

A Mild form of Familial Mediterranean Fever Associated with a Polymorphisms C.Nt 1588,-69G>

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2. Key words

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1. Abstract

Familial Mediterranean fever (FMF) is an autosomal recessive autoinflammatory disease caused by mutation(s) in the Mediterranean fever (MEFV, pyrinmarenostrin) gene. FMF is characterized by recurrent fever crisis combined with serosal, synovial, or cutaneous inflammation. Until now more than 304 sequence variants have been recorded. Here, we describe a case of mild FMF confirmed by analysis of the MEFV gene, characterized by polymorphism c1588-69G>A. The patient had a good answer to the treatment with colchicine, that, unfortunately, he stopped for severe gastrointestinal side effects. The detection of polymorphism for intron 5 c1588-69G>A is not rare, since it was also detected in healthy subjects, and the observation seem to suggest that this polymorphism is associated with a symptomatic pour severe form and other factors can act as triggering factors of symptoms.

3. Introduction

Familial Mediterranean Fever (FMF) is an autosomal recessive autoinflammatory disease caused by mutation(s) in the Mediterranean fever (MEFV, pyrinmarenostrin) gene [1, 2]. FMF is characterized by recurrent fever crisis combined with serosal, synovial, or cutaneous inflammation and, in some individuals, the eventual development, in the long-term, of systemic AA amyloidosis [3, 4]. FMF mainly affects peoples living along eastern Mediterranean Sea (Turks, Sephardic Jews, Armenians) and is not rare disease in other Mediterranean areas such as Greeks, Italians and Iranians [4, 6]. Until now more than 304 sequence variants have been recorded [6]. In Italy M694V, V726A, M680I, M694I and E148Q are the most frequent FMF-associated mutations [7].

Here, we describe a case of mild FMF confirmed by analysis of the MEFV gene, characterized by polymorphism c1588-69G>A.

4. Case report

An fifty four year old women (SD) was referred to our hospital due to recurrent and unpredictable irregular febrile episodes, generally lasting 24 h to 72h. She presented other associated symptoms: mild erysipelas-like skin rash and arthritic attack. Family history revealed that her father died because of leukemia, and mother of

cerebral infarction. Renal disease, periodic fever, autoimmune and metabolic diseases or auto-inflammatory disease were excluded in the family anamnesis. Laboratory features included a moderate elevation of sedimentation rate (40mm/hr; normal: 0-29mm/hr), of C-reactive protein (1,5 mg/dl; normal:<0,5), of fibrinogen (550mg/dL: normal 150-400 mg/dL) with an increased number of leucocytes (11.000/uL with 63% neutrophils, 32% lymphocytes, 4% eosinophils, 1% monocytes). All the other parameters (proteins, immunoglobulins, haptoglobin, prothrombin and tromboplastin time, serum immunofixation electrophoresis, k l-free light chains, creatinine, microalbumin, transaminases, bilirubin, alkaline fosfatase, anti-cyclic citrullinated peptide (CCP) antibody, antinuclear antibody, myeloperoxidase antineutrophil cytoplasmatic antibody (MPO-ANCA) and proteinase -3 (PR3 ANCA) were in the normal range. The analysis of serum amyloid (SAA) was 2,98 mg/L (normal values 6,4) and was always negative in the long run. The abdominal ultrasonography reveals a slight steatosis. Echocardiography was normal.

The genetic analysis was carried out on genomic DNA isolated from peripheral leukocytes by the salting-out method [8]. By PCR and direct sequencing we analyzed MEFV gene, TNFRSF1A gene (for periodic syndrome associated to TNF receptor, TRAPS) and

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exon 2-15 18-24 of NLRP3 (correlated to the periodic syndrome associated to cryopyrin, CAPS) using primers selected from genomic DNA sequences by our self (homemade) in intronic region flanking all exons including promoter region and intron/exon boundaries (data not shown). The results indicate the presence of mutation in intron 5, c. 1588-69G>A of FMF gene.

The patient was treated with 2 mg of betametasone with the resolution of the symptoms in two days' time and normalization of the three altered laboratory parameters. Afterwards she left the hospital with monitoring of clinical signs. Because of new attack after two months, we started, after the resolution of fever and arthritis symptoms with betametasone, colchicine treatment in the first week with 1mg/day e afterwards with 2mg/day. Unfortunately we stopped the therapy after three weeks for severe gastrointestinal side effects, even though the patient had a complete resolution of FMF symptoms. The SD patient has now very rare crisis that are always treated positively with steroid.

As reported in table 1 we detected c1588-69G>A polymorphism in 98 patients over 167 with clinical sign of FMF. 72 expressed it in heterozygosis and 26 in homozygosis. On the other hand, this polymorphism was displayed in 21 over 29 blood donors (17 in heterozygosis and 4 in homozygosis)

5. Discussion

FMF is an autosomal recessive hereditary auto-inflammatory disease, characterized by recurrent and self-limiting attack of fever with abdominal, chest or joints pain and erysipelas-like erythema [1-5] Usually, the periodic attacks show inter and intra-individual variability in term of frequency and severity and they are triggered by apparently innocuous stimuli and may be preceded by a prodromal period [7, 9]. The diagnosis is still based on clinical manifestation according to Tei-Hashomer criteria [4]. Molecular genetic test are considered for diagnostic confirmation [1-4, 10]. The gene responsible maps on chromosome 16 (16p13) encoding the Pyrine/Marenostrin protein [1-5, 10]. Among Italians FMF seem to be more frequent that was believed in the past [5, 7], even though with very low incidence of amyloidosis [5, 7]. The patient reported in this study appears to be in line with the previous observations [5, 7]. The good clinical response to colchicine, even though was interrupted for side effects, seems in line with the diagnosis [5, 7, 11]. The detection of polymorphism for intron 5 c1588-69G>A is not rare, in fact the observed polymorphism also in healthy subjects (Table 1) seems to indicate that other factors can act as triggering factor. However, our data seems to suggest that this polymorphism is associated with a symptomatic pour severe form. Furthermore, since this polymorphism was observed for the first time in Lebanon patient affected by mild FMF [6, 12] (<http://fmf.igh.cnrs.fr/in.fevers,2015>), this observation confirm the very ancient settlement of many communities in Lebanon has had relationship with

other population of the Middle East through the sharing of common MEFV mutations and associated extended haplotypes [12].

Conflict of interest. The authors declare that they have no conflict of interest

Table 1: Expression of polymorphism c1588-69G>A in our population

Patients with clinical signs	Type of polymorphism	Type of variant	
		Single	Associated
98 positive for c.nt1588 -69G>A	72 in heterozygosis	30	42
	26 in homozygosis	10	16
69 negative for c nt1588 -69G>A	----	----	----
Blood healthy donors			
21 positive for c.nt 1588-69G>A	17 in heterozygosis	----	----
	4 in homozygosis	----	----
8 negative for c.nt 1588-69G>A	----	----	----

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