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ORIGINAL RESEARCH
Pediatric Rheumatology

MEFV mutations in pediatric Henoch-Schönlein Purpura: Insights from a single-center study in a high-risk population

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ABSTRACT

Objective: Familial Mediterranean Fever is a common disease in the Turkish population, and its association with childhood Henoch-Schönlein Purpura has been reported to be higher than the general population frequency. Although HSP often resolves spontaneously, analyzing MEFV mutations as a screening tool for FMF in patients with HSP may help prevent potential complications related to FMF.

Material and Methods: This retrospective study included 99 patients aged 0–16 years who were diagnosed with HSP according to the EULAR/PRINTO/PRES criteria and followed for at least six months. Genetic testing for common MEFV mutations was performed in 45 patients with suspected FMF based on their medical history and physical examination findings.

Results: At least one MEFV mutation was detected in 33 out of 45 patients (73.4%) evaluated for suspected FMF. The most common mutations were R202Q, E148Q, M694V, K695R, M680I, V726A, F479L, E167D, R408Q, P369S, and G148I. Gastrointestinal and joint involvement were observed more frequently in patients with MEFV mutations; however, no specific correlation was found between any MEFV mutation type and organ/system involvement in HSP. The relapse rate was 12.1% in patients with at least one MEFV mutation and 8.3% in those without any MEFV mutation.

Conclusion: Given the high prevalence of FMF in children with HSP, the possibility of FMF should always be considered and thoroughly investigated during the initial evaluation, particularly in populations where FMF is also common. However, MEFV gene mutations may not have a significant impact on the clinical presentation of HSP.

Keywords: Familial Mediterranean Fever; Henoch-Schönlein Purpura; MEFV mutations; pediatric; vasculitis.

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Yüksek riskli bir popülasyonda tek merkezli çalışmadan elde edilen bulgular: Pediatrik Henoch-Schönlein Purpurasında MEFV mutasyonları

ÖZET

Amaç: Ailesel Akdeniz Ateşi (AAA), Türk toplumunda sık görülen bir hastalıktır ve çocukluk çağı Henoch-Schönlein Purpurası (HSP) ile birlikteliğinin genel popülasyona göre daha yüksek olduğu bildirilmiştir. HSP çoğu zaman kendiliğinden iyileşse de, HSP'li hastalarda AAA'ya bağlı olası komplikasyonları önlemek amacıyla MEFV mutasyonlarının tarama aracı olarak analiz edilmesi yararlı olabilir.

Gereç ve Yöntemler: Bu retrospektif çalışmaya, EULAR/PRINTO/PRES kriterlerine göre HSP tanısı almış ve en az altı ay süreyle takip edilmiş 0–16 yaş arası 99 hasta dahil edilmiştir. Tıbbi öykü ve fizik muayene bulgularına göre AAA şüphesi bulunan 45 hastada yaygın görülen MEFV mutasyonları için genetik test yapılmıştır.

Bulgular: AAA şüphesiyle değerlendirilen 45 hastanın 33'ünde (%73,4) en az bir MEFV mutasyonu saptanmıştır. En sık tespit edilen mutasyonlar R202Q, E148Q, M694V, K695R, M680I, V726A, F479L, E167D, R408Q, P369S ve G148I idi. MEFV mutasyonu taşıyan hastalarda gastrointestinal ve eklem tutulumu daha sık gözlenmiş olsa da, belirli bir MEFV mutasyon tipi ile HSP'deki organ/sistem tutulumu arasında anlamlı bir ilişki bulunmamıştır. Nüks oranı, en az bir MEFV mutasyonu bulunan hastalarda %12,1 iken, mutasyon saptanmayanlarda %8,3 olarak belirlenmiştir.

Tartışma: HSP'li çocuklarda AAA prevalansının yüksekliği göz önüne alındığında, özellikle AAA'nın yaygın olduğu toplumlarda, HSP'nin ilk değerlendirmesi sırasında AAA olasılığı her zaman akılda tutulmalı ve dikkatle araştırılmalıdır. Bununla birlikte, MEFV gen mutasyonlarının HSP'nin klinik özellikleri üzerinde belirgin bir etkisi olmayabilir.

Anahtar Kelimeler: Ailesel Akdeniz Ateşi; Henoch-Schönlein Purpurası; MEFV mutasyonları; pediatrik; vaskülit.

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INTRODUCTION

Henoch-Schönlein Purpura (HSP) was first described in the 19th century as a paediatric disease, with clinical findings including arthralgia, renal involvement, and a purpuric rash. More recently, in the 21st century, it was revealed to be an immunoglobulin A vasculitis. It is the most prevalent vasculitic disease in childhood, with a reported frequency of 10 to 20 cases per 100,000 children (1). Familial Mediterranean Fever (FMF) represents the most frequently encountered hereditary autoinflammatory syndrome of childhood, characterized by recurrent febrile episodes. The clinical manifestations of FMF include episodic attacks that can last anywhere from 6 to 72 hours, with symptoms such as fever, abdominal pain, arthralgia, arthritis, serositis, and erysipelas (2). The reported prevalence of FMF among children in Türkiye is 9.3 per 10,000 (3). While it is more prevalent in communities such as Turkish, Armenian, Jewish, and Arab, it is a disease that can be seen worldwide. FMF is a disease in which complications such as amyloidosis can be prevented when treated (4, 5).

Several studies have demonstrated a higher frequency of MEFV gene mutations among patients with various vasculitic and rheumatologic disorders, such as inflammatory bowel disease, polyarteritis nodosa, Henoch–Schönlein Purpura (HSP), and juvenile rheumatoid arthritis. This gene is thought to play an important role in the links between FMF and other vasculitic diseases (4, 6–9). The detection of MEFV mutation in patients with HSP suggests that changes in the MEFV gene may be an important risk factor for the development of HSP and may affect the clinical course of the disease (9, 10).

In this study, we analysed the demographic, clinical, and laboratory data of patients with HSP who were suggestive of FMF and underwent genetic investigation. Our objective was to differentiate these patients from other patients with HSP. Although the association of FMF and HSP is not unexpected, it is important to consider this possibility in every case. This approach plays a critical role, especially for the early diagnosis of serious complications such as amyloidosis.

MATERIAL AND METHODS

In this study, 99 cases with HSP were retrospectively analysed from file records, and 45 cases with and without mutations were compared in terms of demographic, clinical, and laboratory findings. Among the 45 cases, 23 common MEFV mutations (R202Q, E148Q, M694V, K695R, M680I, V726A, F479L, E167D, R408Q, P369S, G148I, H478Y, S675N, M680L, T681I, I692del, M694L, K695M, R717S, I720M, V722M, A744S, R761H) were

studied in a contracted genetic laboratory. The study included patients who were monitored at Şişli Hamidiye Etfal Training and Research Hospital for at least six months between 2011 and 2016, and the diagnosis of HSP was established based on the 2005 EULAR/PRES (European League Against Rheumatism/ Paediatric Rheumatology European Society) criteria. According to the EULAR/PRES diagnostic criteria, the presence of palpable purpura is considered a mandatory criterion, and in addition, the presence of diffuse abdominal pain, biopsy findings showing predominant IgA deposition, the presence of arthritis and/ or arthralgia, or at least one of the signs of renal involvement (hematuria and/or proteinuria) should be present (11).

This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of Şişli Etfal Training and Research Hospital (Date: 22.12.2015, Decision No. 602). Written informed consent was obtained from the parents or legal guardians of all participating children prior to inclusion in the study.

Demographic details, including age and gender, as well as initial complaints, were meticulously recorded. The presence of symmetric and purpuric rashes, predominantly affecting the lower extremities, was considered indicative of characteristic rash manifestations and thus evaluated as skin involvement. Pain in the joints (arthralgia) and/or swelling, redness, increased temperature, and restriction of movement (arthritis) were considered as joint involvement. Abdominal pain and/or occult blood in stool, melena, and hematemesis were considered as gastrointestinal involvement. Cases with marked abdominal tenderness and abdominal pain findings sufficient to warrant abdominal ultrasonography (USG) during clinical follow-up were considered as severe abdominal pain. Penile and scrotal oedema, confusion, and convulsions were recorded as other system involvement.

Renal involvement was defined according to findings that may occur during the course of the disease. The presence of microscopic hematuria (>5 erythrocytes/40 magnification in a centrifuged urine sample) and/or mild proteinuria (4–40 mg/m²/h) was defined as mild nephropathy. Severe nephropathy was characterised by the presence of nephrotic syndrome (proteinuria >40 mg/m²/h, hypoalbuminemia, hypercholesterolemia, and oedema) and/or nephritic syndrome (haematuria and/or proteinuria, oedema, hypertension, oliguria, and azotaemia). Renal biopsy was performed in the presence of nephrotic syndrome, rapidly deteriorating renal function, and persistent or increasing proteinuria according to the KDIGO 2025 Clinical Practice Guideline (12). Hemoglobin, white blood cell, platelet, serum urea, and serum creatinine values at the onset of the disease, fecal occult blood positivity, and the presence of hematuria and proteinuria in complete urinalysis were recorded. The categorisation of haemoglobin levels was conducted according to age and sex, with anaemia designated as haemoglobin levels below 12 g/dL, and leukocytosis defined as a white blood cell count above 10,300/mm³. Thrombocytosis was identified as a platelet count above 400,000/mm³. The duration of treatment received by patients was meticulously documented. Inpatient treatment was administered to patients exhibiting clinically severe joint, renal, and gastrointestinal involvement, with the development and duration of relapse being documented. Relapse was defined as the re-emergence of skin eruptions or other systemic manifestations at least two weeks following the resolution of the underlying disease. The duration of outpatient treatment, hospitalisation and readmission, the presence of comorbidities if applicable, and the duration of complete recovery were also recorded. Complete recovery was defined as complete resolution of skin eruptions or other systemic and laboratory findings.

The Turkish paediatric familial Mediterranean fever (FMF) diagnostic criteria encompass the presence of fever with at least three episodes lasting between 6 and 72 hours, abdominal pain, chest pain, arthritis in the form of oligoarthritis, and a family history. The presence of at least two of these criteria is considered sufficient for the diagnosis of familial Mediterranean fever (13).

Patients were initially categorised based on the presence of MEFV variants. Patients exhibiting homozygous, heterozygous, or compound heterozygous mutations were designated as having MEFV mutations.

Statistical Analysis

Statistical analyses were performed using SPSS version 15.0 for Windows. Categorical variables were summarized as frequencies and percentages, while continuous variables were expressed as mean ± standard deviation, along with minimum and maximum values. As the numerical variables did not meet the normal distribution condition, two independent group comparisons were conducted using the Mann-Whitney U test and more than two group comparisons were made using the Kruskal-Wallis test. Subgroup comparisons in more than two groups were made with the Mann-Whitney U test and interpreted with the Bonferroni correction. Proportions in independent groups were tested with the chi-squared analysis. Survival analysis was performed with the Kaplan-Meier analysis. The statistical alpha significance level was accepted as $p<0.05$.

RESULTS

We performed MEFV gene analysis on 45 patients diagnosed with HSP who were suspected of having FMF during follow-up. We found that 33 patients (73.4%) had at least one MEFV mutation, while 12 patients (26.6%) did not carry any mutations. The most common mutations were R202Q, E148Q, M694V, K695R, M680I, V726A, F479L, E167D, R408Q, P369S, G148I, and 12 others examined in the panel (H478Y, S675N, M680L, T681I, I692del, M694L, K695M, R717S, I720M, V722M, A744S, and R761H) were not detected in any patient. The demographic, clinical, and laboratory characteristics of these patients are shown in Table 1. MEFV mutations were more prevalent in females, which was statistically significant ($p<0.05$).

Table 1. Evaluation of MEFV mutation in terms of clinical findings

	MEFV mutation				p
	Present		Absent		
Age, Mean±SD (Min-Max)	7.70±3.33 (2.70-15.02)		7.13±4.00 (2.35-14.17)		0.419
	n	%	n	%	
Gender					0.038
Female	14	42.4	1	8.3	
Male	19	57.6	11	91.7	
Skin involvement	33	100	12	100	–
Gastrointestinal involvement	26	78.8	7	58.3	0.254
Joint involvement	17	51.5	7	58.3	0.746
Abdominal pain	8	24.2	4	33.3	0.706
Renal involvement					1.000
Mild nephropathy	1	3.0	0	0.0	
Severe nephropathy	4	12.1	1	8.3	
Clinical characteristics					1.000
Inpatient treatment	28	84.8	11	91.7	
Outpatient treatment	5	15.2	1	8.3	
Relapse occurrence	4	12.1	1	8.3	1.00
Leukocytosis	17	51.5	7	58.3	0.685
Thrombocytosis	11	33.3	8	66.7	0.045
	Mean±SD		Mean±SD		
Leukocyte count	11112.7±3332.5		14604.2±8265.7		0.182
Platelet count	370454.5±86668.6		445250.0±163442.6		0.130
Serum amyloid A	89.7±105.5		88.4±107.8		0.662
Fibrinogen	341.8±104.5		342.4±85.9		0.990
ESR	24.8±17.5		17.3±8.9		0.291
Hospitalization duration (days)	8.0±5.7		8.5±8.8		0.737
Time to full recovery (days)	19.3±8.8		18.2±10.7		0.415
Treatment duration (days)	11.9±3.9		13.3±11.1		0.389

MEFV: Mediterranean fever; SD: Standart deviation; ESR: Sedimentation rate. Hospitalization duration (days), length of hospital stay; Time to full recovery (days), interval between treatment initiation and complete resolution of symptoms; Treatment duration (days), total period of therapy administered to each patient.

The MEFV mutation was evaluated in terms of system involvement, with gastrointestinal and joint involvement found to be higher in patients with the MEFV mutation compared to those without (p>0.05). The frequency of renal involvement was increased in patients harboring MEFV mutations; nevertheless, this association did not attain statistical significance (p>0.05). The recurrence rate in patients with at least one MEFV mutation was found to be 12.1%, while the recurrence rate in patients without MEFV mutation was 8.3%, with no statistical significance (p>0.05).

A comparison of laboratory findings revealed that thrombocytosis was more prevalent in patients without MEFV mutation compared to those with MEFV mutation (p<0.05). Furthermore, an erythrocyte sedimentation rate that was elevated at a statistically insignificant level was observed in patients with MEFV mutations.

The analysis of the distribution of MEFV mutations (Table 2 and Fig. 1) revealed that among the 20 patients with the R202Q mutation, 10 (50%) had a single heterozygous mutation, 9 (45%) had a double heterozygous mutation, and 1 (5%) had a homozygous mutation. Similarly, among the 11 patients with the E148Q mutation, 6 (54%) had a single heterozygous mutation, and 5 (45%) had a compound heterozygous mutation. Finally, among the 5 patients with the M694V mutation, a single heterozygous mutation was detected in 2 (40%), and a double heterozygous mutation was detected in 3 (60%).

When MEFV variants were stratified according to ACMG classification, patients carrying pathogenic or likely pathogenic

Table 2. Distribution of MEFV mutations

	n	%
No mutation	12	26.7
Heterozygous (single mutation)		
p.R202Q/-*	10	22.2
p.E148Q/-	6	13.3
p.M680I/-	2	4.4
p.M694V/-	2	4.4
Heterozygous (double mutation)		
p.E148Q/p.R202Q	5	11.1
p.R202Q/p.M694V	2	4.4
p.K695R/p.R202Q	1	2.2
p.M694V/p.G148I	1	2.2
p.P369S/p.R408Q	1	2.2
p.R202Q/p.K695R	1	2.2
p.E167D/p.F479L/p.V726A	1	2.2
Homozygous		
p.R202Q/p.R202Q*	1	2.2
Total	45	100

MEFV: Mediterranean fever; *: Variant of Uncertain Significance (VUS).

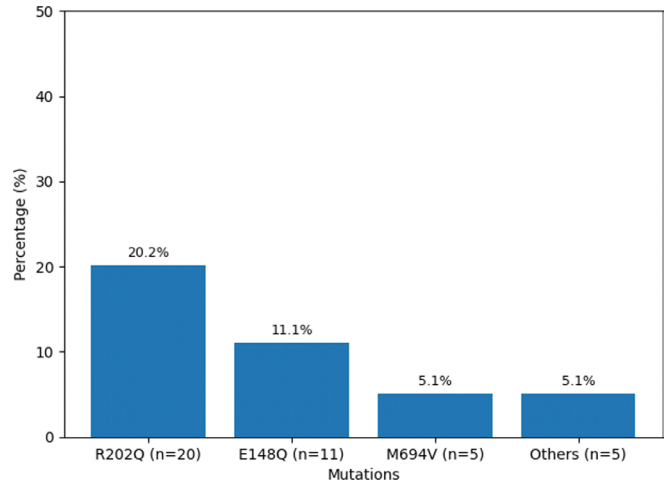

Figure 1. The analysis of the distribution of MEFV mutations.

variants (including M694V and M680I) were compared with those harboring only variants of uncertain significance (VUS), such as R202Q and E148Q. No statistically significant differences were observed between these two groups in terms of gastrointestinal, joint, or renal involvement, hospitalization rate, or relapse frequency ($p>0.05$ for all comparisons). Furthermore, the clinical course and laboratory inflammatory markers were comparable between pathogenic/likely pathogenic and VUS carrier groups. These findings indicate that, within the context of HSP, the presence of pathogenic MEFV variants does not confer a more severe clinical phenotype compared with VUS variants. However, the study did not reveal a statistical correlation between the presence of the MEFV mutation and kidney involvement. Kidney involvement and the presence of the MEFV mutation are described in Table 3.

DISCUSSION

The association between FMF and HSP has been well documented in the literature since the 1950s. The prevalence of FMF in Turkish children has been reported as 0.09%, whereas this rate rises to 1.1% among Turkish children diagnosed with HSP (4, 14). Furthermore, studies have demonstrated that MEFV polymorphism positivity is approximately twice as common in HSP cases compared with healthy controls (15, 16). In addition, an investigation of FMF patients revealed that 20% also presented with HSP (4). A comparative analysis of MEFV gene mutation carriage between healthy Turkish individuals and FMF patients showed a mutation frequency of 67.6% in FMF patients, with M694V (51.5%), M680I (9.2%), E148Q (3.5%), V726A (2.8%), and M694I (0.4%) as the most common variants. In contrast, the prevalence of MEFV mutations in the healthy Turkish population was 20%, distributed as M694V (3%), M680I (5%), E148Q (12%), V726A (2%), and M694I (0%) (17).

Herein, we report that MEFV mutations were identified in 73% of HSP cases. This prevalence, which is markedly higher than that observed in the general population, suggests that systematic evaluation for FMF and screening of family members may be beneficial in children diagnosed with HSP.

In the present study, the identified MEFV variants were additionally evaluated according to the American College of Medical Genetics and Genomics (ACMG) criteria. Accordingly, variants such as M694V and M680I, which have been consistently associated with classical FMF phenotypes, were classified as pathogenic or likely pathogenic, whereas E148Q and R202Q were categorized as variants of uncertain significance (VUS) due to their high allele frequency in the general population and the lack of definitive evidence supporting a causal role in disease pathogenesis (18, 19).

Table 3. Effects of renal involvement on MEFV mutation in patients with Henoch Schönlein Purpura

	Renal involvement						p
	Mild nephropathy		Severe nephropathy		No nephropathy		
	n	%	n	%	n	%	
MEFV mutation	1	100	4	80.0	28	71.8	1.000

MEFV: Mediterranean fever.

Importantly, although several of the detected variants were classified as VUS, their increased frequency among patients with HSP compared with the healthy population suggests that these variants may function as genetic susceptibility factors or disease modifiers rather than direct causative mutations. Therefore, the contribution of MEFV variants in HSP should be interpreted in the context of genetic predisposition and inflammatory burden, rather than strict Mendelian pathogenicity.

Consistent with prior reports, no significant differences in clinical presentation, laboratory findings, or demographic characteristics were observed between HSP patients with and without MEFV mutations. Although fever represents the hallmark manifestation of FMF, approximately 7% of affected individuals may experience afebrile episodes predominantly characterized by musculoskeletal involvement. Accordingly, in populations with a high prevalence of FMF, clinicians are advised to maintain a heightened level of clinical suspicion and awareness of its atypical and phenotypically diverse presentations (10, 15, 20–22). In our cohort, we similarly observed no difference in mean age between the two groups; however, the prevalence of MEFV mutations was significantly higher in females ($p<0.05$). With regard to systemic involvement, consistent with earlier reports, no significant association was identified, nor was any specific mutation found to be linked with particular clinical features. In line with the literature, gastrointestinal involvement was frequent, with a prevalence of 78.8%. By contrast, renal involvement was observed in only 15.1% of cases, a lower frequency compared with previous studies, although this difference did not reach statistical significance (20, 21).

In previous studies, the frequencies of the M694V and E148Q mutations have been reported as 3% and 12% in the healthy Turkish population, and 20–24% and 3.8–9.3% in HSP patients, respectively (9, 10, 17). In our cohort, however, the frequencies of R202Q, M694V, and E148Q were 44.4%, 11.1%, and 24.4%, respectively. These findings indicate a lower prevalence of M694V but a higher prevalence of E148Q compared with earlier reports, highlighting variability across different cohorts (10, 20). Nevertheless, consistent with the existing literature, the overall frequency of MEFV mutations in HSP patients remained higher than in the healthy population, supporting the hypothesis that MEFV variants may contribute to disease susceptibility rather than being incidental findings.

The pathogenic role of the E148Q variant remains particularly controversial. While E148Q has been reported in approximately 3.5% of FMF patients and 12% of the healthy Turkish population, homozygosity for this variant has not been consistently associated with classical FMF manifestations (23). Conversely, another study demonstrated the presence of the E148Q mutation in 30.1% of HSP cases and 13.5% of controls, revealing a statistically significant difference ($p<0.05$) (24). In our cohort, the E148Q mutation was identified in 11% of patients, classified as either single heterozygous or compound heterozygous variants. This frequency is consistent with that reported in the healthy Turkish population and appears to further support the ongoing debate regarding its role in FMF pathogenesis.

Recurrence rates have been reported to range between 19–21.6% in patients with MEFV mutations and 21.7–22% in those without mutations, with no significant difference observed between the groups (15, 20). Similarly, in line with the existing literature, our study also found no significant difference in recurrence rates between HSP patients with and without MEFV mutations.

The main limitations of this study include its retrospective chart review design, the relatively small sample size, the absence of a healthy control group, and the lack of follow-up data regarding the development and management of FMF.

CONCLUSION

HSP is the most common vasculitis of childhood, and the overlap of its clinical features with FMF increases the likelihood that HSP may, in some cases, represent an FMF attack. Therefore, particularly in populations with a higher prevalence of FMF, it is crucial to evaluate HSP cases in larger cohorts and to conduct long-term follow-up studies. Such investigations will contribute to a better understanding of the relationship between these two conditions and aid in improving differential diagnosis.

Ethics Committee Approval: This study was approved by the Ethics Committee of the University of Health Sciences Şişli Etfal Training and Research Hospital, (Date: 22.12.2015, Decision No. 602).

Informed Consent: Written informed consent was obtained from the parents or legal guardians of all participating children prior to inclusion in the study.

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Authorship Contributions: Concept – SÖ, NA; Design – SÖ, NA; Supervision – NA, ZYY; Resources – SÖ; Materials – NA; Data Collection and/or Processing – SÖ; Analysis and/or Interpretation – SÖ, NA; Literature Search – SÖ; NA; Writing – SÖ; NA; Critical Reviews – NA, ZYY.

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Hasta Onamı: Çalışmaya dahil edilmeden önce, katılan tüm çocukların ebeveynlerinden veya yasal vasilerinden yazılı bilgilendirilmiş onam alındı.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Mali Destek: Yazarlar bu çalışma için mali destek almadıklarını beyan etmişlerdir.

Yazma Yardımı için Yapay Zeka Kullanımı: Yapay zeka desteği kullanılmamıştır.

Yazarlık Katkıları: Fikir – SÖ, NA; Tasarım – SÖ, NA; Denetlemeler – NA, ZYY; Kaynaklar – SÖ; Malzemeler – NA; Veri toplanması ve/veya işleme – SÖ, NA; Analiz ve/veya yorumlama – SÖ, NA; Literatür araştırması – SÖ, NA; Yazım – SÖ, NA; Eleştirel incelemeler – NA, ZYY.

Teşekkürler: Bu çalışmaya katılan tüm hastalara ve ailelerine teşekkür ederiz. Ayrıca, hasta takibine katkılarından dolayı Şişli Hamidiye Etfal Eğitim ve Araştırma Hastanesi Pediatri Anabilim Dalı'ndaki hekimlere ve hemşirelik personeline şükranlarımızı sunarız. MEFV mutasyon analizlerinde sağladıkları değerli teknik destekten dolayı Genetik Laboratuvarı ekibine teşekkür ederiz.

Hakemli inceleme: Harici olarak hakemli.

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