

Exploratory epigenetic analysis of host gene-dependent regulation of miR-197-3p in familial Mediterranean fever

Yeliz Z. Akkaya Ulum¹, Emre Nalbant¹, Yağmur Bayındır², Betül Bölükoğlu¹, Tayfun Hilmi Akbaba¹, Seza Özen², Banu Balcı Peynircioğlu¹

¹Department of Medical Biology, Faculty of Medicine, Hacettepe University, Ankara, Türkiye; ²Department of Pediatrics, Hacettepe University, Ankara, Türkiye.

ABSTRACT

Background. Familial Mediterranean Fever (FMF) is an autosomal recessive autoinflammatory disease caused by mutations in the *Mediterranean Fever (MEFV)* gene. Despite its monogenic basis, FMF shows marked clinical heterogeneity, suggesting additional regulatory mechanisms. This exploratory study aimed to investigate host gene-dependent mechanisms underlying altered miR-197-3p expression in FMF.

Materials and Methods. Peripheral blood mononuclear cells from homozygous FMF patients (n=6) and matched healthy controls (n=6) were analyzed. miR-197-3p expression was quantified using RT-qPCR. DNA methylation patterns in regulatory regions of the *GNAI3* promoter and the *MIR197* upstream candidate regulatory region were assessed by bisulfite sequencing.

Results. miR-197-3p expression was significantly reduced in FMF patients compared with controls, as expected. No evidence supporting regulation through the *MIR197* upstream candidate regulatory region was observed. Differential methylation within the *GNAI3* promoter was statistically significant (p = 0.0093), supporting biological relevance despite the limited cohort size.

Conclusion. These pilot findings provide preliminary molecular evidence supporting host gene-dependent regulation of miR-197-3p in FMF. Given the small cohort size, these findings should be considered exploratory and require validation in larger, independent cohorts.

Key words: autoinflammation, DNA methylation, *GNAI3*, Familial Mediterranean Fever, microRNA, miR-197-3p.

Familial Mediterranean Fever (FMF) is an autoinflammatory disease characterized by recurrent episodes of fever and serosal inflammation and is caused by mutations in the *Mediterranean Fever (MEFV)* gene encoding the pyrin protein.^{1,2} Although FMF is inherited as an autosomal recessive disorder, patients carrying identical *MEFV* mutations frequently exhibit substantial variability in disease severity, attack frequency, and response to treatment,

indicating that factors beyond genetic variation contribute to disease pathogenesis.³

Epigenetic regulation has emerged as an important modifier of inflammatory and rheumatic diseases, influencing gene expression without altering the underlying DNA sequence.^{4,5} Among epigenetic mechanisms, microRNAs (miRNAs) play a central role in the post-transcriptional regulation of genes involved in innate

✉ Yeliz Z. Akkaya Ulum • yelizakkaya@hacettepe.edu.tr

Received 10th Apr 2026, revised 25th Jun 2026, 9th Sep 2026, 18th Oct 2026, accepted 18th Oct 2026.

Copyright © 2026 The Author(s). This is an open access article distributed under the [Creative Commons Attribution License \(CC BY\)](#), which permits unrestricted use, distribution, and reproduction in any medium or format, provided the original work is properly cited.

immune signaling, cytokine production, and inflammasome activation.⁴ Altered miRNA expression profiles have been reported in several rheumatic and autoinflammatory diseases, including rheumatoid arthritis, systemic lupus erythematosus, and periodic fever syndromes.^{6,7}

miR-197-3p has been identified as an inflammation-associated miRNA with regulatory effects on cytokine signaling pathways. In our previous work, we demonstrated that miR-197-3p expression is significantly reduced in homozygous FMF patients compared with healthy controls.^{8,9} Functional analyses further showed that miR-197-3p has anti-inflammatory effects by modulating cytokine release, caspase-1 activation, and cell migration.⁸ Despite these findings, the molecular mechanisms responsible for the decreased expression of miR-197-3p in FMF have remained unclear.

miR-197-3p is encoded from the *MIR197* gene within the G Protein Subunit Alpha I3 (*GNAI3*) gene, and to date, no independent promoter has been described for the *MIR197* locus.¹⁰ This genomic organization suggests that miR-197-3p expression is likely regulated in coordination with transcriptional control of its host gene rather than through a separate promoter-driven mechanism. Epigenetic modifications affecting host gene transcription, such as DNA methylation, therefore may contribute to miR-197-3p dysregulation.^{11,12}

In this context, investigating regulatory features of the *GNAI3* locus may provide insight into miR-197-3p expression changes observed in FMF patients. Clarifying whether altered miR-197-3p levels are linked to host gene-dependent regulation is essential for understanding miRNA-mediated control of inflammation and may reveal novel regulatory pathways relevant to autoinflammatory disease pathogenesis.^{12,13}

In the present study, we aimed to investigate the molecular basis of miR-197-3p dysregulation in FMF, focusing on transcriptional and epigenetic mechanisms associated with its host gene, *GNAI3*.

Materials and Methods

Study group

The study group consisted of six patients with FMF homozygous for the M694V variant and six healthy controls without *MEFV* mutations. The FMF and control groups each included three female and three male participants. The mean age was 11.35 ± 3.60 years in the FMF group and 12.25 ± 3.88 years in the healthy control group. Disease duration among FMF patients ranged from 2.9 to 12 years. All patients were receiving colchicine treatment at the time of sampling (1 mg/day, n=5; 2 mg/day, n=1) and had an Autoinflammatory Disease Activity Index (AIDAI) score of 0, indicating clinically inactive disease. No patient had clinical evidence of an acute FMF attack at the time of sampling. *MEFV* mutation analysis was performed using restriction enzyme digestion-based mutation analysis, and homozygosity for the M694V variant was confirmed in all FMF patients. Available hematological parameters and C-reactive protein levels were recorded at the time of sampling. All procedures involving human participants were approved by the Hacettepe University Non-Interventional Clinical Research Ethics Committee (date: 20.09.2022, number: 2022/14-35). Written informed consent was obtained from all participants or their legal guardians prior to enrollment, and the study was conducted in accordance with institutional ethical standards.

Peripheral blood mononuclear cell isolation and stimulation

Peripheral blood samples were collected into heparinized tubes. Peripheral blood mononuclear cells (PBMCs) were isolated by density gradient centrifugation using lympholyte-poly solution. Isolated PBMCs were washed and incubated in serum-free Roswell Park Memorial Institute (RPMI) (Gibco) 1640 medium for 30 minutes. Following incubation cells were harvested for RNA and DNA isolation.

DNA isolation and bisulfite treatment

Genomic DNA was isolated from PBMCs using phenol–chloroform–isoamyl alcohol extraction method. DNA concentration and purity were assessed by spectrophotometry. Bisulfite conversion of genomic DNA was performed using the EpiTect Bisulfite Kit (QIAGEN) according to the manufacturer's instructions to assess DNA methylation patterns. Following conversion, bisulfite-treated DNA was purified and stored at -20°C until further analysis in Tris-EDTA (TE) buffer.

DNA methylation analysis

DNA methylation analysis was conducted using the EpiTect Bisulfite Kit (QIAGEN) according to the manufacturer's instructions by bisulfite sequencing. Regions selected for analysis included regulatory sequences associated with the promoter of *GNAI3* and the region upstream of the *MIR197* gene. Bisulfite-specific primers were designed to amplify CpG-rich regions while avoiding CpG sites within primer sequences. PCR amplification of bisulfite-converted DNA was performed using DreamTaq DNA Polymerase (5 U/ μL ; Thermo Scientific) on a SimpliAmp Thermal Cycler (Applied Biosystems). Sanger sequencing was conducted using the BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems), followed by capillary electrophoresis on an ABI 3130 Genetic Analyzer (Applied Biosystems). Methylation levels at individual CpG sites were determined by direct analysis of sequencing chromatograms.

Because no experimentally validated independent promoter has been established for *MIR197*, the upstream region was investigated as a candidate regulatory region rather than a confirmed promoter. The analyzed regions were selected to evaluate two alternative regulatory models: host gene-dependent regulation associated with the *GNAI3* promoter and possible local regulation associated with the genomic region upstream of *MIR197*. Region selection was guided by genomic position,

CpG density, CpG-associated features, and regulatory annotations within the *GNAI3/MIR197* locus.

Primer sequences used for amplification of bisulfite-treated DNA targeting regulatory regions of the *GNAI3* locus and regions upstream of *MIR197* are listed in Table I. Primer design was based on the length, CpG density, and sequence characteristics of the target regions to ensure efficient amplification of bisulfite-converted DNA and accurate region-specific methylation assessment.

RNA isolation and reverse transcription quantitative polymerase chain reaction (RT-qPCR)

Total RNA was isolated from PBMCs using RNeasy Mini Kit (QIAGEN) according to the manufacturer's instructions. RNA concentration and quality were assessed prior to reverse transcription. For analysis of miR-197-3p expression, complementary DNA (cDNA) synthesis was performed using miRNA-specific reverse transcription protocols with the TaqMan® MicroRNA Reverse Transcription Kit (Applied Biosystems). All reactions were carried out using MicroRNA TaqMan® hsa-miR-197-3p, 000497 and U6 snRNA, 001973 assays (Applied Biosystems) with TaqMan® Universal PCR Master Mix and no AmpErase® UNG (Applied Biosystems) kit. The reactions were conducted on the BioRad IQ5 (Biorad). Small nuclear RNA U6 were used as internal controls, as appropriate. Relative expression levels were calculated using the comparative Ct method ($2^{-\Delta\text{Ct}}$).

Statistical Analysis

Statistical analyses were performed using GraphPad Prism 10.4.1 (GraphPad Software). Data distribution was assessed using the Shapiro–Wilk test, and no significant deviation from normality was detected ($p > 0.05$). Differences between patient and control groups were evaluated using an unpaired t-test with Welch's correction, which does not assume

Table I. Primer sequences used in this study. List of primers used for amplification of bisulfite-treated DNA targeting regulatory regions of the *GNAI3* locus and regions upstream of the *MIR197* gene. Primer sequences are provided in the 5'-3' direction.

Gene	Primer	Sequences
MIR197	1	Fw: TTTTGTAGGTGATTTTGATGTAGTTAAT Rv: CCACTATACTCAACCTATATTAATCTTT
	2	Fw: GAGTGTTATGTTGTTATTTAAAAAGTTT Rv: CCACCATACTCACTAATTTTATATTTT
	3	Fw: GTTAATATGGTGAAATTTTGTTTATT Rv: CCCAACAATTTTCAATAATTTTCTTAAT
	4	Fw: ATTAAGAAAATTATTGAAAATTGTTGGG Rv: ACTAACACTAAACATACAAAACTTTTA
	5	Fw: TATGTAAAAGTTTTGTATGTTTAGTGT Rv: AAAACCTTTATCCTACATAAAACAAAAAT
	6	Fw: TTGTTTTGTTATTTTTGTTTATGTAGG Rv: ACGTTAAATACCTTTATTAATACTACCT
	7	Fw: AGGTAGTATTAATAAAGGTATTTAACGT Rv: TTCTATCTTTTACCATAAAAAAACACT
GNAI3	1	Fw: TTAAATTAGGTAGTCGAAAGGTAAATG Rv: TTAAACCACTCTCCTCAAAAAAAA
	2	Fw: TTGATAGAATTCGAAATTTGTAGATT Rv: AAATAAAAACACCGTCTATTACTAAA
	3	Fw: GAGAGGGTTATCGTTTAGTAATAGA Rv: GAATAACAACAACCTTCACTTCTTT
	4	Fw: GTTAAAGAAGTGAAGTTGTTGTAT Rv: ATACTCCCAAATCTCTCTACTAAAC

Fw, forward; Rv, reverse.

equal variances between groups. Average CpG methylation values (ranging from 0 to 1) were derived from normalized C/(C+T) ratios and are presented as percentages for clarity. Direct bisulfite sequencing was chosen to assess regional methylation patterns rather than single-allele resolution, as the aim of the study was to compare overall methylation differences between FMF patients and healthy controls. Data are presented as mean $\pm$ standard deviation. A p value of ≤ 0.05 was considered statistically significant.

Results

Clinical characteristics of the study population

Six patients with FMF homozygous for the M694V variant and six healthy controls without *MEFV* mutations were included. The groups were balanced for sex, with three females and three males in each group, and had comparable age distributions. The mean age was 11.35 ± 3.60 years in the FMF group and 12.25 ± 3.88 years in the healthy control group. Disease duration among FMF patients ranged from 2.9 to 12 years.

All FMF patients were receiving colchicine treatment and had an AIDAI score of 0 at the time of sampling, indicating clinically inactive disease. No patient had clinical evidence of an acute FMF attack at the time of sampling. Demographic, clinical, and available laboratory characteristics of the study population are summarized in Table II and Table III.

DNA methylation analysis of the *GNAI3* and *MIR197* locus

Bisulfite sequencing was used to evaluate DNA methylation patterns within regulatory regions including a ~500 bp region within the putative *GNAI3* promoter and a ~2000 bp region upstream of the *MIR197* gene (Fig. 1A). Representative bisulfite sequencing chromatograms of the *selected regions* confirm successful bisulfite conversion and enable discrimination between methylated and unmethylated CpG sites (Fig. 1B), while distinct CpG methylation patterns are observed between FMF patients and healthy controls within the *GNAI3* promoter region (Fig. 1C).

Expression levels of miR-197-3p were evaluated in PBMCs from FMF patients and healthy controls. miR-197-3p expression was significantly reduced in FMF patients compared with healthy controls under basal conditions (0.00500 ± 0.00393 vs. 0.01872 ± 0.00884 , respectively; mean $\pm$ SD; * $p = 0.0106$) (Fig. 2A). In parallel, bisulfite sequencing analysis revealed increased DNA methylation within the *GNAI3* promoter region in FMF patients compared with healthy controls ($58.33 \pm 4.37\%$ vs. $44.00 \pm 8.99\%$, respectively; mean $\pm$ SD; ** $p=0.0093$). In contrast, methylation levels in the regions upstream of the *MIR197* gene did not differ significantly between FMF patients and healthy controls ($51.90 \pm 8.07\%$ vs. $48.55 \pm 8.34\%$, respectively; mean $\pm$ SD; $p=0.4957$) (Fig. 2B). These findings suggest that reduced miR-197-3p expression in FMF may be linked to epigenetic regulation of the host gene *GNAI3*, while no significant methylation difference was detected in the examined upstream candidate regulatory region of *MIR197*.

Table II. Individual and summary of demographic and clinical characteristics of FMF patients and healthy controls.

		Date of Birth	Age (years)	Age (years), mean $\pm$ SD	Sex	Sex, female/male	Date of diagnosis	Disease duration (years)	Disease duration (years), mean $\pm$ SD	Colchicine treatment status	Disease activity measures (AIDAI)
MEFV ^{M694V/M694V} patients	1	15.08.2011	12.3	11.35 $\pm$ 3.60	Male	3/3	01.01.2012	12	8.15 $\pm$ 3.00	1 mg/day	0
	2	28.03.2014	9.7		Female		01.10.2015	8.2		1 mg/day	0
	3	21.03.2014	9.7		Male		01.06.2016	7.5		1 mg/day	0
	4	16.09.2017	6.2		Female		01.02.2021	2.9		1 mg/day	0
	5	24.06.2007	16.5		Female		01.12.2014	9		2 mg/day	0
	6	07.04.2010	13.7		Male		01.09.2014	9.3		1 mg/day	0
Healthy controls	1	25.09.2012	11.2	12.25 $\pm$ 3.88	Male	3/3					
	2	31.10.2017	6.1		Female						
No MEFV mutation	3	29.01.2014	9.9		Female						
	4	10.02.2008	15.9		Female						
	5	03.10.2008	15.2		Male						
	6	03.10.2008	15.2		Male						

AIDAI, Autoinflammatory Disease Activity Index; SD, standard deviation. All FMF patients were attack-free at the time of sampling (AIDAI score = 0) and were receiving colchicine treatment. Dates are presented in DD/MM/YYYY format.

Table III. Individual laboratory characteristics of FMF patients and healthy controls at the time of sampling.

		Leukocyte x10 ³ /μL	Lymphocyte %	Monocyte %	Neutrophil %	Eosinophil %	Basophil %	Thrombocyte x10 ³ /μL	C-reactive protein (CRP) mg/dL
Reference Values		4.31 - 11	15.5 – 56.6	4.2 – 12.3	28.6 – 74.5	0 – 4.7	0 – 0.7	206 - 369	0 – 0.8
<i>MEFV</i> ^{M694V/M694V} patients	1	6.5	43.9	8.1	46.3	1.1	0.6	389	0.976
	2	6.3	42.3	6.4	46.1	4.2	1.0	291	0.384
	3	6.8	33.0	7.0	57.5	1.6	0.9	277	0.892
	4	6.8	35.6	6.9	54.8	2.1	0.6	318	5.06
	5	6.4	40.9	8.2	45.9	4.7	0.3	284	0.320
	6	6.5	41.7	8.6	48.6	0.8	0.3	284	0.141
Healthy controls No <i>MEFV</i> mutation	1	8.7	26.7	8.9	61.4	2.4	0.6	246	4.55
	2	5.9	41.1	7.3	49.0	1.9	0.7	233	RV: < 5 mg/L*
	3	6.2	34.4	9.7	50.4	4.7	0.8	289	RV: < 5 mg/L*
	4	5.6	45.1	7.7	44.0	2.7	0.5	261	RV: < 5 mg/L*
	5	4.5	41.3	8.7	47.1	2.5	0.4	221	RV: < 5 mg/L*
	6	5.5	31.6	8.9	56.7	2.4	0.4	219	RV: < 5 mg/L*

RV, Reference Value.

*The analytical instrument was changed; therefore, reference ranges and units were updated accordingly.

Discussion

In this study, we investigated the molecular basis of miR-197-3p dysregulation in FMF, focusing on epigenetic mechanisms associated with its host gene, *GNAI3*. Our results demonstrate a significant reduction in miR-197-3p expression in FMF patients and suggest that this dysregulation is not driven by an

independent *MIR197* upstream candidate regulatory region but may be linked to host gene-dependent regulatory mechanisms.

Previous studies¹⁴⁻¹⁶ have demonstrated that miRNA dysregulation in FMF is heterogeneous and may be influenced by genotype, treatment status, and disease activity. Hortu et al.¹⁴ evaluated 15 inflammation-associated miRNAs

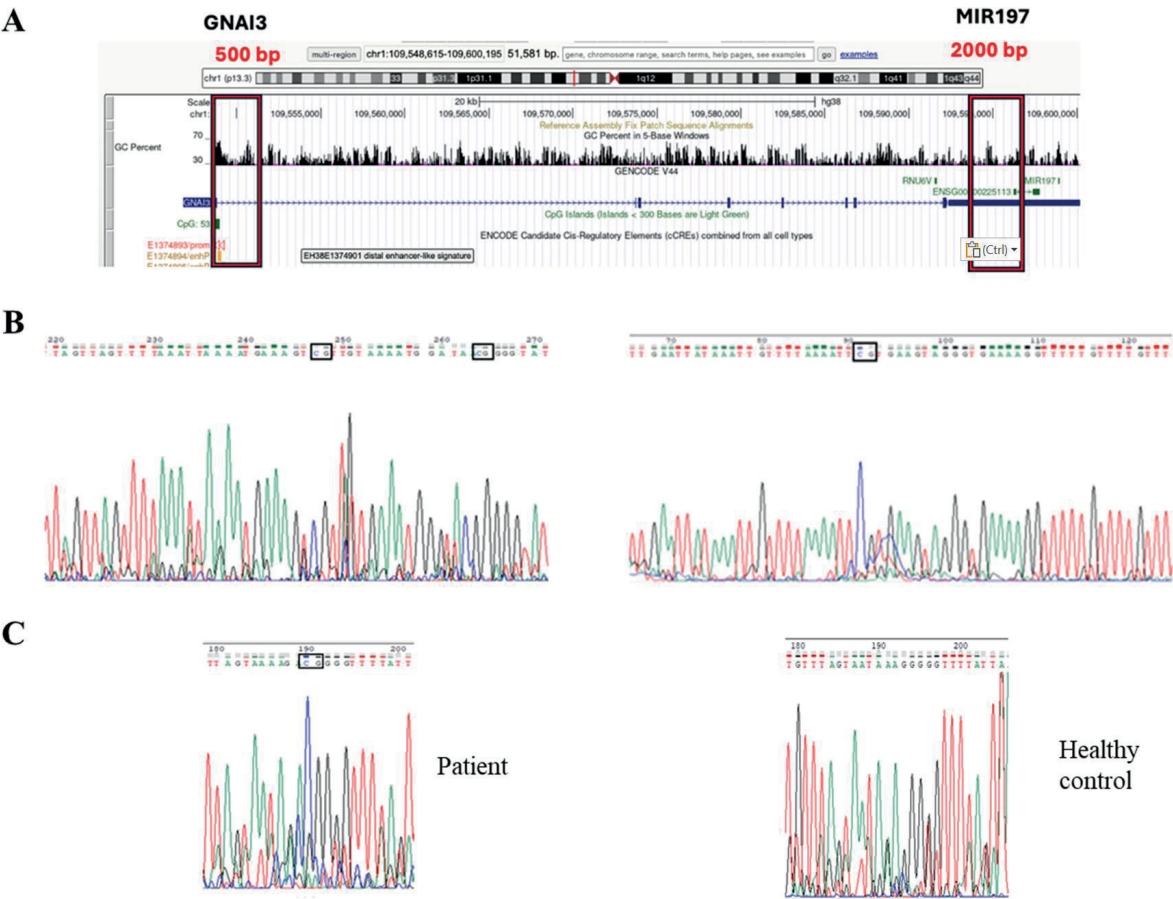


Fig. 1. Epigenetic landscape of the *GNAI3*/*MIR197* locus and bisulfite sequencing analysis. A. Genomic organization of *GNAI3* and intronic *MIR197* with regions analyzed by bisulfite sequencing indicated. CpG density, CpG islands, and ENCODE regulatory features are shown to illustrate the epigenetic landscape of the analyzed regions. B. Representative bisulfite sequencing chromatograms showing methylated (C) and unmethylated (T) CpG sites. C. Representative chromatograms of the *GNAI3* promoter regions from an FMF patient and a healthy control.

and reported reduced expression of multiple miRNAs in FMF, with additional differences related to colchicine treatment and attack status. Kahraman et al.¹⁵ identified a distinct pattern involving both upregulated and downregulated miRNAs and further reported genotype-associated variation, including prominent changes in miR-107 among patients carrying homozygous M694V. In a mechanistically oriented study, Latsoudis et al.¹⁶ linked *MEFV* perturbation to altered miRNA expression and identified an association between miR-4520a, pyrin mutations, and RHEB/mTOR-related signaling. Together, these studies indicate that miRNA dysregulation is a recurring but

molecularly heterogeneous feature of FMF. The present study differs from previous profiling approaches by focusing on a previously identified FMF-associated miRNA, miR-197-3p, and exploring a potential upstream epigenetic basis for its reduced expression. Our findings therefore extend the existing literature from the identification of altered miRNA profiles toward investigation of a possible host gene-associated regulatory mechanism.

Consistent with previous reports implicating miR-197-3p in the regulation of inflammatory pathways, we confirmed that miR-197-3p expression is significantly reduced in FMF patients compared with healthy controls under

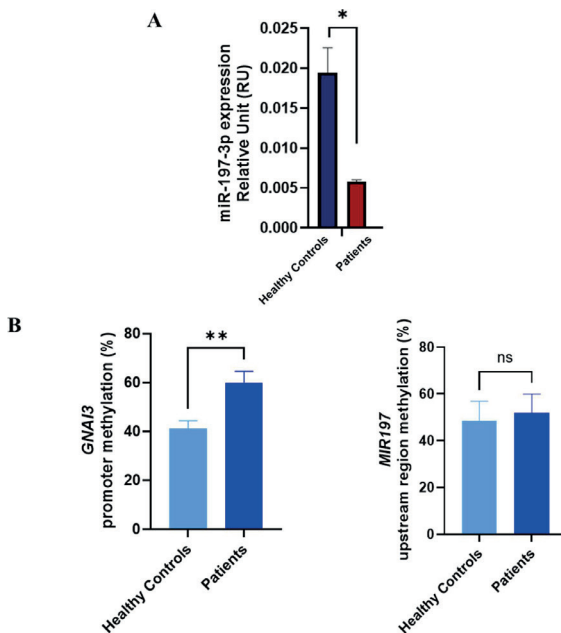


Fig. 2. Reduced miR-197-3p expression and differential promoter methylation of *GNAI3* in FMF patients. A. Relative expression levels of miR-197-3p in healthy controls and FMF patients under basal conditions, measured by RT-qPCR and expressed as relative units (RU). B. DNA methylation analysis of the *GNAI3* promoter region and the *MIR197* upstream region in healthy controls and FMF patients. Bars represent mean $\pm$ SD. Statistical comparisons between FMF patients and healthy controls were performed using unpaired t test with Welch's correction.

* $p < 0.05$ and ** $p < 0.01$ were considered statistically significant. ns, not significant.

basal conditions.⁹ As a possible cause of this reduction, we identified differential DNA methylation within the promoter region of the *GNAI3* gene in FMF patients compared with healthy controls. In contrast, no consistent methylation differences were detected in regions upstream of the *MIR197* gene. Given that no independent *MIR197* upstream candidate regulatory region has been described to date, these results are consistent with a host gene-dependent regulatory model in which epigenetic modifications of *GNAI3* may indirectly influence miR-197-3p expression.

Intronic miRNAs are frequently co-regulated with their host genes, and alterations in host gene transcription can directly affect miRNA

expression levels.¹⁷ Epigenetic mechanisms, particularly DNA methylation, have been shown to regulate both host gene transcription and intronic miRNA expression.¹⁸ miR-197-3p has previously been reported to exert anti-inflammatory effects by modulating inflammatory signaling pathways.⁸ Importantly, the present findings demonstrate an association rather than a causal relationship between increased methylation within the analyzed *GNAI3* promoter region and reduced miR-197-3p expression. The current study did not directly assess *GNAI3* transcription or experimentally manipulate DNA methylation. Therefore, it cannot be concluded from these data alone that altered *GNAI3* promoter methylation causes the reduction in miR-197-3p expression. Functional studies combining *GNAI3* expression analysis with targeted methylation editing, demethylation approaches, or promoter activity assays will be required to establish a direct regulatory relationship.

Dysregulated miRNA expression has been increasingly implicated in autoinflammatory and autoimmune diseases, including FMF.⁵ Reduced miR-197-3p expression may, in turn, impair its anti-inflammatory functions, thereby contributing to enhanced inflammatory responses characteristic of FMF.

This study should be considered a pilot molecular investigation. Although the cohort size is limited, statistically robust methylation differences ($p = 0.0093$) were identified. The analysis was intentionally restricted to M694V homozygous patients to reduce genetic variability. Therefore, the findings should not be generalized to FMF patients with other *MEFV* genotypes without further validation.

The principal limitation of this study is the small sample size. Accordingly, the findings should not be interpreted as establishing the general importance of miR-197-3p across the broader FMF population. Rather, they provide preliminary evidence of a possible association between altered methylation within the *GNAI3* regulatory region and reduced miR-197-3p

expression in a genetically homogeneous group of patients homozygous for the M694V variant. Taken together, our results provide evidence supporting a host gene-dependent regulatory mechanism underlying miR-197-3p dysregulation in FMF. This study adds to the growing body of literature highlighting the role of miRNA regulation in autoinflammatory diseases and underscores the importance of considering host gene-miRNA interactions when investigating epigenetic regulatory networks.

Given the demonstrated anti-inflammatory role of miR-197-3p, its downregulation may contribute to excessive inflammasome activation and cytokine production in FMF. Future studies should explore upstream regulators of *MIR197* transcription and post-transcriptional processing pathways.

Ethical approval

The study was approved by Hacettepe University Non-Interventional Clinical Research Ethics Committee (date: 20.09.2022, number: 2022/14-35). Written informed consent was obtained from all participants or their legal guardians prior to enrollment, and the study was conducted in accordance with institutional ethical standards.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: YZAU; data collection: YZAU, EN, YB, BB, THA, SO; analysis and interpretation of results: YZAU, EN; draft manuscript preparation: YZAU, BBP. All authors reviewed the results and approved the final version of the manuscript.

Source of funding

The authors declare that the study is funded by the Hacettepe University Scientific Research Projects Coordination Unit, grant number: BAP Project No. TKB-2023-20399.

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

1. Özen S, Batu ED, Demir S. Familial Mediterranean fever: recent developments in pathogenesis and new recommendations for management. *Front Immunol* 2017; 8: 253. <https://doi.org/10.3389/fimmu.2017.00253>
2. Masters SL, Simon A, Aksentijevich I, Kastner DL. *Horror autoinflammaticus*: the molecular pathophysiology of autoinflammatory disease (*). *Annu Rev Immunol* 2009; 27: 621-668. <https://doi.org/10.1146/annurev.immunol.25.022106.141627>
3. Ozen S, Demirkaya E, Amaryan G, et al. Results from a multicentre international registry of familial Mediterranean fever: impact of environment on the expression of a monogenic disease in children. *Ann Rheum Dis* 2014; 73: 662-667. <https://doi.org/10.1136/annrheumdis-2012-202708>
4. Krol J, Loedige I, Filipowicz W. The widespread regulation of microRNA biogenesis, function and decay. *Nat Rev Genet* 2010; 11: 597-610. <https://doi.org/10.1038/nrg2843>
5. O'Connell RM, Rao DS, Baltimore D. microRNA regulation of inflammatory responses. *Annu Rev Immunol* 2012; 30: 295-312. <https://doi.org/10.1146/annurev-immunol-020711-075013>
6. Lucherini OM, Obici L, Ferracin M, et al. First report of circulating microRNAs in tumour necrosis factor receptor-associated periodic syndrome (TRAPS). *PLoS One* 2013; 8: e73443. <https://doi.org/10.1371/journal.pone.0073443>
7. Kamiya Y, Kawada JJ, Kawano Y, et al. Serum microRNAs as potential biomarkers of juvenile idiopathic arthritis. *Clin Rheumatol* 2015; 34: 1705-1712. <https://doi.org/10.1007/s10067-015-2922-1>
8. Akkaya-Ulum YZ, Akbaba TH, Tavukcuoglu Z, et al. Familial Mediterranean fever-related miR-197-3p targets IL1R1 gene and modulates inflammation in monocytes and synovial fibroblasts. *Sci Rep* 2021; 11: 685. <https://doi.org/10.1038/s41598-020-80097-4>
9. 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): 90-94.
10. Gulyaeva LF, Kushlinskiy NE. Regulatory mechanisms of microRNA expression. *J Transl Med* 2016; 14: 143. <https://doi.org/10.1186/s12967-016-0893-x>

11. Jaenisch R, Bird A. Epigenetic regulation of gene expression: how the genome integrates intrinsic and environmental signals. *Nat Genet* 2003; 33(Suppl): 245-254. <https://doi.org/10.1038/ng1089>
12. Gay S, Wilson AG. The emerging role of epigenetics in rheumatic diseases. *Rheumatology (Oxford)* 2014; 53: 406-414. <https://doi.org/10.1093/rheumatology/ket292>
13. Ugurlu S, Kilinc OC, Karacan I, Parlar K. Familial Mediterranean fever: a comprehensive review of pathogenesis, genetics, and epigenetic regulation. *Balkan Med J* 2026; 43: 3-14. <https://doi.org/10.4274/balkanmedj.galenos.2025.2025-11-133>
14. Hortu HO, Karaca E, Sozeri B, et al. Evaluation of the effects of miRNAs in familial Mediterranean fever. *Clin Rheumatol* 2019; 38: 635-643. <https://doi.org/10.1007/s10067-017-3914-0>
15. 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. <https://doi.org/10.1155/2021/6495700>
16. Latsoudis H, Mashreghi MF, Gruen J, et al. Differential expression of miR-4520a is associated with gain of function mutations in familial Mediterranean fever (FMF). *Pediatr Rheumatol Online J* 2015; 13(Suppl 1): O10. <https://doi.org/10.1186/1546-0096-13-S1-O10>
17. Kim YK, Kim VN. Processing of intronic microRNAs. *EMBO J* 2007; 26: 775-783. <https://doi.org/10.1038/sj.emboj.7601512>
18. Chuang JC, Jones PA. Epigenetics and microRNAs. *Pediatr Res* 2007; 61: 24R-29R. <https://doi.org/10.1203/pdr.0b013e3180457684>