Exon 2: Is it the good police in familial mediterranean fever?

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Abstract

Objective: Familial Mediterranean fever (FMF) is the most common autoinflammatory disease. Most of the identified disease-causing mutations are located on exon 10. As the number of studies about the effect of the exonal location of the mutation and its phenotypic expression is limited, we aimed to investigate whether the exonic location of the Mediterranean fever (MEFV) mutation has an effect on the clinical manifestation in patients with FMF.

Methods: Study population was derived from the main FMF registry that included 2246 patients from 15 different rheumatology clinics. We categorized the mutations according to their exon locations and retrieved the clinical and demographic information from the database.

Results: Patients having the MEFV mutations on exon 2 or 10 (n:1526) were divided into three subgroups according to the location of the MEFV mutations: Group 1 (exon 2 mutations), Group 2 (exon 10 mutations), and Group 3 (both exon 2 and exon 10 mutations). Group 2 patients were of a significantly younger age at onset, and erysipel-like erythema, arthritis, amyloidosis, and a family history of FMF were more common in this group.

Conclusion: Patients with FMF and exon 10 mutations show more severe clinical symptoms and outcome. Exon 2 mutations tend to have a better outcome.

Keywords: E148Q, exon 2, exon 10, familial Mediterranean fever, M694V

Introduction

Familial Mediterranean fever (FMF) is the most common form of autoinflammatory disease and inherited autosomal recessively. The responsible gene for FMF is located in the short arm of chromosome 16 and named MEFV (Mediterranean fever) (1).

So far, over 300 sequence variations have been identified in the MEFV gene (2). Most of the identified mutations, including M694V, M680I, M694I, and V726A, are located on exon 10, whereas some mutations such as E148Q and R202Q are located on exon 2 (1). It has been reported that there is a genotype-phenotype relation in FMF, such as a more severe disease with M694V and a milder disease course in patients carrying E148Q (3, 4). Mutations located on exon 2, mostly E148Q and R202Q, are commonly considered to lead to a better outcome, less frequent attacks, and amyloidosis (3, 4). Currently there are a limited number of reports addressing exonal location and its phenotypic expression in FMF. Additionally, studies on this subject provided conflicting results. Therefore, in the current study, we aimed to investigate whether the exonic location of the MEFV mutation has an effect on the clinical manifestation in patients with FMF.

Methods

Patients

Study population was derived from the main FMF registry that included 2246 patients from 15 adult rheumatology clinics located in different geographical parts of Turkey (5). The patients in this registry were diagnosed according to the Tel-Hashomer or Sheba Medical Center criteria (6, 7).
We categorized the mutations according to their exon locations (exon 2 and 10) and retrieved the clinical and demographic information from the database. A more detailed description of the national FMF registry has been previously published (5).

The study complies with the Declaration of Helsinki and was approved by the local ethical committee of Eskişehir Osmangazi University (decision date: 27/08/2012; decision number: 2012/184).

### Genetic analysis

There were 1719 patients with available genotype information, which was done by the PCR restriction fragment length polymorphism (PCR-RFLP) or the reverse hybridization assay (FMF StripAssay), depending on the laboratory of the participating clinics.

### Statistical analysis

The normality was tested using the Shapiro-Wilk method. Based on the results, most of the variables showed non-normal distribution. Comparison of the continuous variables was done by the Kruskal-Wallis test, and the nominal or ordinal data were analyzed by a chi-square test. Continuous variables were presented as median and 25-75th percentiles, and the categorical variables are expressed in frequencies and percentages. As there were multiple groups, Bonferroni’s correction (post hoc test) was used to reduce the probability of a Type I error. The adjusted critical significance level was <0.016.

### Results

There were 1719 patients included in the MEFV mutation analysis. One hundred and fifty-four out of 1719 patients did not have any detectable mutation, 39 had rare mutations located in other exons. Remaining 1526 patients (median age 31 [24 to 41] years, 48.4% male) were divided into three subgroups according to the location of the MEFV mutations: Group 1 (exon 2 mutations; E148Q and R202Q), Group 2 (exon 10 mutations; M694V, V726A, M680I, M694I, R761H, K695R), and Group 3 (compound heterozygous; having both exon 2 and exon 10 mutations). The distribution of the MEFV mutations by groups is listed in Table 1.

### Discussion

The MEFV gene is located on the short arm of chromosome 16 and has 10 exons. Most of the disease-causing mutations are located in the 10th exon. On the other hand, E148Q, one of the commonest mutations observed in FMF patients is located in the exon 2, together with R202Q. The mutations in exon 10 of the MEFV gene, such as M694V, V726A, M680I, M694I, R761H, K695R, are considered to cause FMF symptoms (1). In addition, certain mutations such as M694V are responsible for an early onset and severe outcome, including amyloidosis (5). In general, exon 2 mutations, particularly E148Q have been reported to be associated with a late onset disease and favorable outcome (1). Amyloidosis is the most serious complication of FMF and is generally linked with the M694V genotype. In a previous report, it has been shown that patients homozygous for the M694V genotype had six-fold risk of amyloidosis compared to patients with FMF carrying other MEFV gene mutations (5). Aside from amyloidosis, there has been interest to identify clinical features associated with severe disease. Some studies suggested that

### Table 1. The detailed list of mutations by groups

<table>
<thead>
<tr>
<th>MEFV mutations</th>
<th>Group 1 (n=82), (n, %)</th>
<th>Group 2 (n=1304), (n, %)</th>
<th>Group 3 (n=140), (n, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E148Q homozygous</td>
<td>1 (1.2)</td>
<td>414 (31.7)</td>
<td>93 (66.4)</td>
</tr>
<tr>
<td>E148Q heterozygous</td>
<td>71 (86.6)</td>
<td>293 (22.5)</td>
<td>E148Q/Non-M694V 35 (25)</td>
</tr>
<tr>
<td>E148Q/R202Q</td>
<td>1 (1.2)</td>
<td>293 (22.5)</td>
<td>R202Q/M694V 12 (8.6)</td>
</tr>
<tr>
<td>R202Q heterozygous</td>
<td>9 (11)</td>
<td>80 (6.1)</td>
<td></td>
</tr>
<tr>
<td>M694V homozygous</td>
<td></td>
<td>127 (9.8)</td>
<td></td>
</tr>
<tr>
<td>M694V heterozygous</td>
<td></td>
<td>97 (7.4)</td>
<td></td>
</tr>
<tr>
<td>M694V compound heterozygous</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-M694V homozygous</td>
<td></td>
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<tr>
<td>Non-M694V heterozygous</td>
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<tr>
<td>Non-M694V compound heterozygous</td>
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patients with ELE had a more severe clinical course and were also related to M694V homozygosity and amyloidosis (8). In a previous study, researchers showed that amyloidosis, arthritis, family history of FMF, and presence of the M694V allele had been clustered in a severe outcome group (9). In this study, we showed that patients with isolated exon 2 mutations had a higher percentage of females, late onset of disease, lower rates of self, and a family history of amyloidosis, ELE, and arthritis compared to patients with exon 10 mutations. Taken together, our results are in line with the reports suggesting a favorable clinical course in patients with exon 2 mutations.

In our study, 86.5% of the patients in Group 1 had E148Q mutations, and the most common mutation in Group 2 was the homozygous M694V mutation (31.6%). Considered together with a milder disease course, our findings may support the notion that E148Q may be a polymorphism rather than a disease-causing mutation (10). However, there is still no consensus about whether the E148Q mutation is pathogenic or a simple polymorphism. In a study from Japan by Migita et al. (11), the E148Q mutation was found to be higher in FMF patients compared to the healthy population, and these patients had milder disease (11). There is also a possibility that mutations in the other allele may affect the pathogenicity of E148Q. On the other hand, M694V is nearly always blamed for causing a more severe disease (5, 12). As we noted earlier, the other mutation in exon 2 is R202Q. This mutation is reported as one of the most common mutations in some geographic areas of Turkey (13-15). R202Q is also considered to be a polymorphism and is found to be positive in healthy populations (16). Some data suggest that R202Q may be pathogenic when it is in homozygous pattern (16).

Current study has some limitations. One of them is the lack of data to calculate the severity score for FMF. The other one is the lack of full sequencing and therefore the absence of rare mutations in exon 2 and 10.
Conflict of Interest: The authors have no conflict of interest to declare.

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References