RESEARCH ARTICLE

# The cumulative effects of *MEFV* gene polymorphisms and mutations in patients with inflammatory bowel diseases

Mehmet Agin[1], Atil Bisgin[2], Mustafa Yilmaz[3], Aylin Kont Ozhan[4], Ferid Mammadov[5], Gokhan Tumgor[6]

## Abstract

**Objective:** To determine the cumulative effects of Mediterranean fever gene polymorphisms and mutations in patients with ınflammatory bowel diseases.

**Methods:** The case-control study was conducted from January, 2012, to January, 2016,at Cukurova University, Turkey, and comprised patients diagnosed with inflammatory bowel diseases and followed up at the Children Gastroenterology Department. By using molecular methods, 12 Mediterranean fevergene variants most frequently observed in the country were examined in all the diagnosed cases. The results were compared with age-matched healthy population data from the Genetic Diseases Diagnosis and Treatment Centre. Data was analysed using Graph Pad Prism.

**Results:** Of the 151 subjects, 46(30.4%) were cases and 105(69.5%) were controls. Among the cases, there were 23(50%) subjects with a mean age of 14.8±3 years who had ulcerative colitis, and 23(50%) with mean age 14.5±3.2 years who had Crohn's disease. The mean age of the controls was 16.4±3.2 years (p=0.716). Patients with ulcerative colitishad high frequencies of C allele in D102D T>C variant, G allele in G138G A>G variant, A allele in A165A C>A variant and A allele in R202Q G>A variant. Those with Crohn's disease frequently had wild type of R202Q G>A variant. Also, D102D T>C / R314R C>T haplotype was common at a certain level in the UC group.

**Conclusions:** Mediterranean fever gene variant was more frequently found in cases with ulcerative colitis compared to the controls.

**Keywords:** MEFV, IBD, FMF, Polymorphism, Children. (JPMA 71: 479; 2021) **DOI: https://doi.org/10.47391/JPMA.762**

## Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are chronic repetitive diseases caused by the regulation defects of the mucosal immune response which increase against the bacterial antigens in bowel lumen in patients with genetic susceptibility.[1]

Familial Mediterranean Fever (FMF) is the prototype of the inflammatory clinical syndromes and is characterised by joint, chest and abdominal pain.[2] The pyrin protein, which is also known as marenostrin, is encoded by the Mediterranean fever (MEFV) gene.

Experiments performed on animal models and cell lines, as well as the presumed structure of pyrin and the presence of certain protein domains, suggest that the wild type (WT) of the protein has anti-inflammatory properties.[3] Pyrin functions via its caspase recruitment domain (CARD). Both the MEFV and nucleotide-binding oligomerisation domain-containing protein 2 (NOD2)/CARD15 genes are suspected for CD. Additionally, their genetic products are structurally similar (pyrin and NOD2/CARD15), and both belong to the family that regulates apoptosis. They play a key role in processing cytokines and the regulation of inflammation.Mutations in the MEFV gene are responsible for a disease of innate immunity, and are associated with activation in the interleukin -1 (IL-1) beta (β) pathway allowing an uninterrupted inflammatory cascade and resulting in attacks of severe inflammation.[4]

It has been shown that MEFV gene mutations causing FMF can also be found in other autoimmune diseases. It is considered that MEFV could be a potential inflammatory bowel disease (IBD) in line with both epidemiological and clinical data. FMF and IBD have similar clinical and biological features. Chronic inflammation episodes occur during the course of both diseases and neutrophil migration and collapsed apoptosis mechanisms are encountered in the defected areas.[5] In 2001, it was determined that NOD/CARD15 is a CD gene localised on chromosome 16 and encodes the NOD2/CARD15 protein. This gene is responsible for the natural immune response and transcription factor nuclear factor kappa B (NFkB) activation in apoptosis. According to literature, 1/3rd of CD patients are NOD2/CARD15 gene mutation carriers.[6] UC is more common in families who have individuals with UC and seen more frequently in specific ethnicities, such as Jewish, indicating that the disease has a genetic basis. Although more than 30 IBD-related genes were

[1,5,6]Department of Pediatric Gastroenterology, Hepatology and Nutrition, Cukurova University, Turkey; [2]Department of Medical Genetics, Cukurova University, Turkey; [3]Department of Pediatric Rheumatology, Cukurova University, Turkey; [4]Department of Pediatric Allergy and Immunology, Cukurova University, Turkey.

**Correspondence:** Mehmet Agin. e-mail: drmehmet47@yahoo.com

determined, the roles of these genes are not completely described.[7] Pyrin and NOD2/CARD15 proteins are structurally similar and have a key role in apoptosis regulation, cytokine processing, and inflammation. Any mutations and polymorphisms in MEFV gene alleles are considered to be related to subclinical inflammation.[8]

The relation between IBD and MEFV gene mutations has been studied extensively, but no study was found in literature on clinical and laboratory values of MEFV gene polymorphisms and its relation with the high-risk groups in IBD cases. The current study was planned to determine the cumulative effects of MEFV gene polymorphisms and mutations in IBD patients.

## Patients and Methods

The case-control study was conducted fromJanuary, 2012, to January, 2016 at Cukurova University, Turkey. After approval from the institutional ethics review committee, the sample was raised from among IBD patients aged 2-18 years who consented to undergo upper and lower gastrointestinal track (GIT) endoscopy. Those with missing data or not consenting to participate were excluded.

All the patients were followed up at the Children Gastroenterology Department in the Faculty of Medicine, in line with the previously determined endoscopic, histological and radiological criteria.[9] Demographic, clinical and laboratory features of patients were evaluated. Complete blood count (CBC), sedimentation rate, C-reactive protein (CRP), total protein, albumin, immunoglobulin G (IgG) values were determined in all cases. Laboratory, clinical and demographic data of the patients, who were diagnosed with both IBD and FMF were compared with IBD-only cases.

The cases were classified into two groups as UC and CD patients. As the next step, the most common 12 MEFV gene variants were investigated in both groups using molecular genetic techniques. Finally, polymorphisms from each group were compared with age-matched healthy population data from Cukurova University's Adana Genetic Diseases Diagnosis and Treatment Center.

Genomize-Seq and 1000 Genome Frequency were used for the analyses of each variant frequencies. Peripheral blood samples were collected with ethylenediaminetetraacetic acid(EDTA)-treated tubes from all patients, and deoxyribonucleic acid (DNA) was isolated from peripheral blood lymphocytes. MEFV gene exons 2, 3, 5 and 10 were studied with multiplex polymerase chain reaction (MPCR). E148Q, G138G, A165A, R202QD102D amino acid changes in exon 2, R314R amino acid change in exon 3, E474E, Q476Q, D510D amino acid changes in exon 5, and M694V, A744S, V726A, K695R amino acid changes in exon 10 were examined. ClinCalc[10] was used to determine the post-hoc power of the study and to apply the Bonferroni correction.

Data was anlaysed using Graph Pad Prism software. Hardy Weinberg Equilibrium (HWE) analysis was performed for each variant identified. A modified version of the human genome was used as the major allele population-specific reference.[11] Confidence Interval (CI) was used as 95% to estimate the precision of the odds ratio (OR). Chi-square test was used to test the frequencies of the alleles and the genotypes. Statistical significance level was set at $p \leq 0.05$.

## Results

Of the 151 subjects, 46(30.4%) were cases and 105(69.5%) were controls. Among the cases, there were 23(50%) UC subjects with a mean age of 14.8±3 years, and 23(50%) CD subjects with mean age 14.5±3.2 years ($p$= 0.518). The mean age of the controls was 16.4±3.2 years (p=0.716). Age, white blood cell (WBC) count, haemoglobin (Hb), sedimentation, CRP, IgG, total protein and albumin value were not significantly high between UC and CD groups. FMF was observed in 6(13%) cases; 3(50%) UC, and 3(50%) CD. All 3(100%) CD cases 2(66.6%) UC patients were M694V homozygous-positive. Also, 1(4.3%) UC patient was homozygous-positive in respect to D102D, G138G and A65A in exon 2, and R314R in exon 3. Mean age of IBD-FMF patients was 16.6±4.3 years, and in IBD-only patients it was 14.4±2.9 years ($p$=0.513).

The most frequently seen symptoms in IBD-FMF patients and IBD-only patients were abdominal pain and diarrhoea. Sedimentation, CRP, IgG of IBD-FMF patients were significantly high compared to IBD-only patients (Table 1).

There was no effect on age, clinical and laboratory values when MEFV gene mutations and polymorphisms were compared between UC and CD groups ($p$>0.05). MEFV

**Table-1:** Comparison of age and laboratory values of Inflammatory Bowel Disease (IBD) and IBD-Familial Mediterranean Fever (FMF) cases.

| | IBD Mean±SD | IBD-FMF Mean± SD | *p*-value |
|---|---|---|---|
| Mean Age (years) | 14.4 ±2.9 | 16.6±4.3 | 0.513 |
| Mean Age of onset | 13.4±2.7 | 14.5±3.9 | 0.170 |
| WBC | 10515±2502 | 12777 ± 2340 | 0.59 |
| Hb | 10.4 ±1.9 | 12.4±1 | 0.05 |
| Thrombocyte | 550737 ±155909 | 476358 ±89278 | 0.06 |
| Sedimentation | 44.7±21.4 | 117±41.6 | 0.039 |
| CRP | 3.8±3.2 | 11.2±4.8 | 0.039 |
| Ig G | 1571±403 | 2309±300 | 0.02 |
| Total Protein | 8 ±0.8 | 8±0.9 | 0.160 |
| Albumin | 3.3±0.6 | 3.7±0.7 | 0.667 |

WBC: White blood cell count; Hb: Haemoglobin; CRP: C-reactive protein; IgG: Immunoglobulin G; SD: Standard deviation.

**Table-2:** Frequencies of Mediterranean Fever (MEFV) variants in Ulcerative Colitis (UC) and Crohn's Disease (CD) cases.

| MEFV variants | UC n (%) | CD n (%) | IBD n (%) |
|---|---|---|---|
| R314R | 18 (22 %) | 17 (23 %) | 35 (22 %) |
| A165A | 13 (16 %) | 16 (22 %) | 29 (18 %) |
| D102D | 14 (17 %) | 13 (18 %) | 27 (17 %) |
| G138G | 13 (16 %) | 13 (18 %) | 26 (17 %) |
| R202Q | 11 (13 %) | 4 (5 %) | 15 (10 %) |
| M694V | 3 (3 %) | 3 (4 %) | 6 (4 %) |
| E148Q | 1 (1 %) | 2 (3 %) | 3 (2 %) |
| E474E | 2 (2 %) | 1 (1 %) | 3 (2 %) |
| R408Q | 1 (1 %) | 1 (1 %) | 2 (1 %) |
| P369S | 1 (1 %) | 1 (1 %) | 2 (1 %) |
| Q476Q | 2 (2 %) | - | 2 (1 %) |
| D510D | 2 (2 %) | - | 2 (1 %) |
| A744S | 1 (1 %) | 1 (1 %) | 2 (1 %) |
| V726A | | 1 (1 %) | 1 (1 %) |
| K695R | 1 (1 %) | | 1 (1 %) |
| | 83 (100%) | 73 (100 %) | 156 (100 %) |

IBD: Inflammatory Bowel Disease.

mutation frequencies in all IBD patients were noted (Table 2). All frequencies were significantly low ($p<0.01$)

There was a trend towards higher frequency of C allele of D102D T>C, the G allele of the G138G A>G, A allele of the A165A C>A and A allele of the R202Q G>A in UC patients, but in CD patients, WT R202Q G>A was observed in most cases (Table 3).

An association was detected on a genotypic level with heterozygous carriers for R314R C>T in exon 3 with a significantly higher risk of having UC. No significant difference in genotype and allele frequencies of R314R C>T was observed in UC cases compared to CD ($p>0.05$).

There was a high degree of linkage disequilibrium between the two studied Single nucleotide polymorphisms(SNPs) in the UC group. Marginally significant differences were detected in the frequency of carriers of D102D T>C / R314R C>T haplotype between UC and CD ($p<0.05$), suggesting that haplotype had a significantly higher risk of having UC ($p<0.05$).

## Discussion

IBD and FMF are repetitive diseases with periodic symptoms. Genetic screening is needed to determine MEFV gene mutations, especially among Mediterranean populations due to the fact that FMF is more frequently observed in IBD patients in the Mediterranean region. It has been shown that MEFV mutations have an effect on the course of disease among IBD patients. Epidemiological findings among Non-Ashkenazi Jewish indicate that IBD is more common, and causes more severe symptoms in patients with FMF.[12] Mutations in genes like MEFV can cause severe inflammatory diseases, serve a critical function in CD and UC onsets. It has been shown that MEFV expression increases in direct proportion to the severity of the inflammation in previous experiments on animal models in case of colitislike CD and UC. MEFV gene's role in other inflammatory diseases than IBD has also been shown. It was also reported that MEFV mutations were mostly detected in autoimmune diseases.[8,13]

Several genes that increase IBD susceptibility were determined with genetic studies. The first genes which were observed were NOD2 variants. NOD2 gene's role in CD has been shown yet, and its relation with UC is still unknown. The next findings were IL23R, IL-17R, and IL10R which induce CD. All the data and results can only explain the hereditary transition partially.[6,14]

Fidder et al. identified that M694 mutation was the most frequent in CD-FMF cases, while Salah et al. asserted E148Q.[15,16] Giaglis et al. detected M694V and M680I mutations as the most frequent mutations in UC cases.[17] Another study showed that 19 UC cases of 54 had MEFV mutations, and E148Q was the most frequent.[12] The prevalence of FMF in Turkey is 1/1000, and the carrier frequency is 1/5. The most frequent mutation among symptomatic FMF cases is M694V. M694V mutation ratios are 3% and 51% in healthy and symptomatic patients, respectively.[18,19] Other mutations found were 45% M694V; 13% M680I; 11% V726A; 7% M694I; 12% E148Q; 5% M680I; 3% M694V; and 2% V726A.[20] According to our results, there were differences between 2% and 7% in the healthy age-matched population. Beser et al. detected mutation M694V in 41.7% of IBD-FMF cases.[21]

We found homozygous-positive 3 patients each in UC and CD groups. These 3 patients with CD were M694 homozygous-positive; 2 of 3 cases with UC were M694V

**Table-3:** Frequencies of polymorphic alleles and genotypes in Ulcerative Colitis (UC) and Crohn's Disease (CD) cases.

| | Exon 2 D102D T>C | | | Exon 2 G138G A>G | | | Exon 2 A165A C>A | | | Exon 2 R202Q G>A | | | Exon 3 R314R C>T | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | TT | TC | CC | AA | AG | GG | CC | CA | AA | GG | GA | AA | CC | CT | TT |
| UC(n=23) | 7 | 13 | 3 | 8 | 13 | 2 | 8 | 12 | 3 | 12 | 11 | - | 4 | 15 | 4 |
| CD (n=23) | 12 | 7 | 4 | 12 | 7 | 4 | 11 | 8 | 4 | 19 | 4 | - | 7 | 10 | 6 |

homozygous-positive, and the 3rd patient had D102D, G138G, A65A homozygous mutations in exon 2 and R314R homozygous mutation in exon 3. Colchicine treatment was administrated to the 3rd UC patient, who was resistant to therapy, to address the abdominal pain with fever. This might be the result of a cumulative effect that if a patient carrying a combination of polymorphisms and mutation that would favour more inflammation, thus, act as a predisposing genetic factor or to have a more aggressive course through a complex genetic trait.

All the mutations in MEFV-related studies with IBD were investigated, and no study was found in literature on polymorphic genes. Studies about other inflammatory diseases were very few.[20-24] The current study's data had very important points from a practical and clinical point of view to identify the possible mechanism of susceptibility and maintenance of IBD.

Most polymorphisms, such as D102D, G138G, A165A, and R202Q, are located in exon 2. D102D, G138G and A165A polymorphisms are synonymous variants. Basarslan et al. showed that D102D, G138G and A165A polymorphisms are more frequent in FMF cases.[22] In another study on FMF patients with G138G polymorphism, it was reported that these patients were more susceptible to amyloidosis.[23] Oksuz et al. found that A165A and G138G polymorphisms were more frequent in FMF cases, but could not find any relation with FMF.[24] Similarly, Ozturk et al. found no relation between R202Q polymorphism and FMF clinic.[25]

It is considered that R202Q is not a pathogenic mutation and it is substantially common. Previous studies have not shown clinical significance of R202Q, but in some studies, it is considered one of the causes of disease in case the mutation is homozygous.[26] E148 mutation frequency is detected as 9-27% in Turkey.[27,28] Matsuda et al. determined periodic peritonitis and colchicine response relations with E148Q, R202D, P369S and R408Q mutations in exon 2 and 3 in SLE case.28 Whether E148Q is the main gene causing the disease or it is just a polymorphism is still not clear. Ben-Chetrit and Tchernitchko et al. reported that E148Q is a polymorphism, and has no relation with the disease.[29,30]

MEFV polymorphisms are more frequent in other autoimmune diseases than in the healthy population. We observed that polymorphic genes were similar in CD, but D102D, G138G and A165A mutations in UC cases tended to increase.

Fidder et al. reported that FMF-CD patients had more frequent attacks and higher amyloidosis development, and CD onsets were earlier in FMF combined CD patients than CD patients who were not diagnosed with FMF.[15] We did not detect amyloidosis development in any IBD-FMF cases. The age of diagnosis was higher in IBD-FMF patients than in IBD patients. We consider the similarity in those two diseases may cause complications and end with later diagnosis.

It was reported that acute-phase reactants increased between FMF and FMF carriers.[31] We investigated whether there is a relation between FMF gene mutations, inflammation markers and the clinical tables. It was determined that the inflammation marker values were higher in IBD-FMF cases than in IBD cases. No relation between FMF gene mutation and polymorphic genes was determined.

Previous studies have shown that IBD is more prevalent among males.[21] Similarly, the gender distribution in the current study was similar, and male prevalence was observed in both CD and UC cases. Abdominal pain and diarrhoea were the most common symptoms in both IBD and IBD-FMF cases.

The frequency of MEFV gene variants was higher in UC cases compared to the healthy population. It is necessary to broaden the scope of haplotyping studies to determine the high-risk groups of UC and provide genetic counseling with better understanding. If the acute-phase reactants are high despite the treatment, it should be considered that IBD and FMF may occur simultaneously.

## Conclusion

MEFV gene variant was more frequently found in UC cases compared to the age-matched healthy controls.

**Disclaimer:** None.

**Conflict of Interest:** None.

**Source of Funding:** None.

## References

1. Podolsky DK. Inflammatory bowel disease. N Engl J Med 2002; 347: 417-29
2. Livneh A, Langevitz P, Zemer D, Zaks N, Kees S, Lidar T, et al. Criteria for the diagnosis of familial Mediterranean fever. Arthritis Rheum 1997; 40: 1879-85.
3. Chae JJ, Komarow HD, Cheng J, Wood G, Raben N, Liu PP, et al. Targeted disruption of pyrin, the FMF protein, causes heightened sensitivity to endotoxin and a defect in macrophage apoptosis. Mol Cell 2003;11: 591-604
4. Chae JJ, Wood G, Masters SL, Richard K, Park G, Smith BJ, et al. The B30.2 domain of pyrin, the familial Mediterranean fever protein, interacts directly with caspase-1 modulate IL-1 beta production. Proc Natl Acad Sci USA 2006; 103: 9982–7.
5. Lichtenberger GS, Flavell RA, Alexopoulou L. Innate immunity and apoptosis in IBD. Inflamm Bowel Dis 2004; 10 Suppl 1: S58-62.
6. Ogura Y, Bonen DK, Inohara N, Nicolae DL, Chen FF, Ramos R, et al. A frameshift mutation in NOD2 associated with susceptibility to Crohn's disease. Nature 2001; 411: 603-6.

7. Barrett JC, Hansoul S, Nicolae DL, Cho JH, Duerr RH, Rioux JD, et al. Genome-wide association defines more than thirty distinct susceptibility loci for Crohn's disease. Nat Genet 2008; 40: 955-62.
8. Ozen S, Bakkaloglu A, Yilmaz E, Duzova A, Balci B, Topaloglu R, et al. Mutations in the gene for familial Mediterranean fever: do they predispose to inflammation? J Rheum 2003; 30: 2014–8.
9. Levine A, Koletzko S, Turner D, Escher JC, Cucchiara S, de Ridder L, et al. ESPGHAN revised Porto criteriaforthediagnosis of inflammatory-boweldisease in childrenandadolescents. J Pediatr Gastroenterol Nutr 2014; 58: 795-806.
10. Post-hoc Power Calculator. [Online] [Cited 2016 July 10]. Available from: URL: https://clincalc.com/stats/Power.aspx
11. Varsome. [Online] [Cited 2016 July 10]. Available from: URL:https://varsome.com/search-results/human%20genome.
12. Yıldırım B, Tuncer C, Kan D, Tunc B, Demirag MD, Ferda Percin E, et al. MEFV gene mutations and its impact on the clinical course in ulcerative colitis patients. Rheumatology 2011; 31: 859-64.
13. Ayaz NA, Ozen S, Bilginer Y, Ergüven M, Taşkiran E, Yilmaz E, et al. MEFV mutations in systemic onset juvenile idiopathic arthritis. Rheumatology 2009; 48: 23-5.
14. Anderson CA, Boucher G, Lees CW, Franke A, D'Amato M, Taylor KD, et al. Meta-analysis identifies 29 additional ulcerative colitis risk loci, increasing the number of confirmed associations to 47. Nat Genet 2011; 43: 246-52.
15. Fidder HH, Chowers Y, Lidar M, Sternberg M, Langevitz P, Livneh A. Crohn disease in patients with familial Mediterranean fever. Medicine (Baltimore) 2002; 81: 411-6.
16. Salah S, El-Shabrawi M, Lotfy HM, Shiba HF, Abou-Zekri M, Farag Y. Detection of Mediterranean fever gene mutations in Egyptian children with inflammatory bowel disease. Int J Rheum Dis 2016; 19: 806-13.
17. Giaglis S, Mimidis K, Papadopoulos V, Thomopoulos K, Sidiropoulos P, Rafail S, et al. Increased frequency of mutations in the gene responsible for familial Mediterranean fever (MEFV) in a cohort of patients with ulcerative colitis: evidence for a potential disease-modifying effect? Dig Dis Sci 2006; 51: 687-92.
18. Tunca M, Akar S, Onen F, Ozdogan H, Kasapcopur O, Yalcinkaya F, et al. Turkish FMF Study Group (2005) Familial Mediterranean fever (FMF) in Turkey: results of a nationwide multicenter study. Medicine 2005; 84: 1-11.
19. Yilmaz E, Ozen S, Balci B, Duzova A, Topaloglu R, Besbas N, et al. Mutation frequency of Familial Mediterranean Fever and evidence for a high carrier rate in the Turkish population. Eur J Hum Genet 2001; 9: 553-5.
20. Y ilmaz E, Ozen S, Balci B, Duzova A, Topaloglu R, Besbas N, et al. Mutation frequency of Familial Mediterranean Fever and evidence for a high carrier rate in the Turkish population. Eur J Hum Genet 2001; 9: 553-5.
21. Beser OF, Kasapcopur O, Cokugras FC, Kutlu T, Arsoy N, Erkan T. Association of inflammatory bowel disease with familial Mediterranean fever in Turkish children. J Pediatr Gastroenterol Nutr 2013; 56: 498-502.
22. Basarslan F, Yengil E, Gogebakan B. Evaluation of the patients with the diagnosis of familial Mediterranean fever in clinical and genetic aspects. Symrna Med J 2013; 2: 1-6.
23. Akar E, Yalcinkaya F, Akar N. Is the Ala138Gly alteration of MEFV gene important for amyloidosis? Hum Mutat 2001; 17: 71.
24. Oksuz MF, Karkucak M, Gorukmez O, Ocakoglu G, Yıldız A, Ture M, et al. Investigation of MEFV gene polymorphisms (G138G and A165A) in adult patients with familial mediterranean fever. Rev Bras Reumatol Engl Ed 2017; 57: 501-6.
25. Ozturk A, Ozcakar B, Ekim M, Akar. Is MEFV gene Arg 202 Gln(605 G>A) a disease causing mutation? Turk J Med Sci 2008; 38: 205-8.
26. Yigit S, Karakus N, Tasliyurt T, Kaya SU, Bozkurt B, Kisacik B. Significance of MEFV gene R202Q polymorphism in Turkish Familial Mediterranean fever patients. Gene 2012; 506: 43-5.
27. Atagunduz P, Ergun T, Direskeneli H. MEFV mutations are increased in Behcet's disease (BD) and are associated with vascular involvement. Clin Exp Rheumatol 2003; 21(4 Suppl 30): S35-7.
28. Matsuda M, Kishida D, Tsuchiya-Suzuki A, Fukushima K, Shimojima Y, Yazaki M,et al. Periodic peritonitis due to familial Mediterranean fever in a patient with systemic lupus erythematosus. Intern Med 2010; 49: 2259-62.
29. Ben-Chetrit E, Lerer I, Malamud E, Domingo C, Abeliovich D. The E148Q mutation in the MEFV gene: is it a disease-causing mutation or a sequence variant? Hum Mutat 2000;15: 385–6.
30. Tchernitchko D, Legendre M, Cazeneuve C, Delahaye A, Niel F, Amselem S. The E148Q MEFV allele is not implicated in the development of familial Mediterranean fever. Hum Mutat 2003; 22: 339-40.
31. Lachmann HJ, Sengul B, Yavuzsen TU, Booth DR, Booth SE, Bybee A, et al. Clinical and subclinical inflammation in patients with familial Mediterranean fever and in heterozygous carriers of MEFV mutations. Rheumatology (Oxford) 2006; 45: 746-50.