

## CORRESPONDENCE

# Does FMF gene exist in multiple sclerosis and contribute to the progression?

Familial Mediterranean fever (FMF) is an autosomal recessive hereditary disease seen frequently in Turkish, Armenian, Israeli and Arabian populations. The responsible gene has been identified on chromosome 16p, Mediterranean fever gene (MEFV) region. MEFV is dominantly expressed in polymorphonuclear cells and its product is a protein called 'pyrin' or 'marenostrin'. Pyrin is associated with the interleukin (IL)-1-related inflammation cascade and involved in the apoptosis and down-regulation of the inflammation.<sup>1</sup> Coexistence of FMF and other autoinflammatory diseases such as Behçet's disease, polyarteritis nodosa, seronegative arthritis has been reported previously.<sup>2,3</sup> Multiple sclerosis (MS) is an inflammatory disease of the central nervous system (CNS) affecting primarily the genetically susceptible people. There are some publications reporting the coexistence of FMF with MS.<sup>4-8</sup> Akman-Demir *et al.* reported that the rate of FMF among the patients with definite MS is 4 times more frequent than the expected prevalence in Turkey.<sup>9</sup> Some of these previous studies suggested that the MS patients carrying MEFV gene had more severe illness and rapid progression to disability.<sup>10,11</sup> The aim of this study was to demonstrate the effect of MEFV mutation carriage on the course of definite MS patients who have been followed at least for 10 years with well-documented clinical progression.

A total of 600 MS patients had been admitted to MS and Demyelinating Disorders Outpatient Clinic of Istanbul University, Istanbul Faculty of Medicine between October 2007- May 2008. Among these, those with at least 10-year follow up were included in the study. The clinical severity of the disease was established by using the extended disability status score (EDSS). The blood samples of the patients were collected after taking their informed consents. The local ethics committee approved this study. Ten ml of peripheral blood sample was drawn into the tubes with EDTA and the DNA was isolated by Magna Pure (Roche) DNA isolation system. Since 60% of the reported MEFV gene mutations take place in the exon region 10, the whole exon region 10 was screened. All the laboratory analysis was done in the Institute for Experimental Medicine, IU. The findings of the patients with EDSS score  $\leq 3.5$  and EDSS score  $\geq 4$  were compared. Parametric values were compared using t test, while non-parametric values were compared using Fisher's exact test. SPSS 13.0 was used for the statistical analysis.

Fifty-five consecutive patients (40 female, 15 male) were enrolled into the study. There was no significant difference between the patients with EDSS score  $\leq 3.5$  and EDSS score  $\geq 4$  in terms of age and MS duration.

The MEFV mutation was established only in one patient; 2040G>A, M680I, heterozygote. The MS duration of this patient was 10 years and the EDSS score was 5. Since mutation was determined only in one subject, no further statistical analysis could be done.

The molecular pathogenesis of FMF is very complex. MEFV gene encodes a protein called pyrin that is expressed mainly in granulocytes, eosinophils, monocytes, dendritic cells, synovial and peritoneal fibroblasts and it regulates an IL-1 family member; IL-1 $\beta$  via modulating caspase 1, an IL-1 $\beta$  converting enzyme.<sup>12</sup> IL-1  $\beta$  induces inflammatory cytokines and the synthesis of multiple chemokines, particularly those that attract neutrophils to the site of inflammation. IL-1 $\beta$  is also a strong inducer of acute phase proteins and fever. MEFV gene mutations cause pathologic states of these pathways and these complicated interactions account for the predisposition of FMF for inflammation in different regions like serosal, synovial and skin involvement.<sup>13</sup> Known CNS involvement of FMF is aseptic meningitis, which is seen rarely.<sup>12</sup>

Coexistence of FMF and MS was reported in some studies, but a relationship between these two disorders was not clearly demonstrated yet. In a research of 2,800 MS patients, the number of patients

with MEFV mutation was determined as 12.<sup>9</sup> Another study, a large FMF cohort seeking MS findings in 12,000 registered FMF patients revealed 9 patients with MS.<sup>11</sup> While Akman-Demir *et al.* reported that the rate of FMF among patients with definite MS was 4 times the expected prevalence.<sup>9</sup> In another study from Turkey, Unal *et al.* found pryn gene mutation in 20 of the 53 MS patients while they found it 7 of the 66 healthy subjects.<sup>8</sup> In our study we examined 55 MS patients for MEFV gene mutation and we found only one positive result.

A study from Israel reported that the non-Ashkenazi MS patients carrying MEFV mutation showed rapid progression to disability while progression to disability was not enhanced in Ashkenazi MS patients.<sup>5</sup> Accordingly, the main aim of our study was to demonstrate the effect of MEFV mutation carriage on the course of MS patients with well-documented 10- year clinical progressions. However, since there was only one positive result we could not analyze the relationship between the mutation carriage and the clinical progression. The EDSS score of the patient who has MEFV mutation was five. To assess its effect in Turkish MS patients, we need further research.

In conclusion, in a series of 55 MS patients with well-documented long-term follow-up of at least 10 years, we could not find any significant interaction of FMF gene mutations. Sample size may be a factor limiting this study. Therefore, further larger studies are needed to assess this issue.

Conflict of Interest: None

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