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CASE REPORT

# A Unique Complex Variation Profile in a Patient with Familial Mediterranean Fever (FMF): Triple Homozygous E148Q-P369S-R408Q – "Case Report"

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**Abstract:** Familial Mediterranean fever (FMF) is an inherited autoinflammatory disorder resulting in recurrent fever, polyserositis, and arthralgias. It is caused by mutations in the *MEFV* (*Mediterranean Fever*) gene. We report a Lebanese pediatric patient with typical FMF symptoms and unique triple homozygous variations E148Q-P369S-R408Q in the *MEFV* gene. This is the second-ever reported case with this specific triple homozygous variation.

**Keywords:** familial Mediterranean fever, complex variation profile, triple homozygous, E148Q-P369S-R408Q

## Introduction

Familial Mediterranean fever (OMIM: 249100, FMF) is an inherited autosomal recessive autoinflammatory disorder characterized by episodes of recurrent fever, abdominal pain, and arthralgias. It is most prevalent in Mediterranean populations, particularly from Arab, Armenian, Jewish, and Turkish ancestry.[1,2] It is caused by mutations in the *MEFV* (*Mediterranean Fever*) gene, coding for pyrin, a cytoplasmic protein part of the pyrin inflammasome. Pyrin detects imbalances in cellular conditions induced by bacterial toxins, which triggers the assembly and activation of this inflammasome.[3] Five founder mutations (V726A, M694V, M694I, M680I, and E148Q) account for the majority of FMF cases.[4] Some of these mutations affect the function of the pyrin protein, leading to removal of the obligatory requirement for microtubules in inflammasome activation.[2,3] Consequently, activation of the pyrin inflammasome occurs in immune cells leading to subsequent release of pro-inflammatory cytokines in an antigen-independent manner.[5] This leads to inflammation in the serous membranes of multiple organs, in addition to fever. Most notably, the joints, abdomen and skin are involved resulting in synovitis, peritonitis and skin rashes in addition to pericarditis and pleuritis.[1,6] The most worrisome complications of this disease are organ dysfunctions and failure (kidneys and heart), in addition to the chronic long-term sequelae, namely amyloidosis and chronic arthritis. FMF most commonly presents in childhood (75% of patients have their first episode before age 10 and 90% before age 20).[7] The mainstay of treatment for FMF is daily oral colchicine.[8]

A large variety of genetic mutations have been implicated in the pathophysiology and development of FMF, most commonly in exons 2, 3, 5, and 10 of the *MEFV* gene. Moreover, more than one mutation is often found in the same patient, the most common being V726A, M680I, E148Q, M694V, and M694I.[4,9] To date, there are 404 variants that have been evaluated by a consensus of scientists; the data is available online at https://infevers.umai-montpellier.fr/.[10–14] The



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distribution and frequency of MEFV mutations vary significantly across different ethnic and geographic populations, often reflecting historical founder effects.[2,4] Armenians, Turks, Arabs, and Sephardic Jews tend to have higher frequencies of M694V and other exon 10 mutations.[4] In contrast, Ashkenazi Jews and certain Western European populations show a lower prevalence or different mutation spectrum.[2] A recent study by Feghali et al investigated the molecular spectrum of MEFV mutations in Lebanon, revealing a wide array of mutations including rare and complex alleles, and highlighted the challenge of defining clear-cut genotype–phenotype correlations in such a genetically diverse population.[15] Nevertheless, the study observed that M694V homozygosity and compound heterozygosity involving high-penetrance mutations were often linked to more severe clinical courses, whereas individuals with isolated E148Q or low-penetrance variants frequently exhibited milder or atypical features.[15] This was also described in a study from Turkey, where M694V homozygotes had earlier onset, more frequent febrile attacks, and higher rates of amyloidosis compared to those with other genotypes.[16] Another study from Turkey by Aslan et al found that musculoskeletal involvement, particularly arthritis, was more frequent and severe in patients with complex or compound genotypes.[17]

Mutations in the *MEFV* gene may result in various genotypic configurations, which influence the clinical presentation of FMF. These configurations include homozygous, heterozygous, compound heterozygous, and/or complex alleles with various genotype–phenotype correlations.[14,18]

Here, we describe the presentation of a Lebanese child with typical symptoms of FMF and complex genotype (triple homozygous) in E148Q-P369S-R408Q. We report the second patient in the literature.[19]

## Case Description

A seven-year-old Lebanese boy with a history of recurrent fever and abdominal pain, sinopulmonary infections, chronic diarrhea, and rash presented to the clinic for evaluation. His illness started at the age of one year, with recurrent episodes of high-grade fever, occurring every 2–3 weeks, lasting between 3 and 5 days, associated with diffuse abdominal pain, and arthralgias involving the upper and lower extremities. He also suffered from chronic diarrhea for a period of two years. Previous colonoscopy and biopsy were negative. He had chronic maculopapular pruritic rash mostly on the extensor surfaces of the upper and lower extremities in sun-exposed areas. Moreover, he had poor growth, with a weight on the 11th percentile and height on the 7th percentile based on the WHO child growth standards.[20]

The parents are second-degree cousins, and the family history is relevant for a maternal cousin who was diagnosed with FMF (genetic testing not available).

## Diagnosis and Treatment

Work up included immune evaluation with quantitative immunoglobulins and flow cytometry for lymphocyte subpopulations to rule out immunodeficiency; results were within normal for age.

Screening for mutations in the *MEFV* gene was done at a commercial laboratory using the FMF Strip Assay (Reverse Hybridization) from ViennaLab Diagnostics GmbH. FMF StripAssay®., and real-time PCR Genotyping Kit (from DNA-Technology). (https://www.viennalab.com/home/ifu/fmf-stripassay-1 accessed 23 April 2025, and https://dna-technology.com/sites/default/files/mefv_en.pdf, accessed 23 April, 2025).

The FMF Strip Assay screens for the twelve most common mutations in the *MEFV* gene, covering up to about 95% of the common mutations in Lebanese, Armenians, Arabs, Turks, and North Africans. Thus, it does not exclude the presence of any other unidentified rare mutations not accounted for by this method. The patient was found to have a complex genotype with triple homozygous variations in E148Q (c.1123G>A), P369S (c.1105 C>T), and R408Q (c.442G>C). He was started on oral colchicine at a dose of 1 mg per day. He demonstrated an adequate response to treatment, as the severity of his symptoms improved progressively, and he became symptom-free after two months on treatment. The patient's international severity score for FMF (ISSF) was 7 prior to initiating colchicine (severe disease). At the most recent follow-up, the ISSF score went down zero.[21,22]

## Discussion

FMF is diagnosed based on clinical manifestations, genetic testing, and response to colchicine.[23] The results of the genetic testing may be puzzling sometimes, specifically in the presence of a heterozygous mutation in the *MEFV* gene; or

the findings of a variant of unknown significance (VUS). In addition, compound heterozygous or complex alleles may be associated with variable genotype–phenotype presentations.[18,24]

Our patient's clinical presentation fulfilled the diagnostic criteria for FMF in children. We used the Tel-Hashomer criteria for adults, the pediatric criteria described by Livneh, and the New Eurofever/PRINTO classification criteria for hereditary recurrent fevers.[25–27]

Although skin rashes are not typical features in patients with FMF; erysipelas-like skin rashes have been described in some patients.[28] As for the diarrhea, we reported previously patient with severe colitis and FMF.[29] In patients with FMF, the chronic diarrhea might be due to amyloid deposition in the intestinal wall leading to bacterial overgrowth. Even children without amyloidosis might have gastrointestinal mucosal involvement that could be attack-related; this could explain our patient's normal colonoscopy findings.[30]

Our patient is triple homozygous for three variations: E148Q, P369S, and R408Q in the *MEFV* gene. Only one patient with FMF has been reported in the medical literature with the same triple homozygous mutations (E148Q-P369S-R408Q).[19] Karaer et al conducted a fragment analysis in the southeast of Turkey to determine the 19 most common variants of the *MEFV* gene in patients diagnosed with FMF in the Turkish population. Among the 6660 patients included in the study, only one patient had the triple homozygous mutation: E148Q-P369S-R408Q identical to our patient.[19] No clinical information, phenotypic manifestations, or medical history was provided regarding this patient. This particular complex allele containing the three different mutations – E148Q-P369S-R408Q – was first described in 1999 in *cis* configuration in one Armenian patient with FMF.[31] The same complex mutation profile in heterozygous state was subsequently described in one Japanese patient in a study evaluating the clinical and genetic characteristics of 80 Japanese patients with FMF.[32]

Moreover, there is one report of a patient of Ashkenazi Jewish ancestry with triple mutations at the same loci as our patient, who presented with fever, severe abdominal pain, and vomiting. However, he had triple heterozygous mutations in *cis* configuration.[33]

In addition to patients with typical FMF symptoms, the complex allele mutations E148Q- P369S-R408Q was described in heterozygous state in several patients with atypical FMF symptoms, and/or patients with periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA).[34–38]

To explore how unique our patient's MEFV variations might be, we examined previously reported cases of complex triple mutations in the *MEFV* gene. A cohort study on 10.370 Armenian patients with FMF found a large genotype distribution, including 58.26% compound heterozygous genotypes and only sixteen patients with complex triple mutations (0.16%),[39] with none of the patients showing the triple homozygous mutation E148Q-P369S-R408Q found in our patient.

Moreover, G. Celep et al evaluated *MEFV* gene mutations in 213 children from the middle northern region of Turkey. Out of the 213 patients, only two patients had a triple homozygous mutation, namely R202Q-M694V-K695R and R202Q-V726A-M694V, which are different from the mutations of our patient.[40]

Sabbagh et al investigated the *MEFV* gene mutation spectrum in a cohort of Lebanese patients referred for FMF evaluation, a group comparable to our Lebanese patient. Among the 266 patients analyzed, mutations were identified in 129 patients, with only two presenting a triple heterozygous mutation (E148Q-I692del-V726A), a combination distinct from that of our patient.[41]

A recent retrospective analysis conducted on 3167 Lebanese patients found that M694V and V726A were the most common variants (accounting each for 28.98% of the cases), followed by E148 (27.83%) and M694I (13.98%).[15] Whereas, variants in P369S were present in only 3.04% of the cohort. In this large cohort, 20 patients were reported to have complex genotypes with no details regarding specific variants.[15] Each of the three variants—E148Q (exon 2), P369S, and R408Q (both exon 3)—has individually been associated with variable clinical impact. E148Q, in particular, is the most debated MEFV variant: while some studies consider it a benign polymorphism, others suggest a potential pathogenic role, especially in compound or complex allelic contexts.[15,42,43] It has been proposed that E148Q may act as a low-penetrance mutation or disease modifier rather than a fully pathogenic variant. Likewise, P369S and R408Q have been reported in individuals with atypical FMF phenotypes and in non-FMF autoinflammatory conditions.[37] However, when present together in *cis*, particularly with E148Q, the complex allele may exert a cumulative or synergistic effect on pyrin function.[44]

As for the influence of the E148Q, P369S, and R408Q mutations collectively on the pyrin protein function, we speculate that the triple homozygous mutations E148Q-P369S-R408Q in the *MEFV* gene will change the configuration of the protein leading to dysregulation in the inflammasome.

Although each variant is individually classified as a variant of uncertain significance (VUS), their co-occurrence in homozygosity, along with a well-defined phenotype and therapeutic response, supports a potential pathogenic role of this specific allele configuration. Further functional and segregation studies are necessary to confirm this hypothesis. While bioinformatics tools would have offered additional insights into the potential deleterious effects of this complex variation; these analyses require specialized expertise and resources not readily available in our clinical setting.

Despite these limitations, the importance of this case report lies in its novelty and potential contribution to the understanding of genotype–phenotype correlations in FMF. To our knowledge, this is only the second report in the literature describing a patient with the triple homozygous E148Q-P369S-R408Q mutation, and the first to provide a comprehensive clinical characterization, including symptomatology, diagnostic workup, and response to colchicine therapy. The documentation of such rare genotypes and their associated phenotypes is critical, particularly given the ambiguity surrounding the pathogenicity of individual and compound MEFV variants classified as VUS. Our report underscores the value of detailed case studies in expanding clinical and genetic knowledge, especially in underrepresented populations such as the Lebanese cohort.

A further limitation of this case report is that parental genetic testing could not be performed owing to financial constraints.

## Conclusion

In conclusion, we report a pediatric Lebanese patient with typical FMF symptoms and a unique triple homozygous variations E148Q-P369S-R408Q in the *MEFV* gene. In addition to shedding light on the importance of comprehensive genetic testing, the presentation of this patient highlights the need for further research to elucidate the clinical significance of these genomic alterations in pediatric patients with FMF.

## Data Sharing Statement

The datasets generated for this study are available on request to the corresponding author.

## Ethics Statement

A written informed consent was obtained from the patient's father for the publication of this case report.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. To note that Nour Abi-Chakra and Nadine Yazbeck contributed equally to this work as first authors.

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## Disclosure

The authors report no conflicts of interest in this work.

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