Familial Mediterranean fever associated pyrin mutations in Greece

K Konstantopoulos, A Kanta, C Deltas, V Atamian, D Mavrogianni, A G Tzioufas, I Kollainis, K Ritis, H M Moutsopoulos

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Objective: To search for pyrin mutations associated with familial Mediterranean fever (FMF) in Greece.

Patients and methods: 62 patients fulfilling the Tel Hashomer diagnostic criteria for definite (33) or probable (29) FMF diagnosis were studied. Eight point mutations of pyrin gene were tested by standard methods. Of the 62 patients tested, 48 were Greek, four were Jewish, seven were Armenian, and three were Arab.

Results: 42 patients were found to be homozygotes for pyrin mutations; 11 patients were found to carry only one of the tested mutations; in nine patients no mutations were detected.

Conclusion: Molecular detection of pyrin gene mutations seems useful in confirming suspected cases, and in detecting asymptomatic cases, of Mediterranean fever in Greece. It may also be used as a screening tool within affected families.

Familial Mediterranean fever (FMF) is an inherited acute relapsing inflammatory disorder presenting as febrile attacks, synovitis, and with abdominal, thoracic, or cutaneous signs. It is characterised by neutrophil infiltration of affected sites. Attacks last from hours to three days, and some patients develop amyloidosis. FMF mainly affects populations around the Mediterranean basin—namely, Jews, Arabs, Turks, and Armenians. Documented cases are nowadays sporadically reported from other regions.

Mutations of a gene (MEFV) coding for a protein named pyrin have been associated with the disease, but the role of MEFV gene product(s) is still uncertain. The MEFV gene expression is restricted to cells involved in inflammatory response. In view of the gene expression pattern and the clinical presentation of FMF, it is suggested that pyrin normally acts as a rheostatic mediator in controlling inflammation and that the disease results from a lack of this control due to mutated pyrin. Both cellular and molecular data point to this hypothesis.

At present, more than 28 FMF associated pyrin gene mutations have been identified; most of them are mapped on exon 10 and almost all are single missense mutations. Their distribution in different populations is heterogeneous. Clinical expression or complications may differ slightly according to mutations, but this needs further investigation.

In Greece, FMF is rarely diagnosed in daily practice; however, underdiagnosis or misdiagnosis cannot be excluded. Undiagnosed patients are at risk for developing amyloidosis or for being subjected to unnecessary operations. On the other hand, genetic influences on the country population, due to migration from neighbouring racial groups which have a high prevalence of the disease, suggest that FMF may prove to be a problem of considerable importance in this country. Thus, diagnostic confirmation of suspected cases by reliable testing, would be useful.

In Greece, no systemic studies on FMF have been conducted until now. We tested 62 patients who were referred as FMF by recently established molecular tests.

PATIENTS AND METHODS
A total of 62 patients (40 male, 22 female) with a clinical diagnosis of FMF were referred for investigation. They all fulfilled the Tel Hashomer criteria for FMF clinical diagnosis; some patients were referred to this clinic with a strongly suspected diagnosis of FMF for a further investigation. Interestingly, two patients were referred who had had a diagnosis of primary AA amyloidosis for a long time previously, and had no past history suggesting FMF. The patients tested included four first degree relatives. According to the Tel Hashomer criteria, 33 cases were “definite” and 29 cases were “probable” diagnoses of FMF. Forty eight patients were Greek (Christian orthodox religion), four were Jewish, seven were Armenian, and three were Arab.

All patients were given a complete physical examination to exclude any condition and/or disease which might interfere with the diagnosis.

Molecular testing was conducted in DNA extracted from peripheral blood by standard methods. The following MEFV gene mutations were tested with polymerase chain reaction (PCR) experiments based on amplification resistant mutation systems (ARMS): E167D (exon 2), F479L (exon 5), R761H (exon 10), M680I (exon 10), M694I (exon 10), M694V (exon 10), V726A (exon 10), A761H (exon 10). Mutation E148Q (exon 2) was detected according to the RFLP/BsrI digestion pattern of the PCR amplified product.

RESULTS AND DISCUSSION
Within the 33 cases of “definite” FMF, homozygosity or compound heterozygosity was detected in 29; single mutation was detected in three cases; in one case no mutation at all was detected.

Within the 29 cases of “probable” FMF diagnosis, homozygosity or compound heterozygosity was detected in 13; heterozygosity (single gene mutation) was detected in eight; no mutations were detected in eight cases.

A total of 92 mutated genes were found. Table 1 shows the particular mutations and their distribution according to the racial groups. Within the Greek patients (representing the vast majority in the country), the more prevalent mutations were E148Q and M694V, accounting for 14% and 48%, respectively.

Abbreviations: BD, Behçet's disease; FMF, familial Mediterranean fever; PCR, polymerase chain reaction
remain undiagnosed owing to a lack of familiarity with the disease (BD) was noted, nor any symptoms pointing to it. The demonstration of a similar spectrum of variation of MEFV mutations within FMF patients in Greece, indicates that the disease, although not universal, is a not uncommon genetic disease in the whole Mediterranean basin, including Greece. This country, close to the periphery of the region in which FMF originated, has over time been an area for the potential flow of the disease gene owing to migration, intermingling, and selection (if a selection advantage exists in heterozygotes). In view of these observations, it appears that Greece should also be included within the areas affected by FMF.

Despite some limitations, mainly arising from the number of mutations we applied, this study strengthens the value of the current simple and rapid FMF molecular testing. A detailed molecular study should be conducted in any relevant situation as rare or new mutations cannot be excluded. Furthermore, molecular testing of all patients with established AA amyloidosis may lead to a more reliable estimation of phenotype II.

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REFERENCES

Table 1 Pyrin gene mutations found and their distribution in the racial groups tested

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Total</th>
<th>Greek</th>
<th>Jewish</th>
<th>Armenian</th>
<th>Arab</th>
</tr>
</thead>
<tbody>
<tr>
<td>E148Q</td>
<td>14</td>
<td>13</td>
<td>1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>E167D</td>
<td>1</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>F479L</td>
<td>1</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>M680I</td>
<td>10</td>
<td>6</td>
<td>–</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>M694I</td>
<td>11</td>
<td>11</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>M694V</td>
<td>44</td>
<td>25</td>
<td>7</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>V726A</td>
<td>9</td>
<td>6</td>
<td>–</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>A761H</td>
<td>2</td>
<td>–</td>
<td>2</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Some patients presented with complex molecular profiles. Thus, in two unrelated families we studied first degree relatives; in both families the patients were father and daughter. In the first family, although only one mutation was detected, the disease presentation was typical of a “definite” diagnosis. This suggests that additional mutation(s) as yet undetected may exist. In the second family with again both the father and his daughter affected, three MEFV mutations were detected in each of them; such complex haplotypes have been described by others.10

No correlation between severity of the disease and particular mutations was found in this study. It should also be noted that colchicine resistant cases were not recorded; such cases are reported to represent some 25% of the total.11

It is also worth noting that two phenotype II FMF cases have been described within Greek patients.12,13 The phenotype was M694V/V726A in both; mutation M694V is believed, but not by everyone, to predispose to amyloidosis.

Within the cases we examined, no concomitant Behget’s disease (BD) was noted, nor any symptoms pointing to it. The FMF-BD relationship has been cautiously interpreted thus far; clearly, this point deserves further clarification.

Although no mutation at all was detected in 9/62 cases studied, we note that only one such case was found within the 33 “definite” cases compared with eight found within the 29 “probable” cases. We must remember that from a total of more than 29 known MEFV mutations, we tested only eight. Therefore the mutations not yet tested and the mutations as yet unknown cannot be excluded. On the other hand, one should keep in mind that in populations not greatly affected by FMF, other rare mutations are preferentially encountered. It is expected that this is also the case for Greek subjects.15 For the cases where only one mutation was detected (rather than the two expected), we note that such cases were more common in those with a diagnosis of “probable” FMF than in those with a “definite” FMF diagnosis.

Table 1 Pyrin gene mutations found and their distribution in the racial groups tested.


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