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Case Report

A Suspicious Familial Mediterranean Fever Case and Novel p.Y471X Mutation of MEFV Gene

Şüpheli Bir Ailesel Akdeniz Ateşi Olgusu ve MEFV Geninin Yeni p.Y471X Mutasyonu

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Familial Mediterranean fever (FMF, MIM249100) which is the prototype of a group of disorders termed ''systemic autoinflammatory diseases'' is characterized by seemingly unprovoked episodes of inflammation in the absence of high-titer autoantibodies or antigen-specific T cells. The disease is typically common among Mediterranean populations and extending through worldwide by genetic diagnosis reports. In this report, we present a 44-year-old female patient who was admitted with periodic fever in our clinic and diagnosed with FMF. For genetic diagnosis, FMF StripAssay® and DNA sequencing analysis method were used. DNA sequencing analysis of Mediterranean fever gene revealed a nonsense p.Y471X mutation which was featured as the second nonsense mutation in FMF mutation database. This underscored the significance of genetic analysis in the ancestral populations of FMF. An exact clinical and molecular diagnosis is critically essential for the accurate follow-up and treatment of FMF patients. Large scale screening analysis of nucleotide variations may also prevent novel variations from being overlooked.

Key words: Autoinflammatory diseases; Familial Mediterranean fever; MEFV; nonsense mutation; periodic fever.

Ailesel Akdeniz ateşi (AAA, MIM249100), "sistemik otoenflamatuvar hastalıklar" adıyla terimleşen bir grup hastalık prototipi olup, yüksek antikor oranı veya antijene özgü T hücreleri olmadan belirgin düzeyde tetiklenmemiş enflamasyon epizotlarıyla karakterizedir. Hastalık, tipik olarak Akdeniz toplumları arasında yaygındır ve genetik tanı raporları ile dünya çapında yayılmaktadır. Bu yazıda, periyodik ateş yakınmasıyla kliniğimize başvuran ve AAA tanısı konulan 44 yaşında bir kadın hasta sunuldu. Hastanın genetik tanısı için AAA strip analiz ve DNA sekanslama analiz yöntemi kullanıldı. Akdeniz ateşi geninin DNA sekanslama analizinde, AAA mutasyon veri tabanında ikinci anlamsız FMF mutasyonu olarak anlamsız bir p.Y471X mutasyonu tespit edildi. Bu, AAA'lı ata toplumlarda genetik analizin öneminin altını çizdi. Doğru klinik ve moleküler tanı, AAA'lı hastaların takip ve tedavisinde esastır. Geniş ölçekli nükleotid varyasyon taraması, yeni varyasyonların gözden kaçmasını önleyebilir.

Anahtar sözcükler: Otoenflamatuvar hastalıklar; Ailesel Akdeniz ateşi; MEFV; anlamsız mutasyon; periyodik ateş.

Familial Mediterranean fever (FMF) is considered to be one of the most prevalent innate immune system disorders and involves a systemic autoinflammatory reaction that affects the joints, skin, bones, and kidneys. Systemic amyloidosis, the most severe manifestation of the disease, commonly affects the kidneys (11% of cases), but FMF can sometimes involve the adrenals, intestines, spleen, lung, and testes.[1] Apart from the typical implications of the disease, there is increasing evidence regarding the expanding clinical spectrum of FMF that embraces unusual clinical characteristics.[2-4] These are rare presentations of the disease; therefore, the role of molecular analysis becomes more important, especially for suspicious and probable cases. While the disease is traditionally considered to have an autosomal recessive trait, there is increasing evidence that even one allele carrying one demonstrable mutation is sufficient to give rise to a clinical FMF phenotype. The clinical features associated with FMF could occur with the presence of one mutation in one allele, even if the disease has a recessive mode of inheritence. Thus, the results have given rise to the suggestion of a polygenic/complex

genetic trait/digenic inheritance, though other approaches to the investigation of a possible mutation on the second allele of the mediterranean fever (MEFV) gene have so far met with failure.[5-7] In this report, we present a 44-year-old female with periodic fever who was admitted to our clinic and who had participated in our previous comprehensive study.[8]

CASE REPORT

A 44-year-old female from western Turkey had experienced symptoms of short, rare episodes of fever, ongoing abdominal pain, temporary myalgia, and arthralgia since childhood. After her admission to our facility, a physical examination revealed no pathology except for arthritis in the right knee, and her weight, height, and blood pressure were normal. Primarily, she had been diagnosed as having conditions secondary to FMF. Although the screening of family and relatives is of great importance, her past history was noncontributory. She had previously undergone antibiotherapy, steroid treatment, and an appendectomy. The laboratory tests revealed the following acute phase reactants: WBC: 12.100/mm^3, ESR: 81 mm/h, SAA: 76 mg/dl, CRP: 3.46 mg/dl, and fibrinogen: 526 mg/dl. In addition, the patient's renal function tests and other biochemical parameters were normal. Except for StripAssay® tests performed at other centers, no other molecular genetic diagnostic tests had been conducted. Her clinical picture was not contributed to the start of colchicine since they did not fulfill most of the clinical criteria. Therfore, our laboratory performed an FMF StripAssay® test as the first stage of the mutation detection method since it can detect 12 common mutations. However, this revealed no particular mutation. Afterwards, a DNA sequence analysis was conducted revealing that p.Y471X was the responsible nonsense mutation in the MEFV gene (Figure 1). Colchicine therapy (1.5 mg/day) was then promptly started. The patient had no symptoms after this therapy and has continued to do well, with the acute phase reactants having been completely normal over the last three years. Because of the patient's positive treatment response, no tests were performed on other autoinflammatory genes such as mevalonate kinase (MVK), the tumor necrosis factor receptor superfamily 1A gene (TNFRSF1A), and the cold-induced autoinflammatory syndrome 1 (CIAS1) gene.

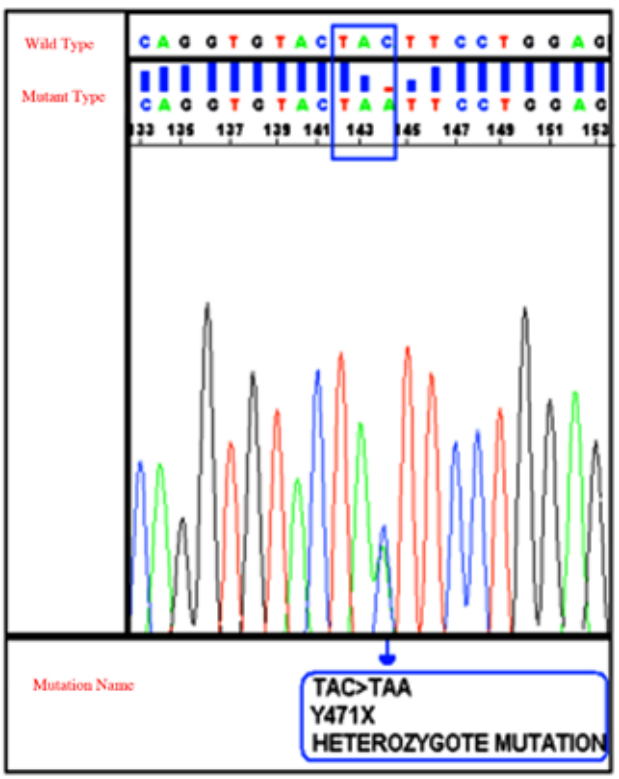

Figure 1. Electropherogram of MEFV gene revealed by DNA sequencing analysis in the Turkish patient.

DISCUSSION

In this report, we present the case of a 44-year-old female who had participated in our previous comprehensive study that involved a large-scale heterogeneous group of 5518 patients[8] who had a clinical pre-diagnosis of FMF that originated from unrelated families with first-degree relatives who had been referred to the Molecular Medicine Laboratory for genetic diagnosis between the years of 2002 and 2009 from various regions throughout Turkey. These cases included suspicious, possible, and definitive cases identified via the family screening.

Our case had been misdiagnosed, particularly during childhood, and a lot of time had been wasted undergoing many unnecessary operations and treatments. Therefore, a definitive diagnosis as determined by detailed DNA sequence analysis is essential for suspicious and undefined cases and for those who had only undergone limited screening methods. The molecular analysis of the MEFV gene c.1413C>A in our previous study identified a nucleotide change in exon 5 resulting in a p.Tyr471X nonsense mutation (Figure 1).

The p.Y471X nonsense mutation in the MEFV gene is the first to be noted in Turkish FMF patients, and the second nonsense mutation in the FMF mutation database worldwide. Inherited missense mutations reported in the fifth exon of the MEFV gene in FMF patients are very rare. Though the fifth exon of the gene could not be called a critical region that carries mutational hotspots, this result could demonstrate that there is still much to be learned about the hidden side of FMF. The novel p.Y471X mutation in

exon 5 of the MEFV gene, located in the coiled-coil domain of the pyrin protein, has been implicated when actin-binding proteins interact selectively with monomeric or multimeric forms of actin. Since the effects of nonsense mutations in the amino acids are known to be damaging and pathogenic, we did not use the Polymorphism Phenotyping (PolyPhen) software[9] to evaluate the potential pathogenicity of this newly found amino acid substitution, although we do this regularly in our laboratory. Nevertheless, expression studies will need to be conducted at a future time.

Due to the abundance of mutations in exon 10 and the clinical heterogeneity of the disease, different screening methods have been developed. The majority of FMF patients in classically affected populations are screened by routine methods for only common mutations. This primarily targets only the most prevalent MEFV mutations in a specific population; therefore, rare or novel mutations can be overlooked. The first nonsense mutation in the FMF era, Y688X, was evaluated by Notarnicola et al.[10] in 2000, and it was suggested that it was located between hot spots for FMF mutations (codons 680 and 694) in exon 10. This finding contributed to the critical role of exon 10 functioning as a hotspot for MEFV. Hence, we determined that the newly found p.Y471X nonsense mutation had a great significance in screening asymptomatic individuals since it was not found in one of the hot spots of MEFV gene.

In conclusion, our findings showed that by using sequencing analysis, detection of common major mutations as well as rare mutations can be carried out. This is significant, especially for at-risk populations. In Turkish patients, this type of analysis would be beneficial when screening for the most common mutations does not reveal any known common disease-causing mutation. In addition, it could also prove to be significant for those patients who lack the typical phenotype due to various reasons (e.g., the effect of other autoinflammatory genes, a resemblance to FMF, or a reduction in penetrance or variable expressivity). Furthermore, specific DNA sequencing mutation screening covering entire coding exons and exon-intron flanking regions should be considered. Therefore, while searching for common mutations that underlie typical attacks, such as abdominal pain, myalgia, arthralgia, and fever, and finding nothing along the gene, we do not suggest that the involvement of other recurrent fever genes be considered before completing the detailed entire coding sequence analysis of the MEFV gene so as to be informed about possible rare FMF mutations, particularly for genetically and clinically heterogenous FMF patient populations like those found in Turkey.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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