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## Original article

# MEFV gene mutation in patients with juvenile-onset systemic lupus erythematosus in upper Egypt

***Background:*** *Juvenile-onset systemic lupus erythematosus ((j)SLE) is an autoimmune/inflammatory disease that can result in significant damage and disability. Familial Mediterranean Fever (FMF), the most common periodic fever syndrome in children, is characterized by episodes of fever, abdominal pain, arthralgia, arthritis, serositis. Given the overlap in clinical features between jSLE and FMF, we sought to assess the prevalence of the common 12 MEFV gene mutations in a group of jSLE patients.* ***Methods:*** *This cross-sectional controlled study analyzed MEFV gene mutations in 60 jSLE patients and 30 healthy controls using PCR and reverse hybridization. The assay included the following gene mutations E148Q, P369S, F479L, M680I (G/C), M680I (G/A), I692del, M694V, M694I, K695R, V726A, A744S, and R761H.* ***Results:*** *Heterozygous MEFV gene mutations were found in 10% of jSLE patients and 13% of the controls, with no statistically significant difference. These mutations were primarily located in exon 10. Fever, abdominal pain, arthritis, and pericardial effusion were the most common clinical presentations in jSLE patients with a heterozygous MEFV gene mutation.* ***Conclusions:*** *jSLE patients carry MEFV variants at rates comparable to the general population. Nevertheless, MEFV genetic mutations may influence the presentation of SLE. Clinicians should consider the possibility of co-occurrence of both diseases in patients with overlapping symptoms. Wider scale studies are needed to validate our findings*

**Keywords:** jSLE, FMF, MEFV.

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## INTRODUCTION

Juvenile-onset systemic lupus erythematosus (jSLE) is a rare but serious autoimmune and inflammatory disease that has the potential to cause harm and even death, it develops before age 18, representing 15-20% of SLE patients.[1] Its prevalence ranges from 1.89 to 34.1 per 100,000 children, with an incidence of 0.36 to 2.5 per 100,000 children,[2] and a female-to-male ratio of 3-5:1.[3] The disease occurrence is influenced by genetic, environmental and racial factors.[4] However, its prevalence and epidemiology among Egyptian children remain unclear due to a lack of nationwide studies, highlighting the need for further attention and research.[5]

Familial Mediterranean Fever (FMF) is considered the most common periodic fever syndrome in children and is commonly inherited in an autosomal recessive pattern. It is characterized by recurrent 6–72-hour episodes of fever, abdominal pain, arthralgia, arthritis, serositis, and erysipelas-like erythema,[6] predominantly affecting population from the Eastern Mediterranean, including Turks, Jews, Arabs, and Armenians.[7]

The relationship between MEFV gene variants and jSLE is still under-researched. Some studies report a negative association, noting the absence of SLE in large FMF cohorts and suggesting MEFV mutations may have a protective effect against renal complications.[8,9] Conversely, other research supports a potential link between FMF and SLE with overlapping symptoms between them.[10] The

relationship between FMF and SLE, the overlapping clinical features, and MEFV mutations' impact on SLE presentation still needs to be investigated. Hence, we investigated the frequency of 12 MEFV gene variants in a group of jSLE patients, in relation to their clinical and laboratory features.

## METHODS

**Study design:** A cross-sectional controlled study (ClinicalTrials.gov ID: NCT04645225) was conducted at the Pediatric Allergy, Immunology, and Rheumatology Unit of Assiut University Children's Hospital, Egypt, from January 2021 to December 2021. The study received approval from the Medical Ethics Committee of the Faculty of Medicine, Assiut University (ethical approval number: 17300535) .

**Sample population:** Sixty children and adolescents diagnosed with jSLE, based on the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria,[11] were consecutively recruited. Participants had to be 18 years or younger at enrollment and diagnosed with jSLE before age 16. Patients not meeting the SLE criteria or with other comorbid autoimmune conditions were excluded. Thirty healthy, age- and sex-matched children were recruited as controls. Informed consent was obtained from participants or their legal guardians before enrollment.

**Study methods:** The assessment of patients included detailed history taking covering personal demographics, family history, organ involvement (such as fever, abdominal pain, arthritis, serositis, rash, renal, neuropsychiatric, and hematological manifestations), and drug use. Clinical evaluation involved detailed systemic examination and lupus disease activity scoring using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI).[12] Laboratory tests included complete blood count, liver and kidney function tests, ESR, urine analysis, albumin creatine ratio in urine, Antinuclear antibody (ANA), anti-double stranded deoxy-ribonucleic acid (anti-dsDNA), complement 3 (C3), and C4 levels.

***MEFV Genetic Testing:*** MEFV gene mutations were investigated using polymerase chain reaction (PCR) and reverse hybridization, employing FMF Strip Assay Kits from Vienna Lab Diagnostics GmbH, Austria (lot numbers 20-DR-19-036 and 10-TW-20-013), provided by HVD Life Sciences.

**Assay Procedure:** Two milliliters of venous blood were collected from both patient and control groups. DNA was extracted using standard protocols and MEFV gene was amplified in vitro using PCR with biotinylated primers. The amplification products were hybridized to a test strip with allele-specific oligonucleotide probes. Biotinylated sequences bound to the probes were detected using streptavidin-alkaline phosphatase and color substrates. The assay targeted 12 MEFV gene mutations: E148Q, P369S, F479L, M680I (G/C), M680I (G/A), I692del, M694V, M694I, K695R, V726A, A744S, and R761H.

**Statistical Analysis** was performed using the Statistical Package for Social Sciences (SPSS), version 16.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± SD, median, and range, while categorical variables were expressed as percentages. The differences between groups were assessed using the Chi-square test, independent samples t-test, and Fisher's exact test. p-value of less than 0.05 was considered statistically significant.

## RESULTS

Clinicodemographic data of enrolled subjects are shown in table 1. The duration of the disease in jSLE patients ranged from 1 month to 7 years. Family history of SLE was positive in 5 patients, while none had positive family history of FMF.

Lupus nephritis (LN) was seen in 25 (41.7%) of the jSLE patients, with 6 presenting with hypertension and generalized edema, while silent LN, identified through urine analysis and albumin-creatinine ratio, was detected in 19 patients (Table 2). Eleven patients had hematuria, and proteinuria was observed in 21 patients. Renal biopsies were performed on 24 of the 25 patients with LN. One patient with LN and significant proteinuria was unable to undergo a biopsy due to concurrent thrombocytopenia. Distribution of histopathological classes of LN in our patients is shown in table 2.

Analysis of 12 mutations in the MEFV gene showed a heterozygous mutation in 10% of the jSLE patients and 13% of the control group, with no statistically significant difference (p=0.7). No homozygous mutations were found in either group (Table 3). The heterozygous mutations found in jSLE patients (10%), all were exon 10 mutations, including common mutations such as M694V, M694I, and V726A, while A744S mutation was found in one patient. Three out of the 4 children who were carriers for FMF mutations among the control group had exon 2 mutation (E148Q).

Fever, abdominal pain, arthritis, and pericardial effusion were the most common clinical presentations in jSLE patients with a heterozygous MEFV gene mutation (Table 4 and Figure 1).

Arthritis and abdominal pain exhibit a mild positive association with MEFV mutations, with odds ratio of 1.545 and 1.231, respectively. In contrast, pericardial effusion shows a stronger association with MEFV mutation; however, the wide confidence interval suggests uncertainty due to the small sample size. Fever demonstrates no significant association, with an odds ratio of 1.122 (95% CI: 1.023–1.231). Statistically significant p-values support the associations observed in arthritis, pericardial effusion, and abdominal pain ($p< 0.001$, 0.026, and 0.026, respectively).

Table 5 summarize the presentation of the 6 patients with the heterozygous MEFV mutations among jSLE patients. All the 6 patients experienced recurrent episodes of fever, arthritis (primarily knee involvement with one case had elbow arthritis that was exacerbated during menstruation), and abdominal pain. Serositis was observed in four patients, including pleural effusion (two cases) with one of them required decortication and pericardial effusion (two cases). All patients were ANA and anti-dsDNA positive, with persistent elevation of inflammatory markers (CRP and ESR) without evidence of infection despite appropriate lupus treatment. Two patients had fulfilled 'Eurofever/ Paediatric Rheumatology International Trials Organization (PRINTO) classification criteria' of FMF[13] and had uncontrolled periodic fever and abdominal pain necessitating the addition of colchicine, which controlled their symptoms. The other 4 patients will undergo strict follow-up to monitor for subclinical inflammation and disease progression.

**Table 1.** Demographic data of the studied jSLE patients

| | **Case (N=60)** | | **Control (N= 30)** | | ***P*-value** |
|---|---|---|---|---|---|
| | **N** | **%** | **N** | **%** | |
| **Sex** | | | | | |
| Male | 18 | 30.0% | 14 | 46.7% | 0.119 |
| Female | 42 | 70.0% | 16 | 53.3% | |
| **Age:** (years) | | | | | |
| Mean ± SD | 12.83 ± 3.10 | | 12.37 ± 1.81 | | 0.449 |
| Range | 6.0-18.0 | | 8.0-16.0 | | |
| **Age at diagnosis:** (years) | | | | | |
| Mean ± SD | 11.08 ± 2.91 | | -- | | -- |
| Range | 4.0-16.0 | | -- | | |
| **Duration of disease:** (months) | | | | | |
| Mean ± SD | 18.62 ± 22.25 | | -- | | -- |
| Median (Range) | 10.0 (1.0-84.0) | | -- | | |
| **Family history of SLE** | | | | | |
| Positive | 5 | 8.3% | -- | -- | -- |
| Negative | 55 | 91.7% | -- | -- | |

N: number; SD: standard deviation; SLE: systemic lupus erythematosus.

**Table 2.** Pattern of Lupus nephritis in the studied jSLE patients

| | **(N=60)** | **%** |
|---|---|---|
| **Lupus nephritis* presentation** | 25 | 41.7% |
| Hypertension | 6/25 | 24% |
| Generalized Oedema | 6/25 | 24% |
| Sterile pyuria | 10/25 | 40% |
| Hematuria | 11/25 | 44% |
| Proteinuria | 21/25 | 84% |
| **Renal biopsy staging** | 24 patients | |
| Class I | 5/24 | 20.8 % |
| Class II | 1/24 | 4.2 % |
| Class III | 5/24 | 20.8 % |
| Class IV | 7/24 | 29.2 % |
| Class V | 5/24 | 20.8 % |
| Class VI | 1/24 | 4.2 % |
| **Serum Albumin in patients with LN /(gm/dl)** | | |
| Mean ± SD | 3.19 ± 0.76 | |
| Range | 1.5-4.8 | |
| **Albumin creatinine ratio in urine in patients with LN (mg/gm)** | | |
| Mean ± SD | 2681.45 ± 1451.34 | |
| Range | 630-6276 | |

N: number; SD: standard deviation; LN: lupus nephritis, mg: milligram; gm: gram.
*Lupus nephritis was considered in patients with biopsy proven LN according to ISN/RPS classification criteria of LN.[27]

**Table 3.** Frequencies of the tested MEFV gene mutations among the studied jSLE patients versus controls

| | **Case (N= 60)** | | **Control (N= 30)** | | ***P*-value** |
|---|---|---|---|---|---|
| | **N** | **%** | **N** | **%** | |
| **Result** | | | | | |
| Wild | 54 | 90.0% | 26 | 86.7% | 0.726 |
| Heterozygous | 6 | 10.0% | 4 | 13.3% | |
| **Type of Mutation** | | | | | |
| A744S | 1 | 16.7% | 0 | 0.0% | |
| E148Q | 0 | 0.0% | 3 | 75.0% | |
| M694I | 1 | 16.7% | 1 | 25.0% | |
| M694V | 2 | 33.3% | 0 | 0.0% | |
| V726A | 2 | 33.3% | 0 | 0.0% | |

MEFV: Mediterranean fever gene; N: number
Fisher exact test was used.

**Table 4.** Frequencies of possible FMF features among SLE patients according to their MEFV mutation testing

| **Manifestation** | **jSLE with negative MEFV gene mutations testing (N= 54)** | | **jSLE with positive MEFV gene mutation testing (N= 6)** | | ***P*-value** | **OR (95% C.I.)** |
|---|---|---|---|---|---|---|
| | **N** | **%** | **N** | **%** | | |
| **Fever** | 49 | 90.7% | 6 | 100.0% | > 0.999 | 1.122 (1.023 - 1.231) |
| **Arthritis** | 11 | 20.4% | 6 | 100.0% | < 0.001* | 1.545 (1.088 - 2.195) |
| **Pericardial effusion** | 1 | 1.9% | 2 | 33.3% | 0.026* | 26.500 (1.955-359.198) |
| **Abdominal pain** | 26 | 48.1% | 6 | 100.0% | 0.026* | 1.231 (1.042 - 1.454) |

n: number, OR: odd's ratio, CI: confidence interval
Fisher exact test was used.

**Table 5.** Characteristics of the 6 jSLE patients with positive MEFV gene mutation testing.

| Case | Age (yr) | Sex | Symptoms | MEFV mutation |
|---|---|---|---|---|
| 1 | 11 | F | Fever, Abdominal pain, knee Arthritis, pleural and Pericardial effusion, LN class III | M694V |
| 2 | 11 | F | Fever, Abdominal pain, knee Arthritis, Malar and Discoid rash, Coombs positive AHA | V726A |
| 3 | 10 | F | Fever, Abdominal pain, Arthritis, Malar rash, Coombs positive AHA. | M694V |
| 4 | 16 | F | Fever, Abdominal pain, Knee and Elbow Arthritis, Pericardial effusion. | A744S |
| 5 | 16 | M | Fever, Abdominal pain, Arthritis, extensive oral ulcers, malar and discoid rash, lupus cerebritis, proteinuria,* thrombocytopenia | V726A |
| 6 | 9 | F | Fever, Abdominal Pain, Arthritis, Malar rash | M694I |

MEFV: Mediterranean fever gene; ESR: erythrocyte sedimentation ratio; CRP: C reactive protein; SAA: serum amyloid A; LN: lupus nephritis; AHA: autoimmune hemolytic anemia

*Renal biopsy was not done due to concurrent thrombocytopenia.

## DISCUSSION

This study investigated the frequency of 12 MEFV gene mutations associated with FMF in jSLE patients in Upper Egypt. We had female-to-male ratio of 2:1, aligning with previous study in Egypt[14] and internationally.[15,16] The mean age at diagnosis of jSLE was 11 years ± 2.9, similar to the 2015 Egyptian study[14] (12 years ± 3.45) and slightly younger than reported median ages in the UK[16] (12.8 years) and Australia[17] (12.6 years). Renal manifestations were observed in 41.7% of jSLE patients, with Class IV LN being the most common finding on renal biopsy (29.2%), consistent with studies from Australia and Latin Ameria.[17-19] In this study, an equal frequency of 20.8% was noted for patients with LN Class I, III, or V.

In this study, upon investigating the frequency of the studied 12 MEFV gene mutations among jSLE patients in Upper Egypt, we found a frequency of 10%, comparable to the 13% observed in healthy controls. A Turkish study also found comparable frequencies of MEFV mutations in jSLE patients (22.7%) and healthy individuals (20%).[20] Additionally, Erer et al. reported that the frequency of common MEFV mutations in jSLE (15%) was not significantly different from that in healthy individuals (10%).[9] The comparable frequencies of MEFV mutations among SLE patients and controls might contradict the previous suggestions of the protective effect of MEFV mutations among SLE patients against development of FMF. [8,9,21]

MEFV mutations in SLE patients was suggested to influence the disease phenotype by intensifying inflammatory episodes and mitigating renal manifestations. [22] In this study, we found that jSLE patients with a heterozygous MEFV gene mutation more often experienced fever, abdominal pain, arthritis, and pericardial effusion compared to those without the mutation. Among these patients, two had significant proteinuria, while the other four showed no renal symptoms. One patient with the M694V mutation had biopsy-proven LN Class III, and another with the V726A mutation did not undergo renal biopsy due to thrombocytopenia and lupus cerebritis. This study supports Shinar et al.'s[8] findings that individuals with common MEFV mutations often reported fever and pleurisy and had fewer renal issues, as four out of our six jSLE patients with positive MEFV mutations had no renal manifestations. However, the two patients with proteinuria had exon 10 mutations, consistent with Deniz et al.[23] findings that exon 10 mutations are linked to LN. Wider scale studies with larger sample size are needed for more conclusive results.

In this study, pericardial effusion was seen in 33.33% of jSLE patients with heterozygous gene mutations, compared to 3.7% in those without mutations. Similarly, another study found that SLE patients with exon 10 mutations tended to develop pericarditis and/or pleural effusion.[9]

MEFV genetic testing usually includes nine pathogenic mutations (M694V, M694I, M680I, V726A, R761H, A744S, I692del, E167D, and T267I) and five of uncertain significance (E148Q, K695R, P369S, E479L, and I591T).[24] In this study, all jSLE patients with positive MEFV heterozygous mutations had exon 10 mutations, predominantly M694V and V726A, both highly pathogenic. The E148Q mutation was the most common MEFV genotype (75%) in the control group with positive MEFV mutations but was absent in jSLE patients with positive MEFV mutations. The role of the exon 2 E148Q variant as a disease-causing mutation or polymorphism is still controversial. Studies by Ben-Chetrit et al.[25] and Tchernitchko et al. [26] suggest E148Q is a polymorphic variation, not typically associated with FMF. A Turkish study

supported the view that E148Q has minimal impact on FMF phenotype or inflammation.[9] Thus, although our patients and controls had comparable frequencies of MEFV mutations in general, yet the specific type of the mutation was different between the two groups, which might have clinical implication if further evaluated through further studies with larger sample size and adequate representation of different MEFV mutations.

We could suggest that periodic nature of some symptoms as fever, abdominal or chest pain, and arthritis in patients with SLE, their persistence despite immunosuppressive therapy, and the consistently elevated inflammatory markers, may raise awareness of possibility of overlap with FMF. Although FMF symptoms are typically periodic, yet the clinical or subclinical persistent inflammation can also occur and is not against the diagnosis. As a result, colchicine may be added to their treatment regimen, helping in the clinical improvement. This highlights the importance of considering FMF-related inflammation in SLE patients with recurrent, treatment-resistant fever, arthritis, and serositis, particularly when inflammatory markers remain persistently elevated despite adequate lupus therapy. However, the improvement on colchicine should not be taken for granted as a proof of FMF diagnosis, this is because colchicine is well known for its anti-inflammatory action as it inhibits a wide variety of pathways related to inflammation and works by inhibiting the NLRP3 inflammasome, microtubule-based inflammatory cell chemotaxis, production of leukotrienes and cytokines, and phagocytosis.[27] Colchicine has also been found to have a valuable role in cardiac disease treatment owing to targeting neutrophils, endothelial cells and platelets, inhibiting mitosis, vascular hyperplasia and fibrosis. Colchicine was observed to improve outcomes of pericarditis, myocardial ischemia and coronary occlusions. [28] Thus, although we could not reach a definite diagnosis for FMF among the studied patients with overlapping features, yet, we suggest that adding colchicine might represent an appealing add on treatment that can help by its anti-inflammatory action whether the patient was truly FMF or not. However, longitudinal wider scale studies are needed before we can make a solid recommendation.

The study's limitations include the small sample size of jSLE patients and the limited number of controls, in addition to the cross-sectional nature of the study and the lack of specific markers that can accurately diagnose FMF among SLE patients. Also, we tested only for 12 FMF gene mutations which might have limited our findings. Additionally, the precise prevalence of FMF in Egypt is still uncertain.

**In conclusion,** our study shows that while jSLE patients may carry MEFV variants at a frequency similar to the general population, yet with more prevalent exon 10 mutations. MEFV genetic mutations might increase the likelihood of symptoms such as fever, abdominal pain, arthritis, and serosal inflammation in jSLE patients. Routine testing for FMF in all SLE patients cannot be recommended. Instead, clinicians should consider the possibility of co-occurrence of both diseases in patients with overlapping symptoms. Thus, FMF should be considered as a potential diagnosis in jSLE patients who present with recurrent/persistent fever and serosal inflammation, who fail to respond to conventional SLE treatment., warranting colchicine treatment if the patient meets the diagnostic criteria for FMF to avoid delay of diagnosis and proper management. Specific diagnostic testing is still lacking.

## AUTHORS CONTRIBUTIONS

**GAA** designed and approved the final version of the study. **NSO** designed the study, clinically diagnosed the patient, performed the study through reviewing the data of the patients, edited and wrote the final version of the study. **SAMS** performed the study through collecting and analyzing the data. **ERB and HB** performed the laboratory testing of the study.

## CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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