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

Arcoleo F1, Fabiano C2, Barone SL3 and Cillari E1,4,*
1Clinical Pathology Unit . Villa Sofia-Cervello Hospital, Palermo
2Molecular Genetics, Villa Sofia-Cervello Hospital, Palermo
3Internal Medical Medicine Unit, Candela Clinic, Palermo
4Palermo and Consultant Baiata Center, Via Capitano Sieli, Trapani

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.

2. Key words
Cutaneous inflammation; Pyrinmarenostrin; Polymorphism

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 fosfate, anti-cyclic citrullinated peptide (CCP) antibody, antinuclear antibody, myeloperoxidase antineutrophil cytoplasmatic antibody (MOPO-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 ultranonography 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

*Corresponding Author (s): Enrico Cillari, Clinical Pathology Unit. Villa Sofia-Cervello Hospital, Palermo, Consultant Clinical Pathology Unit. Villa Sofia-Cervello Hospital, Palermo and Consultant Baiata Center, Via Capitano Sieli, Trapani, E-mail: cillari52@hotmail.it

5. 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 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/Marenosin 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 [7, 9]. The diagnosis is still based on clinical manifestation according to Tei-Hashomer criteria [4].

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

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

<table>
<thead>
<tr>
<th>Patients with clinical signs</th>
<th>Type of polymorphism</th>
<th>Single</th>
<th>Type of variant Associated</th>
</tr>
</thead>
<tbody>
<tr>
<td>98 positive for c.1588-69G&gt;A</td>
<td>72 in heterozygosis</td>
<td>30</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>26 in homozygosis</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td>99 negative for c.1588-69G&gt;A</td>
<td>------</td>
<td>------</td>
<td>------</td>
</tr>
<tr>
<td>Blood healthy donors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21 positive for c.1588-69G&gt;A</td>
<td>17 in heterozygosis</td>
<td>------</td>
<td>------</td>
</tr>
<tr>
<td></td>
<td>4 in homozygosis</td>
<td>------</td>
<td>------</td>
</tr>
<tr>
<td>3 negative for c.1588-69G&gt;A</td>
<td>------</td>
<td>------</td>
<td>------</td>
</tr>
</tbody>
</table>

References