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ORIGINAL ARTICLE

Assessment of Circulating Microribonucleic Acids in Patients With Familial Mediterranean Fever

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ABSTRACT

Objectives: This study aims to evaluate the plasma expression of microribonucleic acids (miRNAs) that may be associated with the pathogenesis of familial Mediterranean fever (FMF).

Patients and methods: Thirty patients with FMF (18 males, 12 females; mean age 9.1±4.7 years; range, 3 to 15.5 years) and 30 age- and sex-matched healthy children (18 males, 12 females; mean age 9.5±4.6 years; range, 4 to 16.5 years) were included in this study. The plasma levels of four candidate miRNAs (miRNA-16, miRNA-155, miRNA-204 and miRNA-451) were measured in all subjects. The plasma levels of miRNAs were analyzed with real-time polymerase chain reaction in attack and remission periods of patients and healthy controls (HCs).

Results: Plasma miRNA-204 levels of FMF patients were decreased 6.5 fold in remission period compared to HCs ($p<0.001$). This decrease was more prominent in M694V mutation carriers. Plasma miRNA-155 levels of FMF patients were lower in remission period ($p=0.03$).

Conclusion: Our findings showed significant alterations in the plasma expression of miRNA-155 and miRNA-204 in FMF patients compared to HCs. Our data suggest that miRNA-155 and miRNA-204 may be related to the pathogenesis of FMF. Further comprehensive and functional researches may help to clarify the role of miRNAs in FMF and elucidate the pathogenesis of the disease.

Keywords: Familial Mediterranean fever, inflammation, microribonucleic acid, periodic fever.

Familial Mediterranean fever (FMF) is an autosomal recessive inherited autoinflammatory disease characterized by short (6 hours to 3 days), recurrent and self-limiting episodes of fever with sterile polyserositis, arthritis or erysipeloid skin rash. In 1997, mutations of the "MEditerranean FeVer" (MEFV) gene were identified to be associated with the disease. The MEFV mutations cause impaired function of a protein called pyrine by incorrect coding and that process results in uncontrolled inflammation.[1]

Microribonucleic acids (miRNAs) are small (16-24 nucleotides), non-coding RNA molecules that have roles on the regulation of gene expression at the post-transcriptional stage. These molecules have many roles in different biological processes in the body such as cellular proliferation, differentiation, metabolism and apoptosis.[2-4] It has been reported that various factors, such as stress and hypoxia, regulate the expression and function of miRNAs. These molecules can be measured in blood and different body fluids; therefore, it has been suggested in the literature that miRNAs can be used as a biochemical marker in different diseases.[2-5]

The plasma expression of miRNAs differs in various autoimmune and autoinflammatory diseases. Thus, miRNAs may have a role in the

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pathogenesis of inflammation and be useful in diagnosis and follow-up of these diseases.[6-10] It has been shown in different studies that miRNA-155 has immunomodulatory functions and miRNA-155 levels were elevated in the macrophages of synovial fluid of patients with chronic arthritis.[11-13] The impacts of miRNA-155 in the physiological function of the immune system have also been shown.[6] Serum miRNA-204 levels were commonly studied in different types of cancer, rheumatoid arthritis (RA) and various inflammatory diseases, with significant alterations detected in plasma expression.[14-19] Moreover, the miRNA-204 was demonstrated to have suppressor effects on inflammatory cytokine production by targeting the phosphoinositide 3-kinase gamma (PI3Kγ) pathway and that plasma miR-204 level can be used as a potential biomarker in patients with FMF.[20] Rosenberger et al.[21] have shown that miRNA-451 has a role in cytokine production in dendritic cells. Also, it has been shown that the serum expressions of miRNA-451 were altered in an autoinflammatory disease named as tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS).[10] A restricted number of studies are available about the relationship between miRNAs and FMF. In a study of plasma miRNA expression-genotype association in patients with FMF, miRNA-452 expression has been shown to increase in M694V carriers.[22] Besides, Hortu et al.[23] have shown that the plasma expressions of 11 different miRNAs are reduced in patients with FMF compared to healthy controls (HCs).

To the best of our knowledge, the role of miRNA-16, miRNA-155, miRNA-204 and miRNA-451 is currently unknown in FMF. These candidate miRNAs have been selected based on the previous studies which showed their association with autoimmunity and inflammation by effects over inflammatory cytokines. Therefore, in this study, we aimed to evaluate the plasma expression of miRNAs that may be associated with the pathogenesis of FMF.

PATIENTS AND METHODS

This study was carried out by the Karadeniz Technical University Medical Faculty Department of Pediatric Rheumatology and Department of Medical Genetics between July 2016 and December 2017. We recruited 30 patients (18 males, 12 females; mean age 9.1±4.7 years; range, 3 to 15.5 years) admitted to our pediatric rheumatology clinic and diagnosed with FMF based on the diagnostic criteria for children.[24] The diagnostic criteria for children (Ankara criteria for FMF) were mainly based on clinical findings, and next generation sequencing was performed for MEFV gene analysis. Patients using steroid or non-steroidal anti-inflammatory drugs before diagnosis or those with other chronic diseases were excluded. Patients were evaluated in two periods: with attack manifestations (serositis, arthritis or erysipeloid skin rash together with fever) on admission and remission period at sixth month of treatment. FMF patients in attack and remission periods were named as "aFMF" and "rFMF", respectively. Age- and sex-matched 30 healthy children (18 males, 12 females; mean age 9.5±4.6 years; range, 4 to 16.5 years) from the Social Pediatrics Outpatient Clinic, who applied for annual physical examination and screening, were enrolled as the HC group. All of them underwent detailed clinical and laboratory examination to rule out inflammatory, infectious and chronic diseases. All participants were of Caucasian and Turkish origins. The study protocol was approved by the Karadeniz Technical University Medical Faculty Ethics Committee (Approval No: 2015/197). A written informed consent was obtained from the legal guardians of each participant. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Blood samples were obtained from FMF patients during attack and remission periods, and at the time of admission to social pediatrics outpatient clinic from HC group. During the remission period, all patients were under colchicine treatment. Patients were divided into two groups based on carrying or not carrying the M694V mutation. Patients with M694V mutation in at least one allele and those with other mutations or without any mutation were named as M694V (+) and M694V (-), respectively.

Peripheral blood samples were taken into ethylenediaminetetraacetic acid tubes and miRNA isolation was carried out on the same day. Manually mixed tubes were centrifuged at 4,000 rpm for

15 minutes and then totally 1,000 µL volume was picked up via 200 µL graduated pipette from the top of the obtained plasma. This 1,000 µL accumulated plasma was again centrifuged at 13,000 rpm for five minutes and just 200 µL volume was picked up from upper centrifuged plasma and filled into another Eppendorf tube. Qiagen miRNeasy serum/plasma kit (QIAGEN GmbH, Hilden, Germany) was used for miRNA isolation. Isolated miRNAs were translated to complementary deoxyribonucleic acid (cDNA) by means of miScript II reverse transcription 50 kit (QIAGEN GmbH, Hilden, Germany) and these gained cDNAs were kept in -80°C until analysis. Obtained cDNAs were amplificated by Qiagen miScript® PreAMP polymerase chain reaction (PCR) kit (QIAGEN GmbH, Hilden, Germany) with regard to the procedures available in this kit. Qiagen miScript Primer Assays kit for miRNA-16, miRNA-155, miRNA-204 and miR-451 primers; miScript® SYBR® Green PCR kit (QIAGEN GmbH, Hilden, Germany) for real-time (RT-PCR) master mix were used. Evaluations of the gene expressions were performed using quantitative RT-PCR (Rotor-Gene Q RT-PCR; QIAGEN GmbH, Hilden, Germany). We used Caenorhabditis elegans cel-miR-39 as an endogenous reference gene to normalize the miRNA expression levels.

Statistics analysis

Plasma expressions of miRNA-16, miRNA-155, miRNA-204 and miRNA-451 were evaluated and results were compared between groups. Plasma miRNA expressions were also analyzed in M694V (+) and M694V (-) groups. In order to designate the differences of miRNA expressions between patient and HC groups, RT-PCR data were analyzed with ΔCt module of QIAGEN GeneGlobe Data Analysis Center Portal (https://www.qiagen.com/dk/shop/genes-and-pathways/data-analysis-center-overview-page). To normalize the data, global Ct mean of expressed miRNAs, available in the same analysis center, was used. ΔCt (mean ± standard deviation [SD]) values were found. The relationship of miRNA expression levels of the groups was evaluated with regard to 2-ΔCT and "fold change" values were calculated. Also, the relationship between the miRNA expression levels of the groups was determined using Student's t-test and the results were considered as statistically significant if *p* value was lower than 0.05. Qualitative data

Table 1. Demographic characteristics and laboratory findings of patients in aFMF, rFMF and HC groups

	aFMF (n=30)				rFMF (n=30)				HC (n=30)				
	n	Mean±SD	Median	Min-Min	n	Mean±SD	Median	Min-Min	n	Mean±SD	Median	Min-Min	*p* (aFMF-HC)
Age (year)		9.1±4.7				9.1±4.7				9.5±4.6			>0.5
Sex													-
Male	18				18				18				
Female	12				12				12				
WBC (/mm^3)		12.5±4.4				7.8±1.2				7.8±1.2			<0.001
CRP (mg/dL)			6.64	2.26-24.90			0.12	0.02-0.65			0.02	0.02-0.60	<0.001
ESR (mm/h)			26	10-64			4	2-17			3	2-9	<0.001
M694V/M694V	7				7				-				-
Other M694V carriers	10				10				-				-
Other mutations	9				9				-				-
No mutation	4				4				-				-

aFMF: Attack period of familal Mediterranean fever; rFMF: Remission period of familial Mediterranean fever; HC: Healthy control; SD: Standard deviation; Min: Minimum; Maximum; WBC: White blood cell count; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate.

Table 2. Fold change and *p* values between aFMF, rFMF and HC groups for miRNAs

	aFMF-HC			rFMF-HC			aFMF-rFMF		
	Fold change	95% CI	*p*	Fold change	95% CI	*p*	Fold change	95% CI	*p*
Hsa-miR16_2-5p	1.05	0.48, 1.37	0.96	1.17	0.54, 1.17	0.52	□1.08	0.67, 1.50	0.40
Hsa-miR-155_2-5p	□1.26	0.44, 2.09	0.18	□1.55	0.66, 2.44	0.03	1.23	0.39, 1.24	0.15
Hsa-miR-204_1-5p	1.11	0.00001, 1.97	0.34	□6.50	0.04, 12.96	0.001	□7.14	0.02, 0.26	0.001
Hsa-miR-451_1-5p	1.17	0.41, 1.30	0.67	1.32	0.42, 1.09	0.85	1.13	0.64, 1.62	0.50

aFMF: Attack period of familial Mediterranean fever; rFMF: Remission period of familial Mediterranean fever; HC: Healthy control; miRNAs: Microribonucleic acids; CI: Confidence interval; Hsa: Homo sapiens (human).

were presented with numeric and percentage values and measurement data were presented with mean value ± standard deviation (SD) or median value. Data were analyzed using the IBM SPSS for Windows 23.0 software (IBM Corp., Armonk, NY, USA).

RESULTS

No statistically significant difference was found between the ages of FMF and HC groups (p>0.5). Among the 30 patients in FMF group, 17 had M694V mutation [seven homozygotes, three compound heterozygous (one with V726A and two with M680I) and seven heterozygotes], and 13 had at least one of the other MEFV mutations. The other mutations detected in patients were as follows: V726A homozygous in three patients, V726A heterozygous in two patients, V726A/M680I compound heterozygous in two patients, M680I heterozygous in two patients, R761H homozygous in two patients, and E148Q homozygous in two patients.

Demographic characteristics and laboratory findings (white blood cell count, C-reactive protein and erythrocyte sedimentation rate [ESR]) of all subjects were shown in Table 1. As expected, acute phase reactants were found to be statistically significantly higher in patients in attack period (p<0.001). Fold change and p values between aFMF, rFMF and HC groups for miRNAs were shown in Table 2. The distribution of expression of each miRNA in the groups was shown in Figure 1. Changes of plasma miRNA expression in the aFMF, rFMF, and HC groups were also shown in Figure 2. The mean 2-ΔCT of plasma miRNAs were compared between M694V (+) and (-) patients (Table 3).

The mean levels of plasma miRNA-16 2-ΔCT were 0.97 in aFMF, 1.05 in rFMF and 0.90 in HC groups. There was no statistically significant difference in plasma miRNA-16 levels between aFMF and rFMF groups (p=0.40). Although miRNA-16 levels were 1.05 fold higher in aFMF (p=0.96) and 1.17 fold higher in rFMF (p=0.52) groups compared to HC group, there was no statistical significance. The mean levels of plasma miRNA-16 in M694V (+) and (-) FMF patients were 1.12 and 0.98, respectively, with no statistically significant difference (p=0.45).

The mean levels of plasma miRNA-155 2-ΔCT were 0.55 in aFMF, 0.44 in rFMF and 0.69 in HC

Figure 1. Distribution of expression of each microribonucleic acid in familial Mediterranean fever patients in attack and remission periods and healthy controls.
Hsa: Homo sapiens (human); aFMF: Attack period of familial Mediterranean fever; rFMF: Remission period of familial Mediterranean fever; HC: Healthy control.

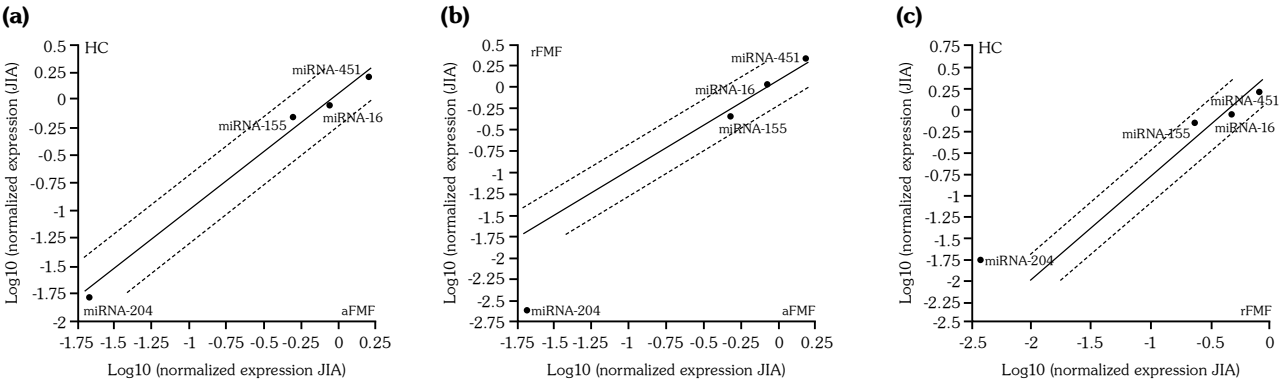

Figure 2. Changes of plasma microribonucleic acid expression in familial Mediterranean fever patients in attack and remission periods and healthy controls.

JIA: Juvenile idiopathic arthritis; HC: Healthy control; miRNA: Microribonucleic acid; aFMF: Attack period of familial Mediterranean fever; rFMF: Remission period of familial Mediterranean fever.

groups. Plasma miR-155 expressions were 1.55 fold lower in rFMF group compared to HC group with a statistically significant difference (p=0.03). These levels were 1.26 fold lower in aFMF group compared to HC group without any statistical significance (p=0.18). miRNA-155 levels were 1.23 fold higher in aFMF group than rFMF group (p=0.15), with no statistical significance. The mean levels of plasma miRNA-155 in M694V (+) and (-) FMF patients were similar (0.36 and 1.58, respectively), with no statistically significant difference (p=0.15).

The mean levels of plasma miRNA-204 2-ΔCT were 0.019 in aFMF, 0.002 in rFMF and 0.017 in HC groups. Plasma miRNA-204 expressions were 6.5 fold lower in rFMF group compared to HC group with statistical significance (p=0.001). These levels were 7.1 fold lower in rFMF group compared to aFMF group with a statistically significant difference (p=0.001). Plasma miRNA-204 levels were similar in aFMF and HC groups with no statistical significance (p=0.34). The mean levels of plasma miRNA-204 in M694V (+) and (-) FMF patients were 0.002 and 0.003, respectively. Although there was no statistically significant difference, miRNA-204 levels were lower in M694V (+) patients (p=0.60).

The mean levels of plasma miRNA-451 2-ΔCT were 1.85 in aFMF, 2.10 in rFMF and 1.59 in HC groups. There was no statistical significance in plasma miRNA-451 expressions between the aFMF and rFMF groups (p=0.50). Also, there was no statistically significant difference between the HC group and aFMF and rFMF groups (p=0.67 and p=0.85, respectively). The mean levels of plasma miRNA-451 in M694V (+) and (-) FMF patients were 2.44 and 1.75, respectively, with no statistically significant difference (p=0.22).

DISCUSSION

Recent studies have shown that plasma expression of miRNAs is altered in various

Table 3. Fold change and *p* values between M694V carriers and non-carriers for miRNAs

	M694V(+) / M694V(-)		
	Fold change	95% CI	*p*
Hsa-miR16_2-5p	1.14	0.59, 1.15	0.45
Hsa-miR-155_2-5p	↓1.59	0.66, 2.53	0.15
Hsa-miR-204_1-5p	↓1.96	0.37, 3.57	0.60
Hsa-miR-451_1-5p	1.39	0.38, 1.06	0.22

miRNAs: Microribonucleic acids; CI: Confidence interval; Hsa: Homo sapiens (human).

autoimmune and autoinflammatory diseases, and miRNAs may also have effects in the pathogenesis of these diseases.[2,5,6,10] In this study, we aimed to analyze the plasma expression of some candidate miRNAs associated with the pathogenesis of autoimmunity and inflammation.

There is a restricted number of studies in the literature examining the role of miRNAs in FMF. Wada et al.[25] have grouped 24 FMF patients according to the MEFV exon in which mutation was identified and shown significant alterations in plasma miRNA levels between the subgroups. They have also suggested that these molecules could be used as a biomarker to identify FMF subgroups. A recent study also has shown alterations in plasma expressions of some miRNA in patients with FMF. Authors have suggested that FMF is not a simple monogenic disease and that miRNAs are one of the epigenetic factors in FMF pathogenesis.[26] Moreover, in a study about the relationship between genotype and plasma miRNA expressions in patients with FMF, it has been shown that the plasma mRNA-452 expressions were increased in M694V (+) patients (more pronounced in homozygous ones) and associated with worse clinical course.[22] In another related study, Hortu et al.[23] have shown that the plasma expression of 11 different miRNAs were reduced in patients with FMF compared to HCs.

To date, the role of miRNAs in the pathogenesis of inflammation has been shown mostly in studies including patients with autoimmune diseases such as systemic lupus erythematosus (SLE), RA and Sjögren's syndrome.[27,28] Pauley et al.[29] have shown that plasma miRNA-155 and miRNA-16 levels were significantly elevated in patients with RA and that miRNA-16 levels were correlated with disease activity, in particular. Ma et al.[30] have determined the elevation of plasma miRNA-16 and miRNA-146 levels in patients with juvenile idiopathic arthritis (JIA) and suggested that these molecules could be used as a biomarker in the diagnosis. There are also studies that examine the role of miRNAs in patients with autoinflammatory diseases such as TRAPS and systemic onset JIA.[10,31] Kamiya et al.[31] have shown a correlation between serum miRNA-223 and mi-RNA-16 levels and ESR in patients with systemic onset JIA. Similar to this study including patients with systemic onset JIA, we have demonstrated that plasma miRNA-16 levels were increased in FMF patients during both attack and remission periods. In particular, this was more significant in M694V (+) patients. Lucherini et al.[10] have revealed alterations at plasma miRNA-451 levels in patients with TRAPS by disease status. Conversely, we have shown that plasma miRNA-451 levels were elevated in patients with FMF, while not significantly. In the Rosenberg et al.'s study,[21] miRNA-451 has been shown to play a role in cytokine production on dendritic cells. In this regard, more comprehensive and functional researches are required to determine the role of miRNA-451 in FMF disease.

Kurowska-Stolarska et al.[13] have revealed elevated levels of miRNA-155 in synovial fluid of patients with RA. They have also suggested that miRNA-155 may have a proinflammatory function by regulating the cytokine release on macrophages and monocytes. Plasma miRNA-155 levels have also been shown to increase significantly in a variety of studies in patients with RA.[29,32] In contrast, Lashine et al.[33] have demonstrated that the plasma expression of miRNA-155 is reduced in patients with juvenile SLE and FMF. We found that the plasma miRNA-155 levels were statistically significantly reduced in patients with FMF, similar to Lashine et al.'s study[33] and contrary to chronic arthritis studies. It was previously shown that the production of interleukin (IL)-2 is decreased in patients with FMF.[34] Furthermore, reduced miRNA-155 levels in T cells were shown to be related with reduced IL-2 production through directly targeting suppressor of cytokine signaling 1 (SOCS1).[35] Our findings suggest that miRNA-155 may be involved in the pathogenesis of FMF with a negative regulatory effect through targeting SOCS1, and that the reduction of plasma levels may be related to disease exacerbation.

There are studies in the literature about alterations of plasma and tissue miRNA-204 levels in different types of cancer and the results of these researches strongly support that miRNA-204 is related with pathogenesis of these cancers.[16,17,36] However, there is a limited number of studies that examined the relationship between inflammatory diseases and miRNA-204. In a study on patients with Crohn's disease, miRNA-204 expressions were

found to be increased in the affected intestinal mucosa.[18] Conversely, Lai et al.[19] have found that the plasma miRNA-204 levels were lower in patients with RA and it was increased after anti-TNF-alpha treatment. In a current research, Koga et al.[20] have demonstrated that miRNA-204 is significantly decreased in plasma of FMF patients. They have shown that the miRNA-204 regulates the production of toll-like receptor 4-associated inflammatory cytokines by targeting 3'-UTR domain of PI3Kγ. They thought that the miRNA-204 serves as a suppressor of inflammatory cytokine production, thus it could be a useful biomarker for patients with FMF. Similarly, we have also found that the plasma miRNA-204 levels were significantly decreased in the remission period of FMF patients. The most significant decrease in plasma miRNA-204 levels was seen in M694V (+) patients. According to the results, we also thought that miRNA-204 may have a role in pathogenesis of FMF. The fact that this decrease is more prominent in M694V (+) patients, which is a particularly strong evidence for genetic transmission in FMF, supports our hypothesis.

This study has some limitations. The fact that all of the patient group was enrolled from the carriers of homozygous MEFV mutation could have been beneficial to composed the genetically confirmed patient group. Also, increasing the number of patients and studying the inflammation-related miRNA panel may be useful to demonstrate possible role between inflammation and miRNAs.

In conclusion, plasma miRNA levels may show alterations in patients with FMF as in other inflammatory diseases. Our results showed that the plasma miRNA-155 and miRNA-204 levels are significantly decreased in patients with FMF and it was thought that these molecules may have roles in the pathogenesis of FMF. Increased plasma levels of miRNA-16 and miRNA-451 in FMF patients also suggest that these molecules may be associated with disease pathogenesis. Further researches on the relationship between FMF and miRNAs may be beneficial.

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Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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