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CASE REPORT

Familial Mediterranean fever in three Japanese patients, and a comparison of the frequency of *MEFV* gene mutations in Japanese and Mediterranean populations

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Abstract We report on three Japanese patients (two families) with familial Mediterranean fever (FMF), a rare disease in the Far East. Two of the patients (siblings with definite FMF) were heterozygous for both *E148Q* and *M694I*, and the remaining patient (with probable FMF and no family history of the disease) was heterozygous for both *P369S* and *R408Q*. Although the *M694I* mutation is less common among Mediterranean populations, it was present in 22 (76%) of 29 Japanese patients with FMF (previously reported cases). We therefore investigated the allele frequency of *M694I* in the healthy Japanese population, as well as other FMF-causing mutations in exon 10 (*M680I, M694V*, and *V726A*) and polymorphisms (*E148Q, P369S*, and *R408Q*) of the Mediterranean fever gene (*MEFV*). The allele frequencies of disease-causing mutations, even *M694I*, were <0.001. While those of *E148Q, P369S*, and *R408Q* were 0.23, 0.057, and 0.054, respectively. Because of the low allele frequencies of disease-causing mutations, FMF is an extremely rare disease among Japanese individuals. However, FMF is an important component of hereditary autoinflammatory syndrome, and a diagnosis of FMF is crucial for the choice of treatment, because of the benefit of colchicine therapy.

Keywords Familial Mediterranean fever · MEFV · Pyrin · Mutation · Periodic fever

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Introduction

Familial Mediterranean fever (FMF) is a common inherited disorder among Mediterranean populations [1]. The gene responsible for FMF, the Mediterranean fever gene (*MEFV*), was recently identified by positional cloning [2]. Approximately 30 mutations or polymorphisms have been associated with FMF. In the Far East, however, FMF is uncommon, because of lower allele frequencies of disease-causing mutations of *MEFV*. Only 29 Japanese patients have been identified as carrying *MEFV* mutations [3–7]. Recently, we treated three Japanese patients with FMF: two siblings, and one patient without a family history of FMF. The genotypes identified were genotypes less commonly observed in Mediterranean patients with FMF, which led us to investigate allele frequencies of the *MEFV* mutations in Japanese individuals.

Case reports

A 17-year-old Japanese girl (patient 1) was referred to Tokyo Women's Medical University because of periodic fever accompanied by chest and back pain and elevated C-reactive protein levels (8.5 mg/dl) since she was 12 years old. Neither leukocytosis nor a left shift was present in the fever-up periods. The symptoms occurred once a month and continued for about 3 days and then

disappeared spontaneously. A chest and abdominal X-ray showed no abnormalities. Arthritis and rashes were absent, and there was no evidence of amyloidosis. Systemic juvenile idiopathic arthritis had been diagnosed but immunosuppressive therapies such as corticosteroids and cyclosporine had been unsuccessful. Serum interleukin (IL)-1β was significantly elevated (85 pg/ml) during fever and decreased (1.2 pg/ml) when she was asymptomatic.

After an informed consent, a genomic search for *MEFV* was performed. The patient was found to be heterozygous for both *E148Q* and *M694I*. Colchicine (0.5 mg per day) has prevented periodic fever for more than 2 years. The patient's younger sister (patient 2) began experiencing periodic fever attacks once a year with preceding chest pain at age 16 and had the same genotype. Genotyping of their mother revealed that she too was heterozygous for the two alleles, although she had never experienced periodic fever. Genotypes of their father and other relatives were not determined.

A 17-year-old Japanese boy (patient 3) had experienced periodic fever, accompanied by abdominal pain, once a year from age 6. He was heterozygous for both *P369S* and *R408Q*. Prophylactic dose of colchicine (0.5 mg per day) was effective, and a diagnosis of probable FMF was made using the Tel Hashomer criteria [8]. His mother had the same genotype but no symptoms, whereas his father carried neither mutations nor polymorphisms in *MEFV*.

The present study was approved by the Genome Ethics Committee of Tokyo Women's Medical University. Allele frequencies of FMF-related mutations or polymorphisms of *MEFV* (*E148Q, P369S, R408Q, M680I, M694V, M694I*, and *V726A*) were investigated by the TaqMan method using specific primers and probes designed by Applied Biosystems (Foster City, CA, USA) in approximately 500 healthy Japanese living around Tokyo. For rare alleles, artificial DNA fragments designed to be homozygous for mutated alleles were synthesized and served as positive controls. As shown in Table 1, the mutated alleles at *M680I, M694V, M694I*, and *V726A* were not detected in healthy Japanese donors, whereas the frequencies of the minor alleles at *E148Q, P369S*, and *R408Q* were 0.23, 0.057, and 0.054, respectively. Two polymorphisms, *P369S* and *R408Q*, were in strong linkage disequilibrium ($D' = 1$).

Table 1 Allelic frequencies of *MEFV* mutations and polymorphisms in the Japanese population

Mutation	No. of chromosomes		Allelic frequency
	Positive	Scored	
E148Q	237	1,012	0.23
P369S	58	1,024	0.057
R408Q	56	1,028	0.054
M680I	0	1,038	<0.001
M694V	0	1,038	<0.001
M694I	0	1,038	<0.001
V726A	0	1,038	<0.001

Discussion

Because FMF is autosomal recessive [9], double mutations can cause the disease. In Mediterranean and Middle Eastern populations, the common genotypes of FMF are *M694V/M694V* and *M694V/V726A* [10]. However, detailed family genotyping can show true dominant inheritance of FMF, and such cases are associated with either Δ*M694* or *M694I* [9]. This observation suggests a crucial role for methionine residue at position 694 in the biological function of the *MEFV* product, pyrin. Of 29 genotyped Japanese patients with FMF, 22 (76%) had *M694I:* three patients were homozygous, and 19 patients were heterozygous [3–7]. Therefore, *M694I* on its own can cause FMF. Although *E148Q* is not considered to cause the disease by itself [11], FMF can result when this polymorphism is combined with disease-causing mutations such as *M694I*, forming a compound heterozygous mutation. As previously reported, of 22 Japanese patients who carried *M694I*, 12 (55%) were heterozygous for both *E148Q* and *M694I.*

In the present study, we demonstrated, for the first time, that allele frequencies of four major disease-causing mutations (*M680I, M694V, M694I*, and *V726A*) in exon 10 of *MEFV* are low in the Japanese population. Even for *M694I*, which seems to be the most common mutation in Japanese FMF, the allele frequency was below 1/1000 chromosomes. The allele frequency of *E148Q* was 0.23. These results contrast with previous observations in Mediterranean populations indicating that one-fifth to one-third of healthy individuals carried mutations, including *E148Q*, and that 1 in 500 individuals had FMF [12]. Thus, we speculate that Japanese FMF spread from a small number of common ancestors bearing *M694I* and that *E148Q* might aid in the development of the disease. Patient 3, who was heterozygous for both *P369S* and *R408Q*, received a diagnosis of probable FMF. These polymorphisms account for less than 5% of FMF cases in Mediterranean and Middle West populations [13]. In the Japanese population, allele frequencies of *P369S* and *R408Q* were found to be 0.057 and 0.054, respectively. Of the 500 healthy Japanese in the present study, two individuals were homozygous for both alleles and had no symptoms. The discrepancy between the relatively high allele frequencies of these polymorphisms and the low prevalence of FMF in the Japanese population might suggest weak involvement of the polymorphisms in the development of FMF.

Wild-type pyrin inhibits activation of caspase-1, resulting in inhibition of cleavage of pro-IL-1β to mature IL-1β.

This inhibitory effect is mediated by its binding to apoptosis-associated speck-like protein containing a CARD (ASC), which composes the inflammasome [14], or by binding to caspase-1 directly [15]. Amino acid substitutions by FMF-causing mutations in exon 10 reduce pyrin's capacity to bind to caspase-1, thus lessening the inhibitory effect on IL-1β release [15]. In patient 1, serum IL-1β levels reflected disease activity, suggesting the involvement of the cytokine in the pathogenesis.

The dose and the position of the mutations in *MEFV* would determine the disease phenotype of FMF. In Arab FMF patients, the highest disease severity was associated with the genotypes of *M694V/M694V* and *M694V/M726A*, while *M694I/M694I* was associated with mild disease [16]. Because most Japanese FMF patients carry only a single dose of *M694I*, they present with less severity and later onset of disease. The present patient 1 was given the score of 3 according to disease severity score created by Pras et al. [17], indicating mild disease severity compared with patients in North Africans (mean score; 9.24) or Iraqi Jews (6.25), [17]. Only one Japanese FMF patient who was homozygous for *M694I* was complicated with renal failure by AA-type amyloidosis [3].

Daily oral colchicine is established in preventing both fever attacks and renal amyloidosis [18]. In adults, the dose of colchicine is generally 1–2 mg/day, and can be increased up to 3 mg/day in severe cases. Most of the reported Japanese patients with FMF had been prescribed with 1 mg of colchicine for prophylactic. In the present cases, only 0.5 mg of colchicine completely prevented the attacks. To know one's genetic background and to diagnose FMF property is crucial because a low dose of colchicine is highly effective in Japanese FMF.

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