Clinical Profile of Familial Mediterranean Fever in a Paediatric Population in Eastern Turkey

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ABSTRACT

Objective: *Clinical and genetic findings of familial Mediterranean fever (FMF) may vary in different populations. Environmental factors may also affect phenotypic features of FMF. In this study, we investigated demographic, clinical and mutational features of FMF patients treated in a single reference hospital in Turkey.*

Subjects and Methods: *One hundred and ninety-seven patients were included. The 11 mutations most frequently seen in FMF were investigated in these patients. Patients were assessed as homozygous, heterozygous, compound heterozygous or non-mutation bearing. Clinical and laboratory examinations in the attack and attack-free periods were recorded. A disease severity score was calculated for each patient.*

Results: *One hundred patients were female and 97 male. The most commonly seen mutations in our region was M694V (51.7%). The most frequent clinical findings in our patients was gastric pain (90.1%), followed by fever (82.2%). The highest disease severity score was determined in patients with homozygous M694V. Sedimentation values were significantly high in patients with homozygous M694V mutation, while no statistically significant difference was determined among other acute phase reactants and haemoglobin and leukocyte values.*

Conclusion: *Changes in acute phase reactants in attack and attack-free periods are used as diagnostic tools in FMF. Severity and frequency of attacks are clearly correlated with mutations. However, the fact that the clinical course can differ even in individuals with mutations reveals the importance of environmental factors.*

Keywords: Acute phase reactants, child, familial Mediterranean fever

Perfil clínico de la fiebre mediterránea familiar en una población pediátrica del este de Turquía

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RESUMEN

Objetivos: *Los hallazgos clínicos y genéticos de la fiebre mediterránea familiar (FMF) pueden variar en diferentes poblaciones. Los factores ambientales también pueden afectar las características fenotípicas de la FMF. En este estudio, investigamos las características demográficas, clínicas y mutacionales de pacientes de la FMF tratados en un hospital de referencia en Turquía.*

Sujetos y métodos: *Novecientos noventa y siete pacientes fueron incluidos. Las once mutaciones más frecuentes observadas en la FMF fueron investigadas en estos pacientes. Los pacientes fueron evaluados como homocigóticos, heterocigóticos, heterocigóticos compuestos, o no portadores de mutación. Se registraron los exámenes clínicos y de laboratorio en los períodos de ataques y libres de ataques. Se calculó una puntuación de gravedad de la enfermedad para cada paciente.*

Resultados: *Cien pacientes eran hembras y 97 varones. La mutación más comúnmente observada en nuestra región fue M694V (51.7%). El hallazgo clínico más frecuente en nuestros pacientes fue el dolor gástrico (90.1%), seguido de fiebre (82.2%). La máxima puntuación de severidad de la enfermedad se determinó en pacientes con M694V homocigótica. Los valores de sedimentación*

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fueron significativamente altos en pacientes con mutación M694V homocigótica, mientras que no se determinó ninguna diferencia estadísticamente significativa entre otros reactantes de fase aguda y valores de hemoglobina y leucocitos.

Conclusión: *Los cambios en reactantes de fase aguda en los períodos de ataques y libres de ataques se utilizan como herramientas de diagnóstico en la FMF. La severidad y la frecuencia de los ataques están claramente correlacionados con las mutaciones. Sin embargo, el hecho de que el curso clínico puede variar incluso en individuos con mutaciones, revela la importancia de los factores ambientales.*

Palabras claves: reactantes de fase aguda, niño, fiebre mediterránea familiar

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INTRODUCTION

Familial Mediterranean fever (FMF) is an autosomal recessive inflammatory disease characterized by repeated painful attacks accompanied by fever, gastric pain, arthritis and pleurisy mainly seen in people of Jewish, Armenian, Arab or Turkish origins (1). The prevalence in Turkey is 1/1000, and the carrier level 1/5. A male/female ratio of 1.2:1 is reported in Turkish FMF Study Group data (1, 2). No laboratory test for the diagnosis of FMF has yet been developed. It is the best described and most widespread of the known hereditary periodic fever syndromes. Clinical findings and course of the disease vary by race and geographical location (3, 4). The purpose of this study was to investigate the prevalence of gene mutations in patients diagnosed with FMF living in a different region and at high altitude, the correlation between mutations and symptoms, acute phase reactants at time of attack and between attacks, the relations between accompanying clinical findings and the mutation alleles carried and features differing from those of other regions and races.

SUBJECTS AND METHODS

Patients diagnosed with FMF and observed at the Erzurum Atatürk University, Faculty of Medicine Pediatric Health and Diseases nephrology clinic, Turkey, between 2002 and 2010 were included. Approval was granted from the Atatürk University, Faculty of Medicine Ethics Committee for the study. One hundred and ninety-seven patients were included. The great majority of these (99%) consisted of families living in the region. All patients were diagnosed using the FMF diagnostic criteria by Lidar and Livneh (5). A study group was established consisting of patients applying as a result of invitations extended, monitored patients applying to the clinic and patients being monitored by telephone. Physical examinations were performed by the same clinician. Detailed histories were taken. The families of children suitable for the study were briefed and they gave consent by signing informed consent forms. Age range for the patients in the study was 2–18 years. The most frequently seen 11 mutations in all the patients in the study (M694V, I692del, M680I, M694I, V726A, M695R, E148Q, A744S, R761H, P369S and F479I) were investigated. Mutation analyses were performed in the Erzurum Atatürk University, Faculty of Medicine Medical Laboratory. Mutation carriers were assessed as homozygous, heterozygous, compound heterozygote or not identified as mutation bearing. Homozygous mutation bearing is the same allele passing to the patient from both the mother and the father. Heterozygous mutation bearing is the identification of mutation in only one region of exon 10. Compound heterozygous mutation is the presence of two or more of the FMF gene mutations in exon 10. Those with no mutation constitute a group with clinical FMF diagnostic criteria, although no mutation was determined, in which differential diagnosis was performed and in which response to colchicine was observed. The relationship between patient mutations and severity scores and the relations between the five most frequently identified mutations (M694V, V726A, M680I, E148Q and R761H) were assessed. In determining clinical and epidemiological characteristics, the entire 197-member study group was assessed. Data for all patients were recorded on form drawn up for the study. Each patient's form recorded age, gender, weight, height, age at diagnosis of FMF, symptoms such as fever, gastric pain, arthralgia, arthritis, chest pain, vomiting, diarrhoea constipation, weight loss, lack of appetite, headache, myalgia, erysipelas-like erythema, presence of FMF in the family, presence of similar symptoms in the family (fever, gastric pain, chest pain, arthralgia or arthritis in the form of attack), presence of amyloidosis in the family, presence of collagen tissue disease in the family, mutations (M694V, L692del, M680L, M694L, V726A, M695R, E148Q, A744S, R761H, P369S and F479L) and acute phase reactant values during and between attacks (sedimentation, fibrinogen, albumin, C-reactive protein [CRP], white blood cell count [WBC]). Additionally, haemogram biochemistry, urogram, ferritin, iron and transferrin values were investigated and recorded on the form. Time of commencement of treatment, response to treatment, pre- and post-treatment episode frequencies and pre- and post-treatment episode durations were established. Presence of any additional disease was identified. A disease severity score was calculated for each patient based on the severity score described by Pras *et al* (6). Patients' severity scores were classified as mild, moderate or severe. A score of 3–5 was classified as mild, 6–8 as moderate and ≥ 9 as severe (7).

Peripheral blood samples were collected for DNA isolation; 2 cc specimens were placed in haemogram tubes and ex-

piration performed on an automated MagNA Pure Compact® ROCHE device. A *CEQ8000* Beckman Coulter® device was used for automatic DNA sequencing analysis.

Statistical analysis

Data analysis was performed on SPSS (Statistical Package for Social Sciences) for Windows 18. The Shapiro Wilk test was used to determine whether distribution of constant variables was close to normal. Descriptive statistics are shown as mean ± standard deviation or median (minimum–maximum) for constant variables, while nominal variables are shown as case number (n) and per cent. Significance of differences between groups in terms of mean values was examined using Student's *t*-test. Significance of differences in terms of median values was assessed using the Mann Whitney test when the independent group number was two or using the Kruskal Wallis test between more than two groups. Nominal variables were analysed using Pearson's Chi-squared or Fisher's exact tests. The independent *t*-test or Wilcoxon's signed rank test were used to determine statistical significance in laboratory tests repeated within groups. Multivariate logistic regression analysis was used to investigate whether the effects of mutations on symptoms were significant when correction was performed on the basis of age at onset of FMF, gender and duration of disease. Odds ratios and 95% confidence intervals were calculated for each variable. Multivariate logistic regression analysis was used to investigate whether the effects of mutations on laboratory values were significant when correction was performed on the basis of age at onset of FMF, gender and duration of disease. Regression coefficients and 95% confidence intervals were calculated for each variable. Since dependent variables were not normally distributed, logarithmic conversion was performed at linear regression analysis; $p < 0.05$ was regarded as significant.

RESULTS

One hundred (50.8%) of the 197 patients in the study were female and 97 (49.2%) male. Mean age of patients was 11.4 ± 3.83 years. Mean age at onset of disease was 5.25 ± 3.63 years and mean age at diagnosis was 8.1 ± 3.56 years.

The most frequently observed clinical findings were repeated abdominal pain in 179 (90.1%) patients, fever in 162 (82.2%) and arthralgia in 114 (57.9%) [Table 1].

Pre-and post-treatment attack numbers in the study group are shown in Table 2. These results show that 89.3% of patients responded to treatment, while 10.7% did not respond adequately. Patients' severity scores meant that 44 (22.3%) were classified as mild, 127 (64.5%) as moderate and 26 (13.4%) as severe.

Distribution of mutations in patients and clinical comparison results

The most frequently seen mutation in our region was M694V. Forty-nine (19.2%) of the patient alleles investigated were homozygous for M694V, while compound heterozygous and heterozygous M694V mutation were in 83 (32.5%). The second most common mutation, V726A, was seen in 45 (17.57%) patients: 4 (1.57%) homozygous and 41 (16.0%) compound heterozygous and homozygous. The third most frequent, M680I mutation, was seen in 44 (17.3%) patients: 5 (2.0%) homozygous and 39 (15.3%) heterozygous and compound heterozygous. Three of the mutations investigated in the study (I692del, M695R and F479L) were not encountered in any patient. The five most frequently encountered alleles were identified on the basis of the total allele frequencies of the patients in the study group. These were, in order, M694V, M680I, V726A, E148Q and R761H. These five alleles represented 98.4% of the total allele frequency. Therefore, since other alleles were identified in insufficient numbers to express statistical significance, correlations between patients bearing these five alleles were analysed. At the same time, the mutation we encountered most commonly, M694V, was classified as homozygous M694V, heterozygous M694V and other (patients bearing mutations other than M694V and patients with no mutation despite being diagnosed with FMF) and comparisons were performed between them. In this way, clinical findings were compared between individuals with M694V and other patients. No significant difference was determined among mutations in terms of gender distribution ($p > 0.05$). Data for the comparison of clinical findings of patients bearing M694V mutation are shown in Table 3.

At comparison of clinical findings, symptoms such as fever, arthritis and arthralgia were more frequent in individuals bearing M684V mutation compared to other mutations.

Table 1: Clinical findings of patients' with familial Mediterranean fever

Clinical findings	n	%
Fever	162	82.2
Abdominal pain	179	90.1
Arthralgia	114	57.9
Arthritis	35	17.8
Chest pain	51	25.9
Vomiting	32	16.2
Diarrhoea	43	21.8
Constipation	15	7.6
Weight loss	7	3.6
Lack of appetite	20	10.2
Headache	16	8.1
Myalgia	27	13.7
Erysipelas-like erythema	23	11.7

Table 2: Distribution by attack frequency

Attack number	Pre-colchicine		Post-colchicine	
	n	%	n	%
No attack	3*	1.5	109	55.3
< 2 attacks per month	27	13.7	67	34.0
≥ 2 attacks per month	167	84.8	21	10.7
Total	**197**	**100**	**197**	**100**

*Mutation was determined in these three patients and family history was present. Attack was not described

Table 3: Examination of the clinical characteristics of patients with M694V mutation

Clinical findings		Mutations: M694V homozygous n	%	M694V heterozygous + compound heterozygous n	%	Other mutations n	%	*p*
Fever	Yes	42	85.7	74	89.2	46	70.8	0.011
	No	7	14.3	9	10.8	19	29.2	
Abdominal pain	Yes	46	93.9	72	86.7	61	93.8	0.231
	No	3	6.1	11	13.3	4	6.2	
Arthralgia	Yes	33	67.3	43	51.8	38	58.5	0.216
	No	16	32.7	40	48.2	27	41.5	
Arthritis	Yes	17	34.7	8	9.6	10	15.4	0.001
	No	32	65.3	75	90.4	55	84.6	
Chest pain	Yes	15	30.6	23	27.7	13	20	0.389
	No	34	69.4	60	72.3	52	80	
Vomiting	Yes	7	14.3	12	14.5	13	20	0.604
	No	42	85.7	71	85.5	52	80	
Diarrhoea	Yes	10	20.6	19	22.9	14	21.5	0.944
	No	39	79.4	64	77.1	51	78.5	
Constipation	Yes	3	6.1	7	8,4	5	7.7	0.889
	No	46	93.9	76	91.6	60	92.3	
Weight loss	Yes	4	8.2	1	1.2	2	3.1	0.110
	No	45	91.8	82	98.8	63	96.9	
Lack of appetite	Yes	5	10.2	7	8.4	8	12.3	0.741
	No	44	89.8	76	91.6	57	87.7	
Headache	Yes	2	4.1	3	3.6	11	16.9	0.006
	No	47	95.9	80	96.4	54	83.1	
Myalgia	Yes	7	14.3	7	8.4	13	20	0.126
	No	42	85.7	76	91.6	52	80	
Erysipelas-like erythema	Yes	5	10.2	8	9.6	9.6	15.4	0.521
	No	44	89.8	75	90.4	90	84.6	

Amyloidosis was determined in two (1%) patients. The presence of amyloidosis was revealed by biopsy in both these patients, one of whom bore homozygous M694V. The other patient was a heterozygous bearer of M694V and E148Q. Both patients with amyloidosis had M694V mutation. Amyloidosis was determined in 10 (5.1%) close relatives of the patients in our study group. Since paediatric patients were assessed, sufficient cases of amyloidosis for a significant study could not be identified.

Table 4: Correlation between mutations and pre-treatment attack frequencies

	M694V homozygous n	%	M694V heterozygous n	%	Other mutations n	%	*p*
1 per month	6	12.2	7	8.7	17	27.0	
1–2 per month	19	38.8	44	54.3	27	42.9	
> 2 per month	24	49.0	30	37.0	19	30.1	

The above *p*-value is the result of a general comparison between the three groups. The situation responsible for the difference is that a greater attack frequency was seen in the homozygous group compared to other mutations ($p = 0.017$). There was no difference between heterozygotes and homozygotes or between heterozygotes and other mutations ($p = 0.430$ and $p = 0.063$).

Table 5: Correlation between disease severity score and mutations

Mutations		Mild n	%	Moderate n	%	Severe n	%	*p*
M694V	Yes	20	15.2	93	70.5	19	14.4	0.003
	No	24	36.9	34	52.3	7	10.8	
M680I	Yes	11	25	30	68.2	3	6.8	0.359
	No	33	21.6	97	63.3	23	15	
V726A	Yes	13	28.9	29	64.4	3	6.7	0.222
	No	31	20.4	98	64.5	23	15.1	
E148Q	Yes	6	40.0	7	46.7	2	13.3	0.253
	No	38	20.9	12	65.9	24	13.2	
R761H	Yes	5	33.3	9	60	1	6.7	0.483
	No	39	21.4	118	64.8	25	13.7	

Frequency of attack in the preceding month was significantly higher in patients with M694V homozygous mutation compared to patients with other mutations (Table 4). No significant difference was observed between individuals with heterozygous M694V mutation and the other group. Correlations between severity scores and mutations in the study group patients are shown in Table 5.

Data showing a correlation between mutations and laboratory findings are shown in Table 6. Sedimentation values were

Table 6: Relation between mutations and laboratory findings

	Sedimentation mm/h		Fibrinogen		C-reactive protein		Albumin		Haemoglobin		White blood cell	
Mutation	Non-attack	During attack	Non-attack	During attack	Non-attack	During attack	Non-attack	During attack	Non-attack	During attack	Non-attack	During attack
M694V homozygous	22.4	58.6	361	497	1.0	7.5	4.2	4.5	12.8	12.3	10300	8147
M680I	17.4	51.9	343	523	1.0	7.5	4.4	4.5	12.9	12.3	10162	8219
V726A	16.5	46.4	339	482	1.3	7.4	4.4	4.6	13.2	12.5	11601	9434
E148Q	16.5	37.3	298	393	1.0	7.0	4.3	4.4	13.0	12.4	11980	10666
R761H	21.3	47.3	324	483	0.7	6.0	4.5	4.7	13.3	12.8	10644	9070
M694V heterozygous	18.6	53.8	330	483	0.9	7.6	4.3	4.5	13.1	12.5	10326	14596

p-value was below 0.05 (0.009) in terms of sedimentation elevation when the group homozygous for M694V mutation was compared with the other groups. It was higher in M694V mutation. There was no difference in terms of other parameters

significantly elevated in patients who were homozygous for M694V mutation, while no significant difference was determined between other acute phase reactants and haemoglobin and leukocyte values. Sedimentation, albumin and fibrinogen values were lowest in the group with E148Q mutation, while CRP values were lowest in the R761H mutation group.

DISCUSSION

Familial Mediterranean fever is a recurring autosomal recessive disease characterized by serositis in the form of attacks in which fever accompanied gastric, chest and joint pain. Diagnosis today is made on the basis of clinical findings, ethnic origin and family anamnesis accompanied by clinical data such as response to colchicine. Mutation analyses have also been used to support diagnosis in the recent decade. Mutations (M694V, M694I, M680I, V726A and E148Q) in the exon 10 and exon 2 regions, which cause FMF, represent 74% of all other mutations (8, 9). Forty-nine (19.2%) of the alleles investigated in the patients in this study were homozygous M694V, while compound heterozygous and heterozygous M694V mutation were determined in 83 (32.5%) patients. The most common mutation type in all ethnic groups is M694V mutation; it constitutes 45% of all mutations in Turks, 20% in Arabs, 65% in Jews and 37% in Armenians (8, 9). The prevalence of M694V mutation in Turkey was similar to that of M694V mutation in our region. Presence of V726A mutation in our region was 17.5%, above average in comparison with other studies in Turkey, while M694I mutation was less common. On comparison of mutations with clinical findings, symptoms such as fever, arthritis and arthralgia were more frequent in individuals carrying the M694V mutation compared to other mutations (6, 10, 11). This was confirmed in our study. In terms of the genotype/phenotype association, several studies have shown that the clinical course of FMF is more severe in homozygous M694V and compound heterozygous M694V (6, 12). Early onset of M694V mutation is reported to be associated with pleurisy, arthritis, erysipelas and increased prevalence of amyloidosis.

Patients with M694V mutation have been revealed to be more at risk compared to patients with other mutations in terms of findings emerging at an earlier age, exhibiting less response to colchicine and a higher prevalence of amyloidosis (10, 11). Our two patients with amyloidosis were identified as having M694V mutation. Amyloidosis frequently varies among ethnic groups. It has been seen in 2% of Arab patients (13), 27.6% of Jewish patients (14), 24% of Armenians (15) and between 12.9% and 15% of Turkish patients (16, 17). Dusunsel *et al* (18) identified the M694V homozygous genotype as a significant risk factor for the development of amyloidosis. The low level of amyloidosis despite the high level of M694V mutation in this study may be due to the information provided regarding the disease and the importance of regular colchicine therapy. Another reason for the difference may be regional variations.

No significance was observed in this study between the clinical findings of patients with M680I, V726A and R761H mutation and patients without. Heterozygous E148Q mutation was determined in 15 (5.88%) patients. Comparison of individuals with E148Q mutation and other individuals revealed less fever compared to patients with other mutations.

No significant difference was determined between other clinical findings. Clinical findings of individuals with E148Q mutation follow a mild course. In terms of attack numbers, these were significantly lower in patients with E148Q compared to other patients. A scan of the literature showed different prevalences of E148Q between races, but that the clinical course was generally better compared to that of other mutations (9, 19, 20). This mutation being identified in only 15 patients may be attributed to patients with this mutation not having much need to attend hospital since it involves milder clinical symptoms.

Symptoms generally appear in the first decade of life in FMF patients. Periodic febrile episodes lasting between a few hours and five days occur in the majority of patients. A typical attack involves one or more acute febrile episodes and peritonitis defined as abdominal pain, arthritis or arthralgia and chest pain. Prevalence of typical clinical signs may vary by community and race (4, 20). The most commonly observed clinical signs in our patients were recurrent abdominal pain in 179 (90.1%), fever in 162 (82.2%) and arthralgia in 114 (57.9%). These were followed by pleurisy, diarrhoea and vomiting, with erysipelas-like erythema in ninth place at 11.7%. Abdominal pain has been reported as the most widespread symptom in studies in Turkey. This is followed by fever, arthritis, pleurisy and erysipelas-like erythema (16, 17). Fever was seen less in patients, under monitoring, with a diagnosis of FMF in our region compared to other regions. The level of patients with chest pain in our study was 25.9%. As stated in the literature, chest pain has been most frequently identified in the Armenian patient population (21). It is observed at a lower level in Turks, although chest pain (4.9%) was reported in the Kayseri region in a study by Dusunsel *et al* (18). In comparison with that study, patients in our region presented with more chest pain symptoms.

Number and severity of FMF attacks is more dependent upon environmental factors. Familial Mediterranean fever attacks are known to be triggered by stress and physical exercise (18, 22). Severity score in our study was 7.65 ± 1.80 in M694V homozygous patients, 6.82 ± 1.52 in M684V heterozygous patients and 6.32 ± 1.51 in the others. Mean monthly attack frequencies were one to two per month in 38.8% of M694V homozygous patients, more than two per month in another 49.0% and one per month in 12.2%. Number of attacks in M694V heterozygous patients was one to two per month in 54.3%, one per month in 8.7% and more than two per month in 37.0%. In other mutations, these levels were one to two attacks per month in 42.9%, one attack per month in 27% and more than two attacks monthly in 30.1%. Mean severity score in our patients was low. In the study by Dusunsel *et al* (18), mean pre-treatment annual attack number was 12, mean

length of attack 27.5 hours and mean severity score 7.3 ± 2.0. Yilmaz *et al* (23) reported a mean disease severity score of 6.1 ± 1.9 and a mean pre-treatment annual attack number of 21.9. Mean annual attack frequency among North African Jews has been reported as 13.6 ± 12.2, compared to 12.9 ± 11.3 in other Jews, 5.2 ± 8.7 in Armenians living in America and 30.8 ± 25.9 in Armenians living in Yerevan (22). At analysis of patients' severity scores classified as mild, moderate or severe, 11 (22.5%) of the individuals with M694V homozygous mutation were in the severe disease group, compared to approximately 10.7% in individuals with other mutations. Five (10.2%) patients with M694V mutation were in the mild disease group, compared to 36.9% in individuals with other mutations. In terms of mutations carried, patients with M694V had a significantly higher level of disease severity compared to those with other mutations. No significant difference was determined when other mutations were compared with one another. Therefore, bearing the M694V mutation was positively correlated with disease severity.

The correlation between patients' attack frequencies and mutations was assessed. When the patients with homozygous M694V mutation and those with heterozygous M694V mutation and the patient group with no M694V mutation were compared within themselves, monthly attack frequency was higher than one in nine (39%) of the M694V homozygous individuals. The number of attacks in patients with homozygous M694V was significantly higher compared to the other groups.

Sedimentation levels in patients with M694V mutation in the attack-free period were significantly higher than those in patients without the mutation. Changes in acute phase reactants in the attack and attack-free periods are used as diagnostic tools in FMF. One study reported that elevated sedimentation persists between attacks in some FMF patients (24).

Clinical findings and chronic complications being more severe in patients with M694V mutation may be due to elevated acute phase reactants following a severe course, even in the attack-free period.

Familial Mediterranean fever is a frequently seen chronic inflammatory disease that can lead to severe morbidity and mortality if left untreated. Severity and frequency of attacks are clearly correlated with mutations. However, the fact that clinical course can differ even in people with mutation reveals the importance of environmental factors. Studies in different geographical regions and with different ethnic populations may be useful in fully clarifying the disease.

AUTHORS' NOTE

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REFERENCES

1. Kosan C, Ozkan B. Once-daily use of colchicine in children with familial Mediterranean fever. Clin Pediatr (Phila); **43:** 605–8.
2. Ureten K, Gönülalan G, Akbal E, Güneş F, Akyürek O, Ozbek M et al. Demographic, clinical and mutational characteristics of Turkish familial Mediterranean fever patients: results of a single center in Central Anatolia. Rheumatol Int 2010; **30:** 911–5.
3. Yigit S, Bagci H, Ozkaya O, Ozdamar K, Cengiz K, Akpolat T. MEFV mutations in patients with familial Mediterranean fever in the Black Sea region of Turkey: Samsun experience [corrected]. J Rheumatol 2008; **35:** 106–13.
4. Berkun Y, Eisenstein E, Ben-Chetrit E. FMF – clinical features, new treatments and the role of genetic modifiers: a critical digest of the 2010-2012 literature. Clin Exp Rheumatol 2012; **30:** S90–5.
5. Lidar M, Livneh A. Familial Mediterranean fever: clinical, molecular and management advancements. Neth J Med 2007; **65:** 318–24.
6. Pras E, Livneh A, Balow JE Jr, Pras E, Kastner DL, Pras M et al. Clinical differences between North African and Iraqi Jews with familial Mediterranean fever. Am J Med Genet; **75:** 216–9.
7. Mor A, Shinar Y, Zaks N, Langevitz P, Chetrit A, Shtrasburg S et al. Evaluation of disease severity in familial Mediterranean fever. Semin Arthritis Rheum 2005; **35:** 57–64.
8. Ozdemir O, Sezgin I, Kurtulgan HK, Candan F, Koksal B, Sumer H et al. Prevalence of known mutations in the MEFV gene in a population screening with high rate of carriers. Mol Biol Rep; **38:** 3195–200.
9. Touitou I. The spectrum of familial Mediterranean fever (FMF) mutations. Eur J Hum Genet 2001; **9:** 473–83.
10. Zaks N, Shinar Y, Padeh S, Lidar M, Mor A, Tokov I et al. Analysis of the three most common MEFV mutations in 412 patients with familial Mediterranean fever. IMAJ 2003; **5:** 585–8.
11. Padeh S, Shinar Y, Pras E, Zemer D, Langevitz P, Pras M et al. Clinical and diagnostic value of genetic testing in 216 Israeli children with familial Mediterranean fever. J Rheumatol 2003; **30:** 185–90.
12. Dewalle M, Domingo C, Rozenbaum M, Ben-Chetrit E, Cattan D, Bernot A et al. Phenotype-genotype correlation in Jewish patients suffering from familial Mediterranean fever (FMF). Euro J Hum Genet 1998; **6:** 95–7.
13. Majeed HA, Barakat M. Familial Mediterranean fever (recurrent hereditary polyserositis) in children: analysis of 88 cases. Eur J Pediatr 1989; **148:** 636–41.
14. Sohar E, Gafni J, Pras M, Heller H. Familial Mediterranean fever. A survey of 470 cases and review of the literature. Am J Med; **43:** 227–53.
15. Aivazian AA, Giulikekhvian NG, Zavgorodniaia AM, Abramian MK, Pashinian SA. [Pathogenesis of amyloidosis in periodic disease]. Klin Med (Mosk) 1982; **60:** 65–8. In Russian
16. Yalcinkaya F, Cakar N, Misirlioglu M, Tumer N, Akar N, Tekin M et al. Genotype-phenotype correlation in a large group of Turkish patients with familial Mediterranean fever: evidence for mutation-independent amyloidosis. Rheumatol 2000; **39:** 67–72.
17. Tunca M, Akar S, Onen F, Ozdogan H, Kasapcopur O, Yalcinkaya F et al. Familial Mediterranean fever (FMF) in Turkey: results of a nationwide multicenter study. Medicine 2005; **84:** 1–11.
18. Dusunsel R, Dursun I, Gunduz Z, Poyrazoglu MH, Gurgoze MK, Dundar M. Genotype-phenotype correlation in children with familial Mediterranean fever in a Turkish population. Pediatrics Int 2008; **50:** 208–12.
19. Al-Alami JR, Tayeh MK, Najib DA, Abu-Rubaiha ZA, Majeed HA, Al-Khateeb MS et al. Familial Mediterranean fever mutation frequencies and carrier rates among a mixed Arabic population. Saudi Med J 2003; **24:** 1055–9.
20. Sharkia R, Mahajnah M, Zalan A, Athamna M, Azem A, Badarneh K et al. Comparative screening of FMF mutations in various communities of the Israeli society. Eur J Med Genet 2013; **56:** 351–5.
21. Schwabe AD, Peters RS. Familial Mediterranean fever in Armenians. Analysis of 100 cases. Medicine 1974; **53:** 453–62.
22. Mimouni A, Magal N, Stoffman N, Shohat T, Minasian A, Krasnov M et al. Familial Mediterranean fever: effects of genotype and ethnicity on inflammatory attacks and amyloidosis. Pediatrics 2000; **105:** E70.
23. Yilmaz R, Ozer S, Ozyurt H, Erkorkmaz U, Sahin S. Familial Mediterranean fever gene mutations in the inner northern region of Turkey and genotype-phenotype correlation in children. J Paediatr Child Health 2009; **45:** 641–5.
24. Musabak U, Sengul A, Oktenli C, Pay S, Yesilova Z, Kenar L et al. Does immune activation continue during an attack-free period in familial Mediterranean fever? Clin Exp Immunol; **138:** 526–33.