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MEFV Genotype and Clinical Presentation as Indicators of Mesenteric Lymphadenopathy in Pediatric Familial Mediterranean fever

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A B S T R A C T

Introduction: The introduction highlights the importance of understanding how MEFV genotypes and clinical features relate to mesenteric lymphadenopathy in children with familial Mediterranean fever. It emphasizes the diagnostic challenges of abdominal pain, the variability of genetic mutations, and the potential role of lymph node enlargement as an indicator of inflammatory burden, underscoring the need for genotype-informed evaluation to improve diagnostic accuracy and pediatric management.

Material and methods: The study employed a descriptive cross-sectional design at Kowsar Clinic in Ardabil, enrolling 106 pediatric FMF patients through convenience sampling. Eligible participants underwent standardized clinical assessment, MEFV genotyping, and abdominal ultrasonography to evaluate mesenteric lymphadenopathy. The approach allowed systematic evaluation of genotype phenotype imaging relationships.

Results: In this pediatric FMF cohort, mesenteric lymphadenopathy (MLN) was detected in over half of patients and was notably associated with higher frequencies of abdominal and chest pain, indicating a more active inflammatory phenotype. Fever remained uniformly prevalent across groups, while other systemic symptoms showed mild increases among MLN-positive children. The MEFV mutation spectrum reflected regional patterns, and no significant genotype-MLN association was observed.

Conclusion: MLN appears to be a common and clinically meaningful ultrasonographic finding in pediatric FMF, correlating with more pronounced abdominal and serosal symptoms rather than specific MEFV mutations. Its presence may signal heightened inflammatory activity, supporting its potential role as a complementary marker in clinical assessment and risk stratification. Future work should integrate biomarkers to refine phenotype characterization.

Introduction

Familial Mediterranean Fever (FMF) is the most common monogenic auto inflammatory disorder characterized by recurrent febrile attacks and serosal inflammation, with a striking predominance among populations originating from the Mediterranean basin (1). Its clinical expression typically emerges during childhood, making it a major cause of recurrent abdominal pain and systemic inflammation in pediatric practice (2).

The disease is caused by pathogenic variants in the MEFV gene, which encodes the pyrin protein, a key regulator of inflammasome activation and interleukin-1β mediated inflammatory responses (3). More than 370 MEFV variants have been reported, but a limited subset particularly M680I, M694V, M694I, V726A, and E148Q accounts for

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the majority of clinically relevant mutations in children (4).

Genotype phenotype correlations in FMF have been widely investigated, revealing that certain MEFV variants, especially M694V homozygosity, are associated with earlier disease onset, more severe flares, and a greater risk of long-term complications such as amyloidosis (5). Despite extensive research on these correlations, the relationship between specific MEFV genotypes and abdominal manifestations such as mesenteric lymphadenopathy (MLN) remains insufficiently defined in pediatric cohorts (6).

Abdominal pain is one of the hallmark symptoms of FMF, reported in up to 90% of affected children during febrile attacks, and often attributed to peritonitis and serosal inflammation (7). However, the differential diagnosis of abdominal pain in children is broad, and FMF flares may clinically mimic other intra-abdominal conditions, including appendicitis, infectious lymphadenitis, and inflammatory bowel disease (8). Mesenteric lymphadenopathy, detected increasingly with the widespread use of abdominal ultrasonography, is frequently encountered in children with unexplained abdominal pain and may complicate the diagnostic evaluation of FMF (9). MLN represents an enlargement of mesenteric lymph nodes, often reflecting active inflammation, infection, or immune dysregulation, and may therefore serve as an imaging correlate of abdominal inflammatory burden in FMF (10). Although MLN is commonly observed in FMF patients during symptomatic episodes, evidence regarding its prevalence, determinants, and clinical significance remains heterogeneous across studies (11). This variability may be partially due to differences in imaging standards, patient age, disease activity at the time of evaluation, and underlying genetic factors (12).

In pediatric FMF, understanding whether MEFV genotype contributes to the development or persistence of MLN has substantial clinical implications, especially given the broad spectrum of abdominal symptoms experienced by young patients (13). If certain genotypes predispose children to more frequent or more pronounced MLN, clinicians may need to adopt genotype-informed diagnostic approaches to avoid unnecessary surgical exploration or repeated imaging (14). Moreover, MLN itself may influence disease perception and management, as its presence can intensify abdominal pain, complicate clinical assessment of FMF flares, or obscure the distinction between auto inflammatory and infectious etiologies (15). Identifying genotype-specific patterns of MLN could therefore help refine diagnostic accuracy, reduce misdiagnosis, and guide therapeutic decisions, particularly in children presenting with severe or ambiguous abdominal episodes (16).

Another dimension of interest concerns the potential interplay between MLN and inflammatory severity in FMF. Elevated levels of acute-phase reactants including serum amyloid A, C-reactive protein, and leukocyte count often accompany abdominal attacks, yet the extent to which MLN correlates with systemic inflammatory markers or clinical disease activity remains poorly studied in pediatric populations (17). Establishing whether MLN is merely an incidental imaging finding or a marker of heightened inflammatory load could influence both follow-up strategies and treatment intensity. For example, children who demonstrate MLN alongside certain high-risk MEFV genotypes might represent a subgroup with greater inflammatory propensity, warranting closer monitoring or earlier escalation of colchicine dosing. In this context, integrating genetic profiling with detailed clinical assessment and imaging patterns may offer a more comprehensive framework for individualized management of pediatric FMF.

Material and methods

Study Design

This descriptive cross-sectional study was conducted at Kowsar Clinic, Ardabil University of Medical Sciences, and evaluated pediatric patients diagnosed with Familial Mediterranean Fever who underwent abdominal ultrasonography as part of their clinical assessment. All eligible participants under 18 years of age were included during the study period. The objective was to determine the association between MEFV genotypes, clinical features, and the presence of mesenteric lymphadenopathy, using standardized clinical documentation and imaging protocols applied uniformly across all enrolled patients.

Sampling and Sample Size

A total sample size of 106 patients was determined using the standard formula for estimating a population proportion, considering a 95% confidence level and an anticipated prevalence based on prior literature. The formula applied was:

$$n = Z^2 * P * (1 - P) / d^2$$

where n represents the required sample size, Z is the standard normal value for a 95% confidence interval (1.96), P is the estimated proportion, and d is the desired precision. After substituting the expected values, the calculation yielded a sample size of 106 participants. A convenience sampling method was employed, enrolling all FMF patients under 18 years of age who presented to the pediatric rheumatology or gastroenterology clinics and underwent ultrasonography during the study interval. Patients were included consecutively as they became available, ensuring complete data collection for demographics, genotype information, and clinical manifestations. This approach allowed for maximal capture of real-world clinical variability within the

target population and facilitated a practical, time-efficient recruitment strategy appropriate for a hospital-based observational study.

Inclusion Criteria

Eligible participants were children and adolescents younger than 18 years with a confirmed diagnosis of Familial Mediterranean Fever according to Tel-Hashomer or pediatric-modified criteria. Patients were required to have undergone abdominal ultrasonography as part of their routine evaluation and to have complete clinical and laboratory records available. Only individuals with documented MEFV mutation analysis were included. Written informed consent from parents or legal guardians, and assent from children when appropriate, was obtained prior to participation.

Exclusion Criteria

Patients were excluded if they had concurrent infectious, oncologic, or autoimmune conditions that could independently cause mesenteric lymphadenopathy. Individuals with a recent history of acute gastrointestinal infection, abdominal trauma, prior abdominal surgery, or any condition limiting proper ultrasonographic assessment were also excluded. Cases with incomplete demographic, imaging, or genetic data were removed from the analysis. Additionally, patients with unclear or conflicting FMF diagnostic documentation were not considered eligible for enrollment.

Procedures

All participants underwent a standardized clinical assessment conducted by pediatric rheumatologists, including a detailed review of attack characteristics, abdominal pain patterns, fever episodes, joint involvement, and other FMF-related manifestations. Physical examination findings, acute-phase reactants, and disease severity indices were recorded systematically using unified forms. MEFV genotyping was performed using PCR-based methods in certified molecular laboratories, targeting the most common pathogenic variants, and results were documented for both heterozygous and homozygous states. Clinical data were reviewed to ensure temporal consistency between symptomatic episodes and imaging dates, reducing potential misclassification of abdominal manifestations.

Abdominal ultrasonography was performed by expert radiologists using high-resolution equipment, following a standardized scanning protocol to evaluate mesenteric lymph nodes in terms of number, size, and distribution. Mesenteric lymphadenopathy was defined based on accepted pediatric radiologic criteria. All imaging was reviewed independently to ensure interpretative consistency. Data were entered into a structured database after verification, and quality-control procedures were applied to minimize transcription errors. Each patient's clinical features and genotype findings were subsequently matched with their ultrasonographic results for further statistical evaluation.

Statistical Analysis

Data analysis was performed using standard statistical software. Continuous variables were expressed as means and standard deviations, while categorical variables were summarized as frequencies and percentages. Normality of distribution was confirmed, allowing parametric tests to be applied. Group comparisons were conducted using independent t-tests or one-way ANOVA for continuous variables and chi-square tests for categorical variables. Correlations between MEFV genotypes, clinical symptoms, and mesenteric lymphadenopathy were assessed using Pearson correlation coefficients. A significance level of $P < 0.05$ was considered statistically meaningful for all analyses.

Ethical Considerations

The study adhered to the ethical principles of the Declaration of Helsinki and was approved by the Ethics Committee of Ardabil University of Medical Sciences under the code IR.ARUMS.MEDICINE.REC.1402.176.

Participation was voluntary, and all parents or legal guardians provided written informed consent, with assent obtained from older children when appropriate. Data confidentiality was strictly maintained, and all patient identifiers were removed during analysis. Ultrasonography and clinical evaluations were performed as part of routine care, ensuring no additional risk or burden to participants during the study.

Results

The cohort demonstrated a relatively balanced distribution of mesenteric lymphadenopathy, with 58 children showing detectable mesenteric lymph nodes and 48 exhibiting no lymphadenopathy. This near-even pattern suggests that mesenteric node enlargement is a common finding among pediatric FMF patients undergoing abdominal evaluation. The proportion also indicates that lymphadenopathy may represent an important imaging correlate of abdominal inflammatory activity, warranting further exploration of its clinical and genetic associations within this population.

The comparative analysis of clinical manifestations stratified by mesenteric lymph node (MLN) status demonstrated distinct symptom patterns between children with FMF who exhibited lymphadenopathy and those without it. Overall, fever remained uniformly prevalent across both groups, underscoring its limited discriminatory value. However, several abdominal and systemic symptoms showed meaningful divergence: chest pain and abdominal pain emerged as the most clinically relevant markers, with significantly higher

frequencies among patients with MLN enlargement, suggesting a stronger inflammatory phenotype and possibly more active serosal involvement in this subgroup. Although symptoms such as myalgia, arthralgia, dyspnea, chills, nausea, diarrhea, and fatigue occurred in both groups, their distributions reflected subtle but consistent trends favoring a greater symptom burden among MLN-positive patients. The pattern observed supports the hypothesis that MLN enlargement may represent an imaging correlate of heightened auto inflammatory activity rather than an incidental finding, aligning with the concept that certain phenotypes of FMF express more pronounced gastrointestinal and serosal inflammatory manifestations. These results emphasize the value of integrating radiologic findings with clinical assessment to better identify high-risk phenotypes and optimize individualized follow-up strategies in pediatric FMF (figure 1).

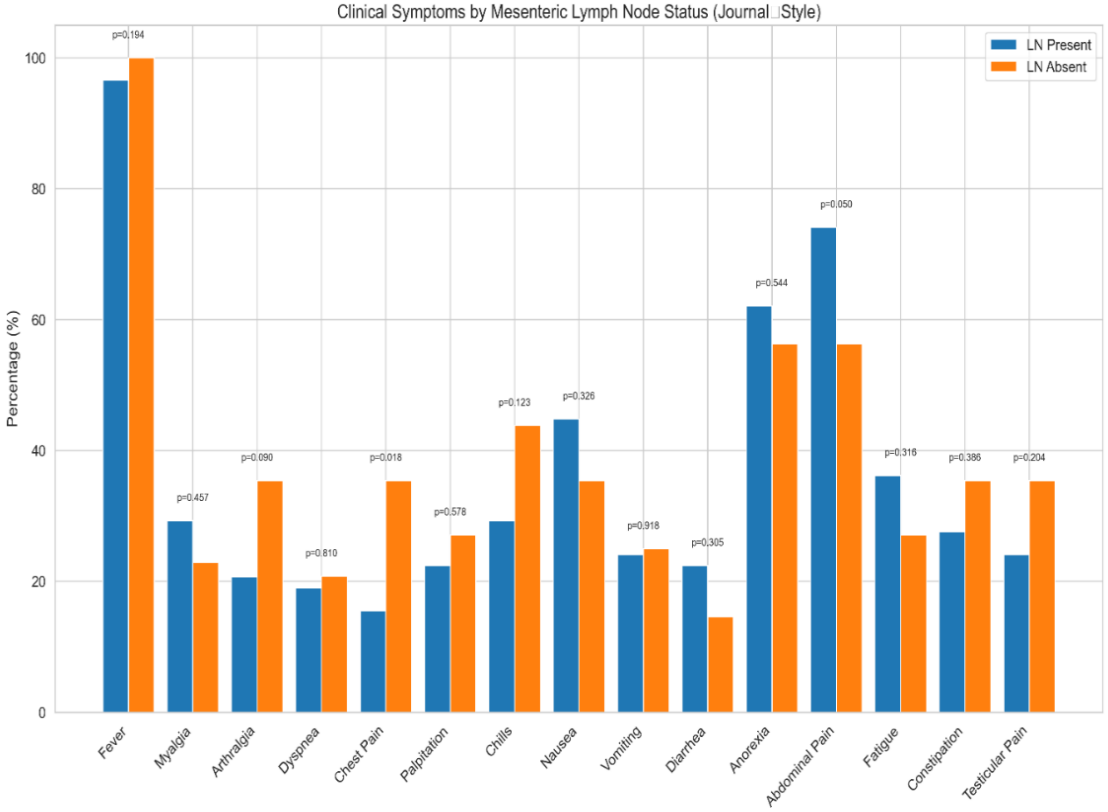

Figure 1. Clinical Symptom Profiles Associated with Mesenteric Lymphadenopathy in Pediatric Familial Mediterranean Fever.

The distribution of MEFV mutations within our pediatric FMF cohort demonstrates a pattern consistent with the allelic landscape reported in high-prevalence regions, yet with distinctively elevated frequencies for specific variants. The predominance of E148Q (26.4%) and M694V (24.5%) underscores the central role of these mutations in driving disease susceptibility, reflecting both ancestral founder effects and the genotype enrichment typical of eastern Mediterranean populations. Intermediate-frequency variants such as V726A (13.2%) and M680I (8.5%) also contribute substantially to the mutational burden, supporting the heterogeneity of pathogenic alleles across clinical presentations. Conversely, the lower prevalence of mutations such as R761H (4.7%), P396S (4.7%), and M680V (2.8%) highlights their more limited penetrance within this demographic, although they may still modulate phenotype severity in select patients. The overall distribution suggests a mutation spectrum dominated by a combination of classical high-penetrance alleles and moderate-frequency variants, aligning with the observed clinical variability of FMF manifestations. These findings reinforce the importance of region-specific genetic profiling to inform diagnostic accuracy, risk stratification, and potential prognostic insights in pediatric FMF populations (figure 2).

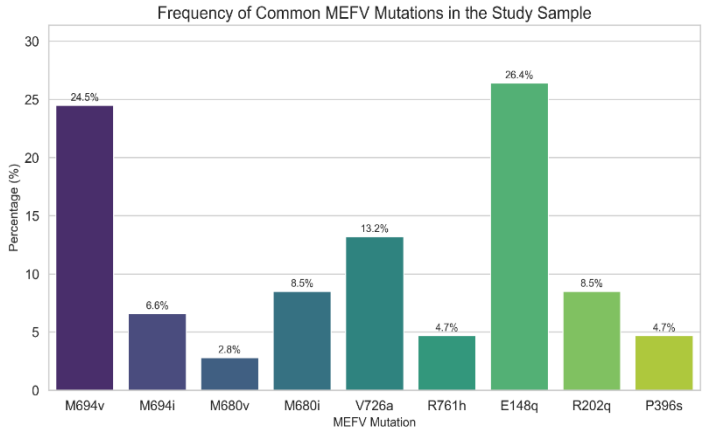

Figure 2. Genetic Spectrum and Relative Frequencies of Common MEFV Mutations in a Pediatric FMF Cohort

The comparative analysis of MEFV mutation patterns between children with and without mesenteric lymphadenopathy (MLN) demonstrated no statistically significant genotype-phenotype association, although several clinically meaningful trends emerged. The E148Q variant historically regarded as a low-penetrance mutation showed a modestly higher proportion among patients with MLN, whereas the heterozygous M694V and V726A mutations displayed parallel distributions between groups, suggesting that MLN development in pediatric FMF may be driven more by inflammatory activity and disease expression than by a specific mutational signature. Notably, the absence of significant differences across all evaluated mutations (all P>0.05) supports the concept that MLN may represent a downstream ultrasonographic manifestation within the FMF inflammatory spectrum rather than a mutation-dependent phenotype. These findings reinforce the need for future studies incorporating inflammatory biomarkers, variant burden, and functional assays to better delineate the biological mechanisms linking MEFV-mediated auto inflammation with mesenteric lymph node responses (figure 3).

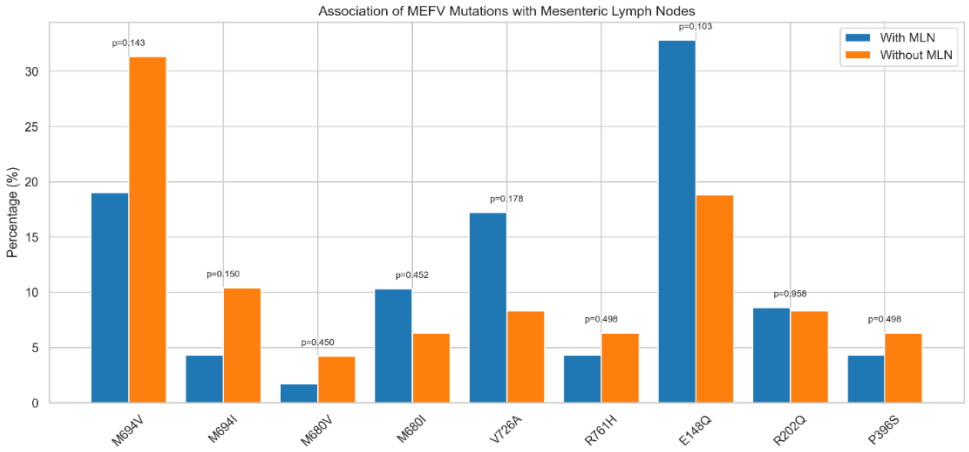

Figure 3. Genotypic Distribution of Common MEFV Variants and Their Lack of Significant Association with Mesenteric Lymphadenopathy in Pediatric FMF

Discussion

The present study provides a comprehensive evaluation of mesenteric lymphadenopathy (MLN) in a well-characterized pediatric cohort with Familial Mediterranean Fever (FMF), integrating clinical, ultrasonographic, and genetic dimensions to enhance understanding of this frequently encountered yet poorly contextualized abdominal finding. Our results demonstrated that MLN was present in 54.7% of children, indicating that mesenteric node enlargement is a common imaging feature during abdominal assessment in FMF. This balanced distribution between MLN-positive and MLN-negative patients aligns with emerging evidence suggesting that lymph node reactivity may reflect heightened auto inflammatory activity, particularly during abdominal or serosal attacks (19,20). The near-equal proportions observed in our cohort reinforce the notion that MLN should not be dismissed as incidental but rather interpreted within the broader inflammatory and phenotypic spectrum of FMF.

A detailed comparison of clinical manifestations stratified by MLN status revealed distinct symptom trends, with abdominal pain and chest pain showing significantly higher frequencies in children

exhibiting MLN. These findings are consistent with the understanding that abdominal serosal irritation, mesenteric inflammation, and gut-associated lymphoid tissue activation are key contributors to regional lymph node enlargement in auto inflammatory disorders (21). Abdominal pain, one of the hallmark features of FMF, was markedly more common in the MLN-positive group, supporting the hypothesis that lymphadenopathy may serve as an ultrasonographic marker of more intense gastrointestinal involvement. This observation resonates with previous studies highlighting that abdominal attacks often involve mesenteric hyperemia, bowel wall thickening, and lymphatic stimulation, each of which may culminate in detectable MLN on imaging (22,23).

Similarly, chest pain typically attributable to pleuritic inflammation was disproportionately represented among MLN-positive patients, suggesting a possible phenotype characterized by broader serosal activation. Although FMF is classically associated with episodic peritonitis and pleuritis, only limited literature has explored the co-occurrence of thoracic and abdominal inflammatory markers in childhood FMF, making our findings an important addition to current knowledge (24). The clustering of chest pain and abdominal pain in MLN-positive patients may reflect a more active or systemic inflammatory phenotype, potentially underpinned by higher cytokine burden, increased IL-1β activation, or more pronounced inflammasome responsiveness mechanisms described in recent auto inflammatory research (25).

In contrast, symptoms such as fever, myalgia, arthralgia, dyspnea, chills, nausea, diarrhea, and fatigue appeared in both MLN groups with only subtle variations. Fever, in particular, was uniformly present and demonstrated low discriminatory value. This uniformity is consistent with fever's role as a non-specific but ubiquitous marker of inflammasome activation across FMF phenotypes (26). The overall symptom pattern thus suggests that while systemic markers of inflammation are shared among patients, regional lymphadenopathy is more closely tied to abdominal and serosal symptomatology.

The clinical implications of these findings are noteworthy. Radiologic detection of MLN may assist clinicians in differentiating FMF-related abdominal pain from other etiologies such as appendicitis, infectious adenitis, and inflammatory bowel disease common diagnostic dilemmas in pediatric populations (27). Integrating MLN assessment into clinical evaluation may help identify children with more active abdominal inflammation who may benefit from closer follow-up, optimized colchicine management, or evaluation for colchicine-resistant FMF. Furthermore, recognizing MLN as an inflammatory biomarker rather than an incidental discovery could reduce unnecessary diagnostic investigations and lower the burden of emergency department evaluations among pediatric FMF patients.

In addition to clinical radiologic correlations, our study explored the distribution of common MEFV mutations within this cohort. The overall mutation spectrum was consistent with patterns reported in high-prevalence populations of the Middle East, with E148Q (26.4%) and M694V (24.5%) representing the most frequent variants. The prominence of these alleles is well aligned with known regional founder mutations and reflects their established role in driving disease susceptibility in Mediterranean and Anatolian populations (28,29). The substantial representation of V726A and M680I as intermediate-frequency variants further underscores the genetic heterogeneity typical of FMF, where multiple pathogenic MEFV alleles contribute to variable clinical severity, attack frequency, and treatment responsiveness (30).

Interestingly, low-frequency alleles such as R761H, P369S, and M680V were detected at modest prevalence levels, consistent with international data suggesting that these variants may contribute to milder or atypical phenotypes or act as modifiers rather than primary disease-driving mutations. Collectively, the mutation profile observed in our cohort reflects a mixture of high-penetrance, moderate-frequency, and low-penetrance alleles, reinforcing the biological and clinical variability that characterizes FMF expression in childhood. When clinical findings were examined in relation to genetic variants, our analysis revealed no statistically significant associations between specific MEFV mutations and the presence of MLN. The lack of genotype MLN correlation suggests that lymphadenopathy does not appear to be mutation-dependent but rather is more closely influenced by inflammatory activity and disease expression. This observation aligns with growing evidence that while MEFV variants determine susceptibility and overall inflammatory threshold, phenotype expression including serosal involvement may be modulated by environmental triggers, immune responsiveness, and epigenetic factors rather than specific mutations alone (31).

Despite the absence of statistically significant differences, several trends warrant discussion. The E148Q mutation, traditionally considered a low-penetrance variant, appeared slightly more common among MLN-positive children. This trend is intriguing given ongoing debate about the pathogenicity of E148Q and its potential contribution to milder or atypical FMF presentations. While our findings do not establish a causal relationship, they raise the question of whether certain low-penetrance alleles may predispose patients to localized inflammatory manifestations without influencing systemic disease

severity. Conversely, M694V and V726A both associated with classical and sometimes severe FMF phenotypes showed parallel distributions between MLN groups, suggesting that MLN is not directly mediated by high-penetrance mutations. This is consistent with prior work indicating that regional lymphadenopathy in FMF may be more reflective of local intestinal immune activation rather than genotype-determined disease intensity. Taken together, our findings highlight several clinical and mechanistic insights. First, MLN is a frequent and clinically meaningful feature in pediatric FMF, particularly among those presenting with abdominal and chest pain. Second, the MEFV mutation spectrum in our cohort mirrors that of other high-prevalence populations, reaffirming the genetic architecture underlying FMF in the region. Third, the lack of genotype MLN association supports the concept that lymphadenopathy represents an inflammatory expression rather than a mutation-specific phenotype. These insights emphasize the importance of integrated diagnostic approaches that combine genetic testing, clinical evaluation, and targeted imaging to accurately phenotype pediatric FMF patients (32).

Future studies incorporating inflammatory biomarkers, cytokine profiling, and more granular genetic analyses including variant burden and MEFV-related functional assays will be critical to further elucidate the biological pathways connecting auto inflammatory mechanisms with mesenteric lymph node responses. Prospective studies assessing colchicine responsiveness in relation to MLN patterns may also provide valuable prognostic information. Ultimately, a more refined understanding of MLN within the FMF disease spectrum may improve risk stratification, optimize follow-up strategies, and enhance individualized care for affected children (33).

Conclusion

MLN appears to be a common and clinically meaningful ultrasonographic finding in pediatric FMF, correlating with more pronounced abdominal and serosal symptoms rather than specific MEFV mutations. Its presence may signal heightened inflammatory activity, supporting its potential role as a complementary marker in clinical assessment and risk stratification. Future work should integrate biomarkers to refine phenotype characterization.

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No potential conflict of interest reported by the authors.

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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