Clinical Rheumatology (2024) 43:2661–2667
https://doi.org/10.1007/s10067-024-07023-1

ORIGINAL ARTICLE

Altered expression of miR-17 and miR-148b in pediatric familial mediterranean fever patients

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Received: 16 February 2024 / Revised: 26 May 2024 / Accepted: 31 May 2024 / Published online: 15 June 2024

Abstract

Familial Mediterranean fever (FMF) is a recessively inherited autoinflammatory disorder with wide phenotypic variation that has been observed among individuals who have the same genotype. Modifying genes, epigenetic factors, or environmental factors might all have an impact on genotype–phenotype correlation in FMF. The current research aims to determine the expression levels of microRNAs (miR-148b and miR-17) in Egyptian FMF participants. We also aimed to investigate *Caspase -1* gene expression to make a correlation with disease severity. The study comprised 25 clinically diagnosed FMF cases and 25 healthy subjects matched for age and sex. The molecular diagnosis of FMF cases was assessed using real-time SNP genotyping assay. MiR-148b and miR-17 expression were profiled using TaqMan assay technology. The expression level of *Caspase -1* gene was also verified using qRT-PCR. MiR-17 in the studied cases was significantly upregulated compared to healthy individuals ($P=0.006$), whereas miR-148b was significantly downregulated in the examined patients ($P=0.030$). Moreover, statistically significant upregulation of *Caspase-1* expression was also elucidated in relation to normal subjects ($P=0.033$). The results obtained indicated that miR-17 and miR-148b might be potential regulatory biomarkers in FMF cases. We further hypothesized that the upregulation of *Caspase-1* could hint at its significance as a future therapeutic target to alleviate the inflammatory process in these patients.

Key Points

- *The role of miRNAs in FMF and various mechanisms involved in FMF pathogenesis has received increasing attention.*
- *Studying the expression profiles of miR-17 and miR-148b in FMF patients revealed their potential role as regulatory biomarkers in these patients.*
- *Significant upregulation of Caspase-1 expression in FMF cases could hint at its significance as a future therapeutic target.*
- *Future studies on larger cohorts are warranted to clarify and better understand the role of miRNAs in the pathogenesis and severity of FMF.*

Keywords Caspase-1 gene · Familial Mediterranean Fever · miRNAs · miR-17 · miR-148b

Introduction

FMF is a hereditary periodic fever syndrome (HPF) that is more prevalent in the Mediterranean regions, particularly among Armenians, Turks, Arabs, Sephardic Jews, Italians, and Greeks. The clinical onset typically starts in childhood, with recurring attacks of fever, serositis, and increased inflammatory markers lasting 12–72 h [1].

FMF arises from gain-of-function mutations in the *MEFV* gene that codes for pyrin (TRIM20), which is expressed particularly in cells of innate immunity, mostly monocytes, neutrophils, eosinophils, and fibroblasts [2]. Mutant pyrin triggers deregulated activation of pyrin inflammasome, which

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consequently forms the *Caspase-1*-activating inflammasome and secretes IL-1β and IL-18 secondary to various bacterial toxins or effectors inactivating Rho GTPases [3, 4]. It also diminishes NLRP3 clearance by autophagy [5].

Different modifiers, such as epigenetic factors, can be the reason for FMF varied phenotypes that cannot be explained by the genotype alone. Newly published data claims that epigenetic dysregulation has a role in the pathogenesis of inflammation and autoimmunity [6]. Among epigenetic changes, microRNAs (miRNAs) play a role as gene expression regulators and have emerged as key players in numerous biological processes like cellular proliferation, differentiation, and apoptosis [7].

The miRNAs are short ncRNA (non-coding RNA) fragments (approximately 22 nucleotides long) that control gene expression post-transcriptionally. They have been shown to modulate gene activity by attaching to particular segments of messenger RNA (mRNA) and hindering their translation or enhancing their degradation, thereby repressing gene expression [8]. Thus, miRNAs may be implicated in the development of autoinflammatory disorders by generating post-transcriptional and/or translational modifications in inflammatory proteins [9].

It was previously reported that miR-17 inhibited the autophagy-related gene 7 (ATG7), a key component of the autophagy cascade [10]. It was also described as essential in cell cycle, proliferation, and apoptosis [11]. Other miRNAs as miR-148b, have been reported to control AMPK-mTORC1, which acts as a center of autophagy regulation. MiR-148b has also been shown to inhibit cell proliferation and invasion by targeting AMP-activated protein kinase 1 (AMPK1) [12]. Additionally, miR-148b was also recorded to limit the secretion of cytokines including IL-12, IL-6, and TNF-α [13].

Up to date, many studies have highlighted the critical involvement of different miRNAs in the pathogenesis of various types of malignancies, immune-mediated, and neurodegenerative disorders [8]. Nevertheless, their association with FMF is not yet fully elucidated. Therefore, we aimed to validate the role of two miRNAs, hsa-miR-17 and hsa-miR-148b in FMF patients through investigation of their expression levels in selected patients compared to healthy subjects. We additionally aimed to investigate *Caspase-1* gene expression to confirm their role in the pathogenesis of FMF.

Patients and methods

Ethical statement

The study was performed following approval by the Medical Research Ethics Committee of the National Research Centre (NRC) according to Helsinki Declaration 1975, and written informed consent was obtained from all patients or their parents.

Study subjects

In this pilot study, 25 FMF patients were included, with age from 2 to 13 years old. Patients were recruited from the Clinical Genetics clinic, Centre of Excellence, National Research Centre, Egypt. FMF patients were diagnosed according to the Tel-Hashomer Diagnostic Criteria [14]. Mutation analysis was done to confirm the diagnosis. The disease severity was estimated using the criteria of F-SS-1 [15]. All patients were subjected to full history-taking and clinical examination. Patients who had systemic diseases (including diabetes mellitus, chronic renal failure, malignancy, and ischemic heart disease) or were administered drugs other than colchicine were excluded.

Twenty-five age- and sex matched healthy subjects were also included in the study as a control group.

Methods

DNA extraction and mutation analysis

The DNA was extracted from peripheral blood samples taken on EDTA using the ZYMO Quick-DNA Miniprep Kit (Zymo, USA) following the manufacturer's instructions. The DNA concentration was measured using a NanoDrop spectrophotometer (Thermo Scientific, Wilmington, USA). The genotyping of common thirteen mutations of the *MEFV* gene (E148Q in exon 2, P369S and R408Q in exon 3, F479L in exon 5; M680I G/C, M680I G/A, M694V, M694I, V726A, K695R, A744S, R761H and I692 del in exon 10) was performed using real time SNP genotyping commercial kits (DNA Technology, Moscow, Russia) according to the manufacturers' protocols.

Total RNA extraction

Total RNA, containing miRNAs was extracted from blood samples of patients and control subjects using direct-Zol Zymo RNA extraction kit (Zymo, USA) following the manufacturer's instructions. RNA concentration and purity were measured using a NanoDrop spectrophotometer (Thermo Scientific, Wilmington, USA).

MicroRNA expression analysis

TaqMan microRNA assay quantification was performed using real-time PCR (qRT-PCR). In the reverse transcription process, cDNA was obtained from total RNA samples using TaqMan MicroRNA RT Kit containing specific miRNA primers (Thermo Scientific, Wilmington, USA) following

thermal conditions: 16 °C for 30 min, 42 °C for 30 min, and finally 5 min at 85 °C.

Expression levels of target miRNAs (hsa-miR-148b and hsa-miR-17) was determined in patients and controls using TaqMan MicroRNA Assay and TaqMan Universal PCR Master Mix by Light Cycler 480 real time PCR (Roche, Mannheim, Germany). The u6-snRNA was used as a control to normalize differences in total RNA levels in each sample.

Caspase- 1 gene expression analysis

RNA was reverse transcribed to cDNA using COSMO cDNA synthesis kit (COSMO, USA) according to the manufacturer's instructions. Reverse transcription was performed through incubation at 37 °C for 2 h and 80 °C for 20 min. qRT-PCR was carried out to quantify the expression level in triplicate of RNA using Hera Syber Green Master Mix (Cosmo, USA). Expression of the target gene (*Caspase-1)* and housekeeping gene (*GAPDH*) has been calculated in FMF cases and standardized with controls.

For both RNA and miRNA expression analysis, Ct was determined, and then ΔCT, ΔΔCT, and relative quantification (RQ) representing the fold change were calculated using the following equation: $RQ = 2^{-\Delta\Delta CT}$ [16].

Statistical analysis

All statistical analysis was performed using the statistical software SPSS (version 20). Quantitative data was statistically represented in terms of mean and standard deviation (SD). Qualitative data was statistically represented in terms of numbers and percents. The normality assumption was tested with the Shapiro–Wilk test. T-Test was used for comparing two parametric groups and Mann–Whitney Test for comparing two nonparametric groups. One-way ANOVA test was used for comparing more than two parametric groups. A comparison between different groups' proportions was done using Chi-Square test with Odds ratio. A probability value (P value) less than 0.05 was considered significant ($P < 0.05$).

Results

Clinical results

The study involved 25 FMF patients (14 males and 11 females) with mean age 8.6 ± 3.77 years. FMF cases were diagnosed according to the Tel-Hashomer criteria. Analysis of the presenting clinical manifestations of the studied cases showed that 98% of patients manifested abdominal pain, that was the most common clinical feature. This was followed by fever in 95.5%, joint pain in 87%, chest pain in 32%, and skin rash in 19.6% (Table 1). The average age of onset in FMF individuals was 4.4 ± 2.59 years old. Regarding the frequency of attacks, it was 6.5 ± 2.5 per month. All patients were under colchicine treatment. Twenty-five age- and sex-matched healthy subjects also participated.

Molecular results

Investigating the common thirteen *MEFV* mutations showed that homozygous state was detected in 4/25 patients (16%), heterozygous state in 15/25 patients (60%), and compound heterozygotes in 6/25 patients (24%). The genotyping of FMF patients was illustrated in Table 2. The M680I allele was the most common detected allele with allele frequency of 24%. E148Q and M694I were 14% each, and V726A was 8% (Fig. 1).

Results of miRNAs expression:

All data comparing the results of expression analysis (RQ) between the patients and controls is summarized in Table 3

Regarding miR-17 expression, patients with FMF showed a mean fold change of 44.17 ± 48.07, whereas the healthy volunteers showed a mean of 1.06 ± 0.39-fold change, with statistically significant variance noted between both groups ($P = 0.006$) (Fig. 2A).

Interestingly, a significant increase in miR-17 expression was noticed in carriers of the M680I allele in comparison with those carrying other alleles ($P = 0.018$) (Fig. 2C).

Patients with FMF showed a mean of 0.42 ± 0.038-fold change in miR-148b expression compared to the control group (1.05 ± 0.39), indicating a statistically significant lower expression of miR-148b in the affected cases than in healthy volunteers ($P = 0.030$) (Fig. 2B).

Statistically significant upregulation of *Caspase-1* expression was detected (5.58 ± 3.54-fold change) in relation to normal control ($P = 0.033$) (Fig. 3).

Table 1 Clinical findings of FMF group

Age (Mean ± S.D.)	8.6 ± 3.77 years
Age of onset (First attack) (Mean ± S.D)	4.4 ± 2.59 years
Attack duration (Mean ± S.D.)	3.04 ± 0.56 days
Attacks, frequency /month (Mean ± S.D)	6.5 ± 2.5
Clinical manifestation (during attack)	Percent of patients (%)
Abdominal pain	98%
Fever	95.5%
Joint pain	87%
Pleurisy (chest pain)	32%
Skin rash	19.6%

SD: standard deviation.

Table 2 Genotyping of the studied FMF patients

Homozygous		Compound heterozygous		Heterozygous	
Genotype	Number (%)	Genotype	Number (%)	Genotype	Number (%)
M680I/M680I	2 (8%)	M680I/ M694I	2 (8%)	E148Q/	6 (24%)
M694I/M694I	2 (8%)	P369S /R408Q	1 (4%)	M680I/	4 (16%)
		M680I/E148Q	1 (4%)	V726A/	3 (12%)
		M694I/V726A	1 (4%)	A774S/	2 (8%)
		M680I / R761H	1 (4%)		

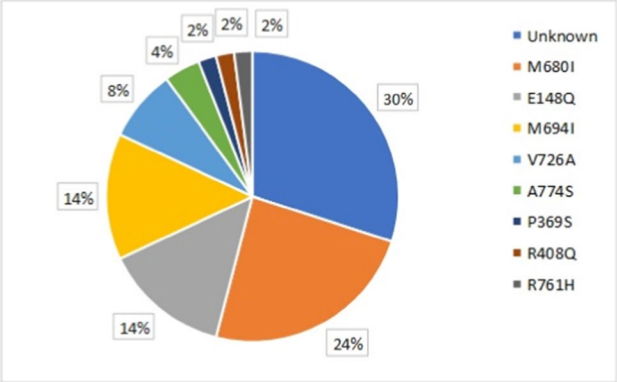

Fig.1 Bar chart showing frequency of *MEFV* alleles

Regarding the disease severity, no significant relationship was detected regarding the expression profiles of miR-17, miR-148b, or *Caspase-1* in FMF patients (all $P > 0.05$).

Discussion

The role of miRNAs in FMF has drawn more attention, and there is growing evidence of the involvement of miRNAs in various pathophysiological mechanisms of FMF, such as apoptosis, inflammation, and autophagy [17]. Hence, the current investigation is intended to determine the relative expression of microRNAs (miR-17 and miR-148b), *Caspase -1* gene in 25 Egyptian Familial Mediterranean Fever patients and to establish a correlation with disease severity.

Our results detected that miR-17 was highly expressed in FMF cases and that the expression of miR-148b was significantly reduced in relation to control subjects. We also found significant upregulation of *Caspase-1* gene in the examined patients.

Mir-17, as a member of the Mir17-92 cluster is proved to target important autophagy molecules, and reduced expression of any autophagy protein by boosted miRNAs can disrupt autophagic function that cannot be restored by other autophagy proteins [18]. However, as mentioned by Fu., one of the target genes of miR-17 is toll-like receptor (TLR) 4, an upstream regulator of the nuclear factor β inflammatory signaling pathway, whose translation was suppressed in vitro and in vivo by miR-17 [19]. Thus, miR-17 has been considered a regulatory molecule of the inflammatory response in several diseases.

Our research results showed upregulation of miR-17 in the studied cases with highly significant variance compared to healthy participants illustrating the proinflammatory role of miR-17 in FMF subjects. The impact of this micro-RNA may be through inhibition of autophagy as deduced by Li et al. who mentioned that miR-17 is a negative regulator of ATG7 expression, the key autophagy promoting gene [20]. Chatterjee et al. also reported that miR-17-5p is closely attached to the 3'-UTR of Beclin-1 gene, one of the essential autophagy modulators [21]. Autophagy dysfunction in FMF leads to an augmentation of the inflammatory process with overactivation of the NLRP3 inflammasome [22].

On the other hand, Karpuzoglu et al. studied the expression of 33 apoptosis-related miRNAs in FMF subjects and mentioned that miR-17-5p and miR-25 were considerably downregulated, supposing that these miRNAs might be implicated in FMF pathogenesis through apoptotic pathways [23].

Considering *MEFV* genotypes, our statistical results showed significant increase in miR-17 expression in patients carrying the M860I allele, compared to those having other

Table 3 Differentially expressed miR-17, miR-148b & *Caspase-1* in FMF group vs. control group

miRNA / mRNA	Expression pattern in FMF patients	RQ of patients Mean ± SD	RQ of controls Mean ± SD	P -value
hsa-miR-17	Upregulated	44.17 ± 48.07	1.06 ± 0.39	0.006*
hsa-miR-148b	Downregulated	0.42 ± 0.038	1.05 ± 0.39	0.030*
Caspase-1	Upregulated	5.58 ± 3.54	1.002 ± 0.03	0.033*

SD: standard deviation, RQ: relative quantification, * *P* -value ≤ 0.05 considered significant.

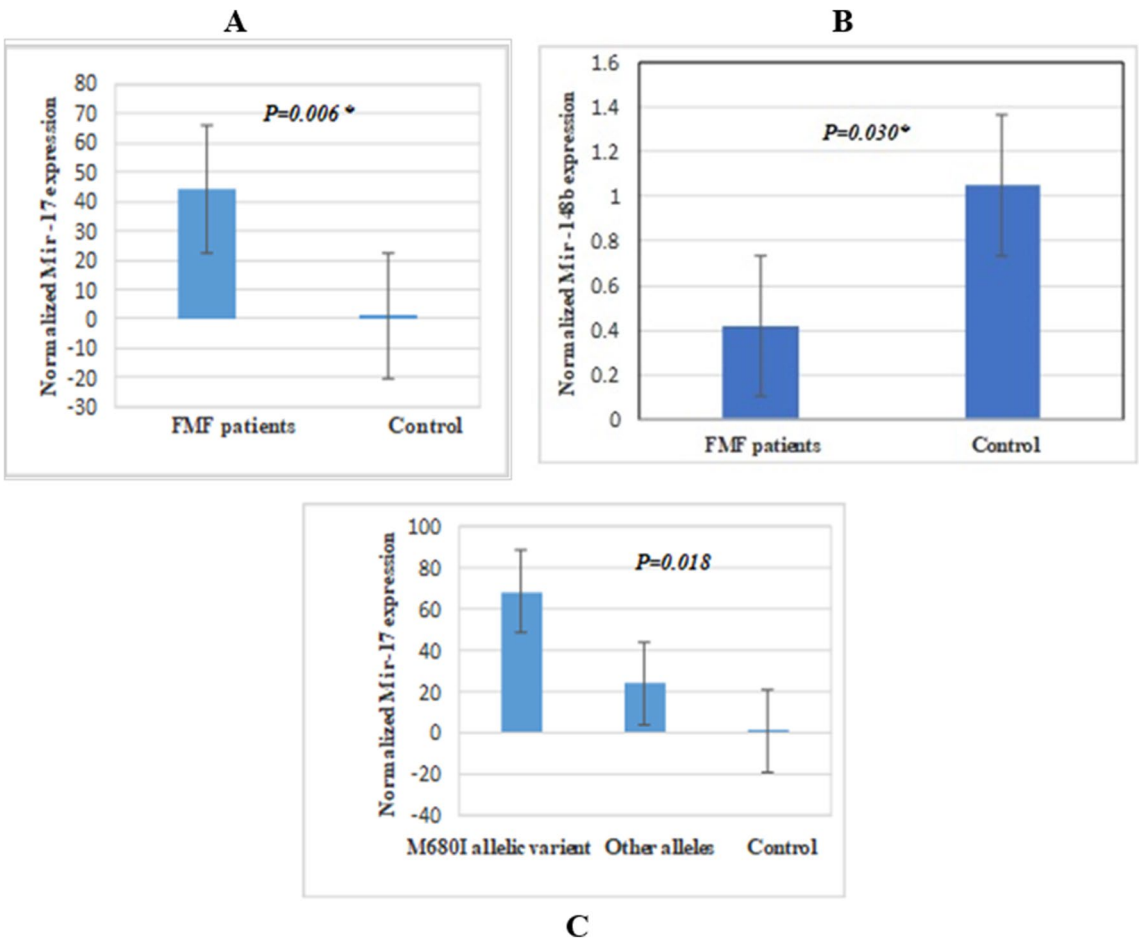

Fig. 2 Graph showing miRNAs expression (RQ). **A:** miR-17 expression in cases and healthy participants. **B**: Normalized miR-148b expression cases and healthy participants. **C**: expression level of miR-17 in the M680I allelic variant and other alleles in comparison with controls. **C**: $*P < 0.05$ considered significant

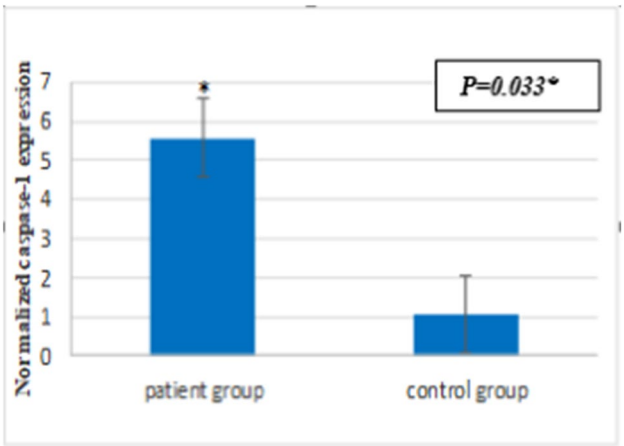

Fig.3 Graph showing Caspase-1 gene expression (RQ) in patients and controls. $*P < 0.05$ considered significant

alleles. The M680I variant leads to a loss of control of pyrin inflammasome, causing more severe clinical symptoms, as explained by Chirita et al. [24].

Karpuzoglu et al. achieved different results, finding no statistically significant variation between the expression profiles of the studied 33 miRNAs, including miR-17 and FMF genotypes [23].

Moreover, our investigation showed significantly lower miR-148b expression in FMF cases than in control subjects. In line with our findings, Amarilyo et al. measured the expression levels of 798 microRNA s in ten M694V homozygous FMF patients and reported a significant decrease in the expression level of miR-148b. He declared that miR-148b negatively regulates the innate immune response and antigen presenting capacity of dendritic cells [25].

According to Liu et al., miR-148b has been involved in suppression of cytokine release as IL-12, IL-6, and TNF-α [13], indicating its potential role as an anti-inflammatory miRNA in FMF.

Additionally, miR-148b has been confirmed to target DNMT1 (DNA methyltransferase 1) and to inhibit cell proliferation and tumorigenesis by inducing cell apoptosis [26, 27].

In comparison with the disease severity in terms of frequency and duration of inflammatory attacks, no significant variance was observed in regards to the expression of miR-17 or miR-148b in FMF cases. Karpuzoglu et al. reached similar results and reported that the expression of 33 miRNAs was the same in FMF patients during or between the inflammatory attacks [23].

Our research results also indicated upregulation of *Caspase-1* expression in the FMF participants, which was significantly increased in comparison to healthy subjects. In agreement with our results, Çaldıran and his colleagues observed higher amounts of Caspase-1, IL-1β, and IL-18 in 60 FMF cases compared to normal individuals [28].

This may be attributed to that *Caspase-1* is the first and extensively inflammatory caspase that is activated through inflammasome assembly. Also, Pyrin, the FMF mutated protein, affects *Caspase-1* stimulation and IL-1β secretion through the interplay of its N-terminal motif with the apoptosis-associated speck-like protein (ASC) and the negative regulation of NLRP3 inflammasome assembly [29, 30]. Altered interaction between pyrin and *Caspase-1* in FMF leads to elevated *Caspase-1* activity and IL-1β release [31], and therefore, blocking of *Caspase-1* activity would offer a therapeutic benefit to patients suffering from FMF [32].

Furthermore, Kimura et al. demonstrated that *MEFV* functions as a receptor for the autophagy of inflammasome components. *MEFV* identifies inflammasome components, attaches ULK1 to *NLRP3-MEFV* receptor-target recognition complexes, and causes autophagosomes to assemble in order to sequester and degrade the target. Consequently, *MEFV* reduces *Caspase-1* stimulation and IL-1β release. In FMF cases, common *MEFV* mutations disrupt the autophagy apparatus, aggravating the inflammatory process [33].

Our research was restricted by the small sample size. Nevertheless, our results showed significant variation in the expression profile of the studied miRNAs and *Caspase-1* gene between the patients and controls. Another limitation was the lack of comparison of the expression results in FMF with diseased controls having other autoinflammatory diseases.

In conclusion, our research results indicated that Mir-17 and Mir-148b could be potential regulatory biomarkers in FMF cases. We also proposed that caspases might represent a target for future therapies to prevent augmented inflammatory response in FMF patients.

Future studies on larger cohorts are recommended to figure out the role of different miRNAs in the pathogenesis of FMF and aid in the discovery of novel and effective miRNA-targeted diagnostic and therapeutic strategies.

Author contribution M.F.S: Performing molecular methodology, writing the initial draft of the manuscript. G.N.E: study design, performing molecular methodology and writing the initial draft of the manuscript. R.S.L: Performing molecular methodology and data collection. M.M.K: Performing molecular methodology and data collection. W.A.Z: Molecular verification, editing and final proofing of the manuscript. H.T.E: Clinical evaluation, case selection, editing and final proofing of the manuscript: All authors reviewed and approved the final manuscript.

Funding The manuscript is self-funded.

Data availability All data generated or analyzed during the study are included in the article.

Declarations

Competing interests The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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