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Case Report

# A mild form of Familial Mediterranean Fever associated with a polymorphisms C.NT 1588,-69G>

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## 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 crises combined with serosal, synovial, or cutaneous inflammation and, in some individuals, by the eventual development, in the long-term, of systemic amyloidosis [3,4]. FMF mainly affects peoples living along eastern Mediterranean Sea (Turks, Sephardic Jews, Armenians) and it is not a 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 recent case of mild FMF, characterized by all the clinical manifestations indicative of FMF described in the literature, according to Tei-Hashomer criteria [4] and by the analysis of MEFV gene, characterized by polymorphism c1588-69G>A. This is in agreement with previous our observations in a wider sample collected in the years. We are training to define the relations among gene mutations and clinical forms of FMF.

## Case report

A fifty four year old women (SD) was referred to our hospital due to recurrent and unpredictable irregular febrile episodes, generally lasting 24 h to 72 h. She presented other associated symptoms: mild erysipelas-like skin rash and arthritic attack. Family history revealed that her father died because of leukaemia, and mother of cerebral infarction. Renal diseases, periodic fever, autoimmune and metabolic diseases or auto-inflammatory diseases were excluded in the family anamnesis. Laboratory features included a moderate elevation of sedimentation rate (40 mm/hr; normal: 0-29 mm/hr), of C-reactive protein (1,5 mg/dl; normal: < 0,5), of fibrinogen (550 mg/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, haptoglobulin, 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, myeloproxidase antineutrophilcytoplasmatic 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 analysed MEFV gene, TNFRSF1A gene (for periodic syndrome associated to TNF receptor, TRAPS) and exon 2-15 18-24 of NLRP3 (correlated to the periodic syndrome associated to cryopirin, 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 betamethasone 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 appearance of clinical signs of recurrence after two months, we started to treat the patient with colchicine, in the first week with 1mg/day and afterwards with 2mg/day. The patient had a prompt resolution of symptoms, but, unfortunately, she stopped the therapy after three weeks for severe gastrointestinal side effects. The SD patient has now very rare crises that we treat 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 the polymorphism 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). The relevant difference is the association with other variants. In fact, 58,3 per cent of the patients expressing the polymorphism in heterozygosis displayed an association with MEFV gene mutations (42 out of 72) and 61,5% in the patients with the polymorphism in homozygosis (16 out of 26). However, there were patients that presented only the single polymorphism (30 out of 72 in heterozygosis and 10 out of 26 in homozygosis), as our patient SD reported here in detail.

## Discussion

FMF is an autosomal recessive hereditary auto-inflammatory disease, characterized by recurrent and self-limiting attack of fever with abdominal, chest or joint 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 manifestations according to Tei-Hashomer criteria [4]. Molecular genetic tests are considered for the diagnostic confirmation [1-4,10]. The gene responsible maps on chromosome 16 (16p13) encoding the Pyrine/Marenostrin protein [1-5,10]. Among Italians, FMF seems to be more frequent than it was believed in the past [5,7], even though the incidence of amyloidosis is very low [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, further confirm the diagnosis [5,7,11]. The detection of polymorphism for intron 5 c1588-69G>A is not rare in our population, in fact, this polymorphism was also detected in healthy subjects (Table 1). In diseased subjects was also relevant the type of variant that affects MEFV gene and FMF phenotype that was not detected in healthy individuals (Table 1). The high incidence of this polymorphism in Italian population indicates that other factors can act as triggering events of FMF. However, our data seems to suggest that this polymorphism is associated with a symptomatic pour severe form. This polymorphism was also frequently detected in Iranian and in Lebanon patients affected by mild FMF [6,12] (http.//fmf.igh.cnrs.fr/in.fevers,2015). This observation confirms that the very ancient settlement of many communities in Mediterranean area has had relationship with other populations of the Middle East through the sharing of common MEFV mutations and associated extended haplotypes [12].

**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 |
| 69 negative for c nt1588 -69G>A | 26 in homozygosis | 10 | 16 |
| **Blood healthy donors** | | | |
| 21 positive for c.nt 1588-69G>A | 17 in heterozygosis | ---- | ---- |
| 8 negative for c.nt 1588-69G>A | 4 in homozygosis | ---- | ---- |

We are doing the follow up of all these patients to evaluate, in the long-term, if this polymorphism is really associated with a mild form of FMF without systemic amyloidosis and, furthermore, if these MEFV gene mutations and polymorphisms are associated with particular haplotypes that are less frequent among controls.

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This study was funded by Hospital funds.

### Ethical proposal

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study does not contain any studies with animals performed by any of the authors.

### Informed consent

Informed consent was obtained from all individual participants included in this study.

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