs as biomarkers offers valuable insights into disease monitoring and prognosis, paving the way for improved clinical management of FMF patients.

Novel Therapies in FMF

Colchicine, a medication derived from the autumn crocus plant, has indeed been employed for centuries in treating various conditions, including gouty arthritis. Its mechanism of action was elucidated in the 1960s, and its effectiveness in treating FMF. Since its recognition as the treatment of choice for FMF in 1974, colchicine has transformed the management of this condition (66). Colchicine is subject to usage constraints owing to its narrow therapeutic index and the possibility of adverse effects. Gastrointestinal disturbances are prevalent, with about one-third of patients experiencing partial remission, while 5–10% do not respond to treatment (66).

The approval of novel IL-1 antagonists, such as canakinumab and anakinra, alongside the accumulated experience with alternative medications in targeted treatment contexts, is broadening the therapeutic repertoire available for managing FMF (66-68). Canakinumab has been found effective in controlling and preventing flares in patients with colchicine-resistant FMF (68).

The safety and efficacy of RIST4721, an oral antagonist of acidic CXC chemokine receptor 2 (CXCR2), in FMF subjects, is being investigated in a phase 2 study

Table 6. Key Findings and Implications of miRNA Studies in FMF

Key Findings	Implications
Dysregulated miRNA expression in FMF patients	Insight into molecular mechanisms underlying FMF pathogenesis.
Identification of miRNAs targeting inflammatory pathways	Potential therapeutic targets for modulating inflammation in FMF.
Association between miRNA expression and treatment response	Understanding mechanisms of action of colchicine and other treatments in FMF.
Dysregulated miRNAs in apoptotic pathways in FMF children	Implications for disease progression and potential therapeutic interventions.
Evaluation of miRNAs as biomarkers of inflammation in FMF	Potential diagnostic and prognostic markers for monitoring disease activity.

(69). Due to the proven role of TNF-α's involvement in FMF, studies have promised that TNF-α blockade agents like infliximab, etanercept, and adalimumab may demonstrate favorable outcomes in managing FMF attacks (70). Although FMF patients show alterations in the gut microbiota, the therapeutic role of a commercial probiotic formulation, Lactobacillus acidophilus INMIA 9602 Er-2 strain 317/402 (Narine), did not improve the quality of life and crisis onset in FMF patients, hence the need for additional investigations in this context (71). The potential role of CRISPR-Cas9 gene editing technology in various diseases such as rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, multiple sclerosis, type 1 diabetes mellitus, psoriasis, and coeliac disease has been investigated recently (54). CRISPR-Cas9 may represent its immunomodulatory effects by regulating cytokines like IL-1, IL-36, and TNF-α, as well as T cell-related factors. However, these studies have remained in an experimental model (54,72).

CONCLUSION

The exploration of epigenetic mechanisms in FMF has revealed intricate regulatory pathways that contribute to the disease's pathogenesis and clinical manifestations. DNA methylation and histone modifications, two major epigenetic processes, play pivotal roles in gene expression regulation and chromatin remodeling, thereby influencing various aspects of FMF.

Studies have highlighted the involvement of DNA methylation in modulating the expression of the MEFV gene, which encodes the pyrin protein. While inconsistencies exist regarding the correlation between MEFV methylation and disease severity, emerging evidence suggests a potential link between MEFV methylation status and patient response to colchicine treatment. Additionally, investigations into the epigenetic regulation of inflammasome components, such as NLRP13 and NLRP3, have unveiled novel insights into FMF pathophysiology.

Moreover, histone modifications, including methylation, acetylation, and phosphorylation, have been implicated in the activation of the NLRP3 inflammasome and the regulation of inflammatory responses in FMF. Although research on histone modifications in FMF remains limited, insights from related autoimmune and autoinflammatory disorders provide valuable directions for future investigations.

DECLARATIONS

Conflict of interest: None

Informed consent form: Not available

Funding source: No funding was received for the research

REFERENCES

1. Alghamdi M. Familial Mediterranean fever, review of the literature. *Clin Rheumatol*. 2017;36(8):1707-1713. doi:10.1007/s10067-017-3715-5
2. Ben-Chetrit E, Touitou I. Familial mediterranean Fever in the world. *Arthritis Rheum*. 2009;61(10):1447-1453. doi:10.1002/art.24458
3. Familial Mediterranean fever (FMF) in Turkey: results of a nationwide multicenter study. *Medicine (Baltimore)*. 2005;84(1):1-11. doi:10.1097/01.md.0000152370.84628.0c
4. Cobankara V, Fidan G, Türk T, Zencir M, Colakoglu M, Ozen S. The prevalence of familial Mediterranean fever in the Turkish province of Denizli: a field study with a zero patient design. *Clin Exp Rheumatol*. 2004;22(4 Suppl 34):S27-S30.
5. Sarkisian T, Ajrapetian H, Beglarian A, Shahsuvarian G, Egiazarian A. Familial Mediterranean Fever in Armenian population. *Georgian Med News*. 2008;(156):105-111.
6. Livneh A. *Reported at familial mediterranean fever and beyond: The 4th International Congress on Systemic Autoinflammatory Diseases,* November 6-10, 2005, Bethesda, Maryland.
7. Li J, Wang W, Zhong L, et al. Familial Mediterranean Fever in Chinese Children: A Case Series. *Front Pediatr*. 2019;7:483. Published 2019 Nov 19. doi:10.3389/fped.2019.00483
8. Wu D, Shen M, Zeng X. Familial Mediterranean fever in Chinese adult patients. *Rheumatology (Oxford)*. 2018;57(12):2140-2144. doi:10.1093/rheumatology/key218
9. Debeljak M, Toplak N, Abazi N, et al. The carrier rate and spectrum of MEFV gene mutations in central and southeastern European populations. *Clin Exp Rheumatol*. 2015;33(6 Suppl 94):S19-S23.
10. Samuels J, Aksentijevich I, Torosyan Y, et al. Familial Mediterranean fever at the millennium. Clinical spectrum, ancient mutations, and a survey of 100 American referrals to the National Institutes of Health. *Medicine (Baltimore)*. 1998;77(4):268-297. doi:10.1097/00005792-199807000-00005
11. Ancient missense mutations in a new member of the RoRet gene family are likely to cause familial Mediterranean fever. The International FMF Consortium. *Cell*. 1997;90(4):797-807. doi:10.1016/s0092-8674(00)80539-5
12. French FMF Consortium. A candidate gene for familial Mediterranean fever. *Nat Genet*. 1997;17(1):25-31. doi:10.1038/ng0997-25
13. Van Gorp H, Huang L, Saavedra P, et al. Blood-based test for diagnosis and functional subtyping of familial Mediterranean fever. *Ann Rheum Dis*. 2020;79(7):960-968. doi:10.1136/annrheumdis-2019-216701
14. Touitou I. The spectrum of Familial Mediterranean Fever (FMF) mutations. *Eur J Hum Genet*. 2001;9(7):473-483. doi:10.1038/sj.ejhg.5200658
15. Ben-Zvi I, Herskovizh C, Kukuy O, Kassel Y, Grossman C, Livneh A. Familial Mediterranean fever without MEFV mutations: a case-control study. *Orphanet J Rare Dis*. 2015;10:34. Published 2015 Mar 25. doi:10.1186/s13023-015-0252-7
16. Chaaban A, Salman Z, Karam L, Kobeissy PH, Ibrahim JN. Updates on the role of epigenetics in familial mediterranean fever (FMF). *Orphanet J Rare Dis*. 2024;19(1):90. Published 2024 Feb 26. doi:10.1186/s13023-024-03098-w
17. Marek-Yagel D, Berkun Y, Padeh S, et al. Clinical disease among patients heterozygous for familial Mediterranean fever. *Arthritis Rheum*. 2009;60(6):1862-1866. doi:10.1002/art.24570
18. Rowczenio DM, Iancu DS, Trojer H, et al. Autosomal dominant familial Mediterranean fever in Northern European Caucasians associated with deletion of p.M694 residue-a case series and genetic exploration. *Rheumatology (Oxford)*. 2017;56(2):209-213. doi:10.1093/rheumatology/kew058
19. Stoffels M, Szperl A, Simon A, et al. MEFV mutations affecting pyrin amino acid 577 cause autosomal dominant autoinflammatory disease. *Ann Rheum Dis*. 2014;73(2):455-461. doi:10.1136/annrheumdis-2012-202580
20. Rowczenio DM, Youngstein T, Trojer H, et al. British kindred with dominant FMF associated with high incidence of AA amyloidosis caused by novel MEFV variant, and a review of the literature. *Rheumatology (Oxford)*. 2020;59(3):554-558. doi:10.1093/rheumatology/kez334
21. Jéru I, Hentgen V, Cochet E, et al. The risk of familial Mediterranean fever in MEFV heterozygotes: a statistical approach. *PLoS One*. 2013;8(7):e68431. Published 2013 Jul 3. doi:10.1371/journal.pone.0068431
22. Grossman C, Kassel Y, Livneh A, Ben-Zvi I. Familial Mediterranean fever (FMF) phenotype in patients homozygous to the MEFV M694V mutation. *Eur J Med Genet*. 2019;62(6):103532. doi:10.1016/j.ejmg.2018.08.013
23. Shinar Y, Livneh A, Langevitz P, et al. Genotype-phenotype assessment of common genotypes among patients with familial Mediterranean fever. *J Rheumatol*. 2000;27(7):1703-1707.
24. Davies K, Lonergan B, Patel R, Bukhari M. Symptomatic patients with P369S-R408Q mutations: familial Mediterranean fever or mixed auto-inflammatory syndrome?. *BMJ Case Rep*. 2019;12(7):e228858. Published 2019 Jul 1. doi:10.1136/bcr-2018-228858
25. Yamagami K, Nakamura T, Nakamura R, et al. Familial Mediterranean fever with P369S/R408Q exon3 variant in pyrin presenting as symptoms of PFAPA. *Mod Rheumatol*. 2017;27(2):356-359. doi:10.1080/14397595.2017.1267173
26. Kandur Y, Kocakap DBS, Alpcan A, Tursun S. Clinical significance

of MEFV gene variation R202Q. *Clin Rheumatol*. 2022;41(1):271-274. doi:10.1007/s10067-021-05906-1
27. Sgouropoulou V, Farmaki E, Papadopoulos T, Tzimouli V, Pratsidou-Gertsi J, Trachana M. Sequence analysis in Familial Mediterranean Fever patients with no confirmatory genotype. *Rheumatol Int*. 2022;42(1):15-22. doi:10.1007/s00296-021-04913-4
28. Migita K, Uehara R, Nakamura Y, et al. Familial Mediterranean fever in Japan. *Medicine (Baltimore)*. 2012;91(6):337-343. doi:10.1097/MD.0b013e318277cf75
29. Koné Paut I, Dubuc M, Sportouch J, Minodier P, Garnier JM, Touitou I. Phenotype-genotype correlation in 91 patients with familial Mediterranean fever reveals a high frequency of cutaneomucous features. *Rheumatology (Oxford)*. 2000;39(11):1275-1279. doi:10.1093/rheumatology/39.11.1275
30. Tchernitchko D, Legendre M, Cazeneuve C, Delahaye A, Niel F, Amselem S. The E148Q MEFV allele is not implicated in the development of familial Mediterranean fever. *Hum Mutat*. 2003;22(4):339-340. doi:10.1002/humu.9182
31. Topaloglu R, Ozaltin F, Yilmaz E, et al. E148Q is a disease-causing MEFV mutation: a phenotypic evaluation in patients with familial Mediterranean fever. *Ann Rheum Dis*. 2005;64(5):750-752. doi:10.1136/ard.2004.026963
32. Eyal O, Shinar Y, Pras M, Pras E. Familial Mediterranean fever: Penetrance of the p.[Met694Val];[Glu148Gln] and p.[Met694Val];[=] genotypes. *Hum Mutat*. 2020;41(11):1866-1870. doi:10.1002/humu.24090
33. Touitou I, Picot MC, Domingo C, et al. The MICA region determines the first modifier locus in familial Mediterranean fever. *Arthritis Rheum*. 2001;44(1):163-169. doi:10.1002/1529-0131(200101)44:1<163::AID-ANR20>3.0.CO;2-Z
34. Bakkaloglu A, Duzova A, Ozen S, et al. Influence of Serum Amyloid A (SAA1) and SAA2 gene polymorphisms on renal amyloidosis, and on SAA/C-reactive protein values in patients with familial mediterranean fever in the Turkish population. *J Rheumatol*. 2004;31(6):1139-1142.
35. Waddington CH. The epigenotype. 1942. *Int J Epidemiol*. 2012;41(1):10-13. doi:10.1093/ije/dyr184
36. Dupont C, Armant DR, Brenner CA. Epigenetics: definition, mechanisms and clinical perspective. *Semin Reprod Med*. 2009;27(5):351-357. doi:10.1055/s-0029-1237423
37. Lotfy R, Ali O, Zarouk W, El-Bassyouni H, Nour El-Din G. Epigenetics and familial mediterranean fever. *Azhar Int J Pharm Med Sci*. 2021;1(2):1–12.
38. Zhang L, Lu Q, Chang C. Epigenetics in Health and Disease. *Adv Exp Med Biol*. 2020;1253:3-55. doi:10.1007/978-981-15-3449-2_1
39. Lim WJ, Kim KH, Kim JY, Jeong S, Kim N. Identification of DNA-Methylated CpG Islands Associated With Gene Silencing in the Adult Body Tissues of the Ogye Chicken Using RNA-Seq and Reduced Representation Bisulfite Sequencing. *Front Genet*. 2019;10:346. Published 2019 Apr 16. doi:10.3389/fgene.2019.00346
40. Ulum YA, Peynircioglu BB, Batu E, Guler C, Karadag O, Ertenli A, et al. MEFV gene methylation pattern analysis in familial Mediterranean fever patients with altered expression levels. *Pediatr Rheumatol.* 2015;13(1):P113. doi: 10.1186/1546-0096-13-S1-P113.
41. Kirectepe AK, Kasapcopur O, Arisoy N, et al. Analysis of MEFV exon methylation and expression patterns in familial Mediterranean fever. *BMC Med Genet*. 2011;12:105. Published 2011 Aug 7. doi:10.1186/1471-2350-12-105
42. Doğan E, Gürsoy S, Bozkaya G, Çamlar SA, Kılıçarslan ÖA, Soylu A, et al. The effects of epigenetic regulation on phenotypic expressivity in Turkish patients with familial mediterranean fever. *Indian J Rheumatol*. 2019;14(4):297. doi: 10.4103/injr.injr_24_19.
43. Zekry ME, Sallam AM, AbdelHamid SG, Zarouk WA, El-Bassyouni HT, El-Mesallamy HO. Genetic and Epigenetic Regulation of MEFV Gene and Their Impact on Clinical Outcome in Auto-Inflammatory Familial Mediterranean Fever Patients. *Curr Issues Mol Biol*. 2023;45(1):721-737. Published 2023 Jan 13. doi:10.3390/cimb45010048
44. Vento-Tormo R, Álvarez-Errico D, Garcia-Gomez A, et al. DNA demethylation of inflammasome-associated genes is enhanced in patients with cryopyrin-associated periodic syndromes. *J Allergy Clin Immunol*. 2017;139(1):202-211.e6. doi:10.1016/j.jaci.2016.05.016
45. Cedar H, Bergman Y. Linking DNA methylation and histone modification: patterns and paradigms. *Nat Rev Genet*. 2009;10(5):295-304. doi:10.1038/nrg2540
46. Bannister AJ, Kouzarides T. Regulation of chromatin by histone modifications. *Cell Res*. 2011;21(3):381-395. doi:10.1038/cr.2011.22
47. Fellous A, Lefranc L, Jouaux A, Goux D, Favrel P, Rivière G. Histone Methylation Participates in Gene Expression Control during the Early Development of the Pacific Oyster *Crassostrea gigas*. *Genes (Basel)*. 2019;10(9):695. Published 2019 Sep 10. doi:10.3390/genes10090695
48. Alaskhar Alhamwe B, Khalaila R, Wolf J, et al. Histone modifications and their role in epigenetics of atopy and allergic diseases. *Allergy Asthma Clin Immunol*. 2018;14:39. Published 2018 May 23. doi:10.1186/s13223-018-0259-4
49. Gkoutsias A, Makis A. The role of epigenetics in childhood autoimmune diseases with hematological manifestations. *Pediatr Investig*. 2022;6(1):36-46. Published 2022 Feb 21. doi:10.1002/ped4.12309
50. Araki Y, Mimura T. The Histone Modification Code in the Pathogenesis of Autoimmune Diseases. *Mediators Inflamm*. 2017;2017:2608605. doi:10.1155/2017/2608605
51. Ma X, Wang X, Zheng G, et al. Critical Role of Gut Microbiota and Epigenetic Factors in the Pathogenesis of Behçet's Disease. *Front Cell Dev Biol*. 2021;9:719235. Published 2021 Oct 5. doi:10.3389/fcell.2021.719235
52. Liu CC, Huang ZX, Li X, et al. Upregulation of NLRP3 via STAT3-dependent histone acetylation contributes to painful neuropathy induced by bortezomib. *Exp Neurol*. 2018;302:104-111. doi:10.1016/j.expneurol.2018.01.011
53. Mezher N, Mroweh O, Karam L, Ibrahim JN, Kobeissy PH. Experimental models in Familial Mediterranean Fever (FMF): Insights into pathophysiology and therapeutic strategies. *Exp Mol Pathol*. 2024;135:104883. doi:10.1016/j.yexmp.2024.104883
54. O'Brien J, Hayder H, Zayed Y, Peng C. Overview of MicroRNA Biogenesis, Mechanisms of Actions, and Circulation. *Front Endocrinol (Lausanne)*. 2018;9:402. Published 2018 Aug 3. doi:10.3389/fendo.2018.00402
55. Okuyan HM, Begen MA. miRNAs as attractive diagnostic and therapeutic targets for Familial Mediterranean Fever. *Mod Rheumatol*. 2021;31(5):949-959. doi:10.1080/14397595.2020.1868674
56. Lindsay MA. microRNAs and the immune response. *Trends Immunol*. 2008;29(7):343-351. doi:10.1016/j.it.2008.04.004
57. Balci-Peynircioglu B, Akkaya-Ulum YZ, Akbaba TH, Tavukcuoglu Z. Potential of miRNAs to predict and treat inflammation from the perspective of Familial Mediterranean Fever. *Inflamm Res*. 2019;68(11):905-913. doi:10.1007/s00011-019-01272-6
58. Amarilyo G, Pillar N, Ben-Zvi I, et al. Analysis of microRNAs in familial Mediterranean fever. *PLoS One*. 2018;13(5):e0197829. Published 2018 May 22. doi:10.1371/journal.pone.0197829
59. Kahraman CY, Egin ME, Tatar A, Turkez H, Mardinoglu A. The Assessment of Selected miRNA Profile in Familial Mediterranean Fever. *Biomed Res Int*. 2021;2021:6495700. Published 2021 Oct 13. doi:10.1155/2021/6495700
60. Koga T, Migita K, Sato T, et al. MicroRNA-204-3p inhibits lipopolysaccharide-induced cytokines in familial Mediterranean fever via the phosphoinositide 3-kinase γ pathway. *Rheumatology (Oxford)*. 2018;57(4):718-726. doi:10.1093/rheumatology/kex451
61. Latsoudis H, Mashreghi MF, Grün JR, et al. Differential Expression of miR-4520a Associated With Pyrin Mutations in Familial Mediterranean Fever (FMF). *J Cell Physiol*. 2017;232(6):1326-1336. doi:10.1002/jcp.25602
62. Akkaya-Ulum YZ, Balci-Peynircioglu B, Karadag O, et al. Alteration of the microRNA expression profile in familial Mediterranean fever patients. *Clin Exp Rheumatol*. 2017;35 Suppl 108(6):90-94.
63. Hortu HO, Karaca E, Sozeri B, et al. Evaluation of the effects of miRNAs in familial Mediterranean fever [published correction appears in Clin Rheumatol. 2019 Jan 7;:]. *Clin Rheumatol*. 2019;38(3):635-643. doi:10.1007/s10067-017-3914-0
64. Abdelkawy RFM, Kholoussi S, Eissa E, Hamed K, Raouf HA, El-Bassyouni HT. Differential expression of micro RNAs and their association with the inflammatory markers in familial mediterranean fever patients. *Biomed Pharmacol J*. 2021;14(3):1351–1358. doi: 10.13005/bpj/2236.
65. Ehlers L, Rolfes E, Lieber M, et al. Treat-to-target strategies for the management of familial Mediterranean Fever in children. *Pediatr Rheumatol Online J*. 2023;21(1):108. Published 2023 Sep 26. doi:10.1186/s12969-023-00875-y
66. Ben-Zvi I, Kukuy O, Giat E, et al. Anakinra for Colchicine-Resistant Familial Mediterranean Fever: A Randomized, Double-Blind, Placebo-Controlled Trial. *Arthritis Rheumatol*. 2017;69(4):854-862. doi:10.1002/art.39995
67. De Benedetti F, Gattorno M, Anton J, et al. Canakinumab for the Treatment of Autoinflammatory Recurrent Fever Syndromes. *N Engl J Med*. 2018;378(20):1908-1919. doi:10.1056/NEJMoa1706314
68. Phase 2 Study to Evaluate the Safety and Efficacy of RIST4721 in Subjects With Familial Mediterranean Fever. Identifier NCT05448391, U.S. National Library of Medicine (2023). https://clinicaltrials.gov/study/NCT05448391
69. El Hasbani G, Jawad A, Uthman I. Update on the management of colchicine resistant Familial Mediterranean Fever (FMF). *Orphanet J Rare Dis*. 2019;14(1):224. Published 2019 Oct 15. doi:10.1186/s13023-019-1201-7
70. Pepoyan A, Balayan M, Manvelyan A, et al. Probiotic *Lactobacillus acidophilus* Strain INMIA 9602 Er 317/402 Administration Reduces the Numbers of *Candida albicans* and Abundance of Enterobacteria in the Gut Microbiota of Familial Mediterranean Fever Patients. *Front Immunol*. 2018;9:1426. Published 2018 Jun 26. doi:10.3389/fimmu.2018.01426
71. Jing W, Zhang X, Sun W, Hou X, Yao Z, Zhu Y. CRISPR/CAS9-Mediated Genome Editing of miRNA-155 Inhibits Proinflammatory Cytokine Production by RAW264.7 Cells. *Biomed Res Int*. 2015;2015:326042. doi:10.1155/2015/326042
72. Karpuzoglu EM, Kisla Ekinci RM, Balci S, Bisgin A, Yilmaz M. Altered expression of apoptosis-related, circulating cell-free miRNAs in children with familial Mediterranean fever: a cross-sectional study. *Rheumatol Int*. 2021;41(1):103-111. doi:10.1007/s00296-020-04541-4