Clinical and Genetic Features of Familial Mediterranean Fever in Japan

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ABSTRACT. ***Objective.*** Familial Mediterranean fever (FMF) is thought to be a rare disorder in Japan, and the clinical features of Japanese patients with FMF remain unclear. Our aim was to elucidate the clinical characteristics of FMF in Japanese patients.

Methods. We analyzed clinical and genetic data of 80 patients based on the results of a nationwide questionnaire survey and review of the literature.

Results. From clinical findings of 80 Japanese patients, high-grade fever was observed in 98.8%, chest attacks (pleuritis symptoms) in 61.2%, abdominal attacks (peritonitis symptoms) in 55.0%, and arthritis in 27.5%. Twenty-four percent of patients experienced their first attacks before 10 years of age, 40% in their teens, and 36% after age 20 years. Colchicine was effective in many patients at a relatively low dose (< 1.0 mg/day). AA amyloidosis was seen in only 1 patient. Common *MEFV* mutation patterns were E148Q/M694I (25.0%), M694I alone (17.5%), and L110P/E148Q/M694I (17.5%), and no patient carried the M694V mutation, the most common mutation in Mediterranean patients with FMF.

Conclusion. A larger than expected number of patients with FMF exist in Japan, and the clinical presentation of Japanese FMF patients seems to be relatively milder than those of Mediterranean FMF patients. AA amyloidosis rarely occurs in Japanese patients, probably due to difference in patterns of the *MEFV* genotype between Japanese and Mediterranean patients. (First Release June 15 2009; J Rheumatol 2009;36:1671–6; doi:10.3899/jrheum.081278)

Key Indexing Terms:
FAMILIAL MEDITERRANEAN FEVER — *MEFV* GENE — JAPANESE PATIENTS
NATIONWIDE QUESTIONNAIRE — AA AMYLOIDOSIS

Familial Mediterranean fever (FMF) is an autosomal recessive disorder characterized by recurrence of fever, polyserositis, and erysipelas-like skin lesions[1]. This disorder is the most common form of hereditary periodic fevers and there are over 100,000 patients around the world[2], but it predominately affects populations from the Mediterranean basin including non-Ashkenazi Jews, Arabs, Armenians, and Turks[1,3]. FMF is caused by mutations in the Mediterranean fever gene (*MEFV*) on chromosome 16p13.3, encoding a 781-amino acid protein denoted pyrin/marenostrin[4,5]. Over 170 sequence variants have been recorded in the dedicated database of the Registry of Familial Mediterranean Fever and Hereditary Auto-inflammatory Disorders Mutations, infevers (http://fmf.igh.cnrs.fr/ISSAID/infevers/). The variants V726A, M694V, M694I, M680I, and E148Q are the most frequent, accounting for 74% of all sequence variants[6]. Development of reactive AA amyloidosis is the most devastating complication of the disease[1,7]. The mainstay of therapy is daily colchicine, which prevents the attacks and the development of reactive AA amyloidosis[7].

In Japan, several patients with recurrent fever were clinically diagnosed as having FMF after 1976[8]. In 2002, the *MEFV* gene mutation was confirmed in a few Japanese patients with periodic fever[9,10], and since then a number of FMF patients diagnosed by DNA analysis have also been described. However, FMF is still recognized as quite rare in Japan, and it remains unclear whether the clinical features of Japanese patients are the same as those of Mediterranean patients or not. To elucidate the clinical features of Japanese patients with FMF, we studied clinical findings from 80 patients.

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MATERIALS AND METHODS

Patients. Clinical records of 80 Japanese FMF patients with *MEFV* gene mutations were studied. Clinical diagnosis of FMF was performed according to the Tel-Hashomer criteria[11]. Thirty-nine patients were diagnosed at Shinshu University Hospital between 2002 and 2007, including some previously reported[9,12-15]. Clinical data of the remaining 41 patients were obtained from a nationwide questionnaire survey (described below) and/or by review of the literature.

Nationwide questionnaire. To determine clinical features of patients, we carried out a nationwide questionnaire survey on FMF in 2006. The questionnaire was mailed to 1850 departments of internal medicine and pediatrics in Japan, asking about the number of FMF patients clinically diagnosed on the basis of the Tel-Hashomer criteria and/or the number of patients confirmed genetically, and the number of FMF patients with reactive systemic AA amyloidosis, between 1996 and 2006. Departments that answered that they had patients with FMF were sent another questionnaire asking for more detailed clinical information including the type of *MEFV* gene mutations. The protocol of these surveys was approved by the ethical committee of Shinshu University.

DNA testing of MEFV gene. DNA analysis of the *MEFV* gene was performed in patients with suspected FMF. Exon 2 and exon 10 with their flanking intronic sequences of the *MEFV* gene were amplified by polymerase chain reaction (PCR) using primers shown in Table 1. Exon 2 was amplified in 2 overlapping PCR fragments, exon 2a and exon 2b. Amplified PCR products were analyzed by direct sequencing (DNA Analyzer 3730xl; Applied Biosystems, Foster City, CA, USA). In patients without mutations in either exon 2 or 10 of the *MEFV* gene, other exons were also analyzed by direct sequencing after amplification of each exon[16]. An L110P mutation in exon 2 was analyzed by restriction fragment-length polymorphism (RFLP) analysis with *Sma* I restriction enzyme in addition to the DNA sequence analysis. An E148Q in exon 2 was also detected by RFLP with *BstN* I restriction enzyme after amplification using Exon2E148QF and Exon2E148QR as primers (Table 1).

Allele frequency analysis. Allele frequencies of L110P, E148Q, and M694I were analyzed in 51 healthy individuals and were compared to those in 39 patients with genetically diagnosed FMF at our institution. L110P and E148Q were analyzed by RFLP and M694I by the amplification refractory mutation system[17]. Differences in allele frequencies between the 51 healthy controls and the 39 FMF patients were compared statistically by the chi-square test.

Prior to the study, detailed informed consent was obtained from all patients following a clear explanation of the purpose of the study. Our genetic study protocol was approved by the local ethics committee.

RESULTS

The results of the questionnaire survey are shown in Table 2. Total response rate was 37.9%. The total number of patients who met the diagnostic criteria[11] was 131. Of the 131, 86 patients carried *MEFV* gene mutations (Table 2). Among these, detailed clinical data including the type of *MEFV* mutation were obtained from 58 patients (Figure 1); 39 of these patients were diagnosed at Shinshu University. The clinical data of the remaining 19 patients were obtained by the second survey; 13 of these patients had also been reported previously[10,18-22]. Unfortunately, further information such as the genotype in the other 28 of the 86 patients could not be obtained in the second survey.

In the nationwide survey, reactive AA amyloidosis associated with FMF was noted in 5 patients (3.8%; Table 2). One of them had already been described[10], but detailed clinical information on the other 4 patients could not be obtained from the second survey.

Clinical data. The results for the 58 patients whose clinical data were obtained by the nationwide survey (Table 2) and also those of 22 patients who had been described elsewhere[12,22-27] were studied (total 80 patients; Figure 1), as summarized in Table 3. Forty-nine patients (61.3%) did not have a family history suggestive of FMF (data not shown in the table). The male to female ratio was 33:47. The mean age at onset was 17.3 ± 10.7 years (data not shown); 19 patients (23.8%) experienced their first attacks before 10 years of age, 32 patients (40.0%) in their teens, 20 patients (25.0%) in their twenties, and 9 patients (11.3%) after age 30 years. Surprisingly, the age of onset was 53 years in one patient[26]. The mean age at diagnosis was 29.5 ± 13.7 years and the mean period from disease onset to diagnosis was 13.2 ± 11 years (data not shown).

High-grade fever (febrile attack) was the symptom seen most frequently (98.8%). Chest attack (pleuritis symptoms) was observed in 61.2% of patients and abdominal attack (peritonitis symptoms) in 55.0%. The frequency of arthritis was 27.5% and erysipelas-like erythema was seen in 10% of patients.

Colchicine was orally administered to 47 patients, and a favorable therapeutic effect was seen in at least 40 (85.1%). Information on efficacy was not obtained in the questionnaire survey in 5 patients. The daily dose of colchicine in 28 patients is shown Table 4, and 26 of these were treated with a relatively low dose (< 1.0 mg/day), among whom were 3 patients under 15 years of age. No patient required over 2.0

Table 1. Primers and polymerase chain reaction conditions.

	Primer	Annealing Temperature, °C
Exon2aF	5'-GCA TCT GGT TGT CCT TCC AGA ATA TTC C-3'	62
Exon2aR	5'-CTT TCC CGA GGG CAG GTA CA-3'	
Exon2bF	5'-CAG GCC GAG GTC CGG CTG CG-3'	62
Exon2bR	5'-CTT TCT CTG CAG CCG ATA TAA AGT AGG-3'	
Exon10F	5'-CCG CAA AGA TTT GAC AGC TG-3'	60
Exon10R	5'-TGT TGG GCA TTC AGT CAG GC-3'	
Exon2E148QF	5'-GCC TGA AGA CTC CAG ACC ACC CCG-3'	55
Exon2E148QR	5'-AGG CCC TCC GAG GCC TTC TCT CTG-3'	

Table 2. Results of the nationwide questionnaire survey.

Feature	Internal Medicine	Pediatrics	Total
Departments surveyed	1338	512	1850
Response rate (%)	437 (32.7)	264 (51.6)	701 (37.9)
Total no. of FMF patients	86	45	131
No. of FMF patients determined by gene analysis	49	37	86*
FMF patients with AA amyloidosis	4	1	5

* Clinical data of 58 out of 86 patients were available in this study.

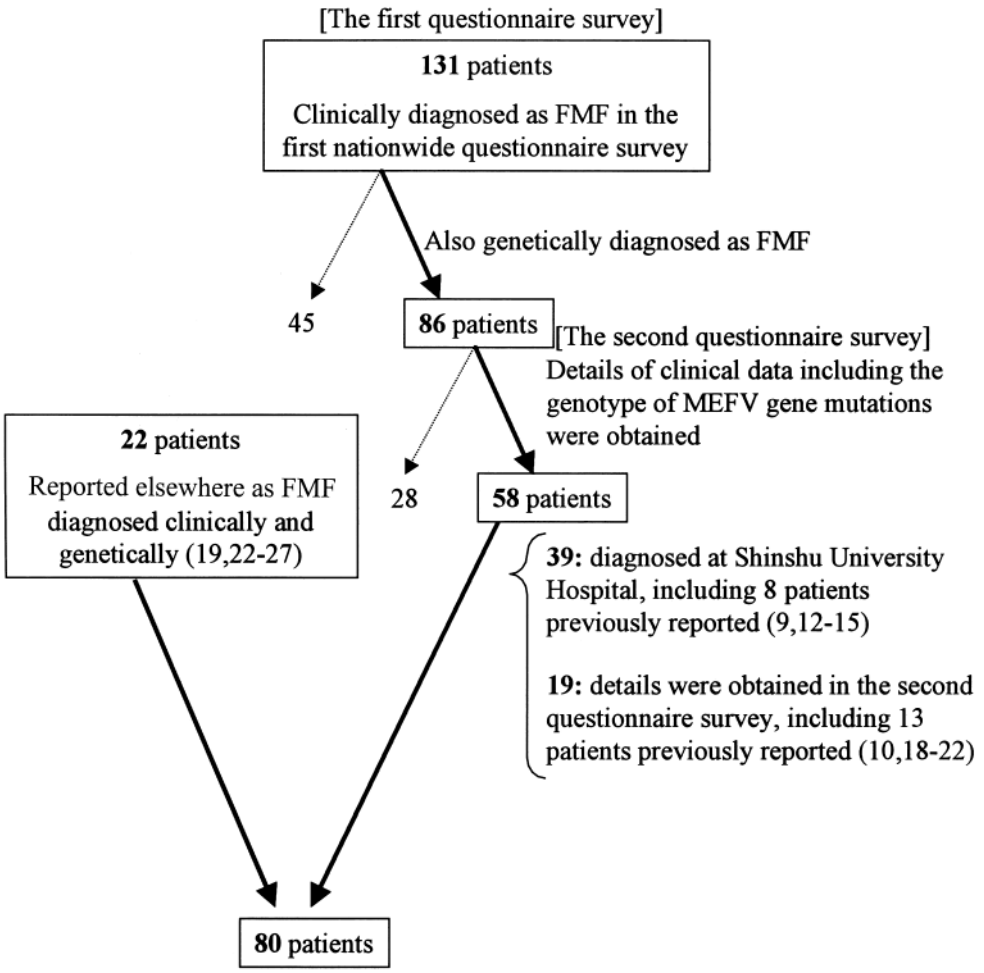

Figure 1. The process of patient selection in this study.

mg/day colchicine to prevent attacks. No effect was observed in 2 patients receiving 1.0 mg/day colchicine (Table 4), but the daily dose could not be increased due to severe diarrhea and bone marrow suppression[10,12,13]. At least 21 patients had not been treated with colchicine. As alternative treatments to colchicine, azelastine was used in one patient, with mild effectiveness, and a combined therapy with infliximab and low-dose methotrexate was effective in one patient[12,13]. In one patient interferon-α was also effective[25], and the herbal medicine "Sho-Saiko-To (TJ-9)" (Tsumura, Tokyo, Japan) was reported to be effective in another patient[20].

Five patients (6.3%) had also been diagnosed as having Behçet's disease (data not shown) before the *MEFV* mutation was identified. Of the 80 patients, only one (1.3%), who was homozygous for the M694I mutation, had reactive systemic AA amyloidosis[10].

MEFV gene mutations. The genotypes of the *MEFV* gene in the 80 patients are shown in Table 5. Common *MEFV* mutation patterns were E148Q/M694I (20 patients, 25.0%),

Table 3. Clinical presentations of 80 patients with FMF.

Age at Onset, yrs, n (%)						Sex, Male, n (%)	Clinical Manifestations, n (%)					
< 10	10–19	20–29	30–39	40–49	> 50		Fever	Pleuritis	Peritonitis	Arthritis	Erysipelas-like Erythema	Amyloidosis
19 (23.8)	32 (40.0)	20 (25.0)	6 (7.5)	2 (2.5)	1 (1.3)	33 (41.3)	79 (98.8)	49 (61.2)	44 (55.0)	22 (27.5)	8 (10.0)	1 (1.3)

Table 4. Dose of colchicine in 28 patients. Number of patients in whom colchicine was effective is given in parentheses.

Dose mg/day	No. Patients
≤ 0.5	13 (11)*
1	13 (10)**†
1.5	1 (1)
2	1 (1)
> 2.0	0

* The efficacy was unclear in 2 patients. ** Efficacy was unclear in one patient in our survey. † No efficacy was observed in 2 patients.

Table 5. Genotypes of *MEFV* gene of the 80 cases.

MEFV mutation	No. Patients (%)
E148Q/M6941	20 (25.0)
M6941/normal	14 (17.5)
L110P/E148Q/M6941	14 (17.5)
L110P/E148Q	9 (11.3)
M6941/M6941	5 (6.3)
L110P-E148Q/E148Q	4 (5.0)
L110P/M6941	2 (2.5)
E148Q/P369S/R408Q/S503C	2 (2.5)
L110P-E148Q/L110P-E148Q	2 (2.5)
R202Q/M6941	1 (1.3)
E148Q/E148Q-R761H	1 (1.3)
L110P/E148Q/P369S/R408Q	1 (1.3)
E148Q/P369S/R408Q	1 (1.3)
P369S/R408Q	1 (1.3)
E148Q/R202Q	1 (1.3)
E148Q/E148Q	1 (1.3)
E84K/normal	1 (1.3)

M694I alone (14 patients, 17.5%), and L110P/E148Q/M694I (14 patients, 17.5%). Nine patients (11.3%) had L110P/E148Q and 5 (6.3%) were homozygous for the M694I mutation. The majority of patients carried E148Q (56 patients) or M694I (56 patients) at least on an allele, but L110P was also identified in 32 patients. As minor mutations, E84K[19], R202Q, P369S, R408Q, S503C[18], and R761H were found in some patients (Table 5), but most of those mutations were detected with L110P, E148Q, or M694I. Only 2 patients, who had P369S/R408Q or E84K alone[19], did not carry L110P, E148Q, or M694I. The other mutations, including M694V, M680I, and V726A in exon 10, which were common in Mediterranean patients with FMF[28], were not found in these 80 patients.

Allele frequencies of L110P, E148Q, and M694I in 51 healthy individuals (102 alleles) were 0.039, 0.26, and 0, respectively. On the other hand, allele frequencies of these 3 mutations were examined in 39 FMF patients and the results were 0.31 (L110P), 0.44 (E148Q), and 0.35 (M694I). The differences in allele frequencies between healthy populations and those with FMF were statistically significant ($p < 0.001$ for L110P and M694I; $p < 0.02$ for E148Q).

DISCUSSION

Clinical features of Japanese patients with FMF. Our study shows that the clinical pictures of Japanese patients with FMF seem to be different from those of Mediterranean patients. The frequencies of cardinal clinical symptoms during attacks in Japanese and Mediterranean FMF patients[2] are shown in Table 6. Mediterranean patients almost always have abdominal symptoms due to peritonitis[2]. However, the frequency of abdominal symptoms in Japanese patients was relatively low (55.0%). Because the frequencies of chest symptoms due to pleuritis, arthropathy, and erysipelas-like erythema are quite variable even among Mediterranean FMF patients, no clear differences were seen in such symptoms between Mediterranean and Japanese patients. In the literature, the relation between severity of the disease and the diet low in animal fat is discussed, and in particular, it was reported that butter ingestion appeared to provoke peritonitis attacks[29]. Although the mechanism of the low frequency of abdominal symptoms in Japanese patients remains unclear, the difference in diet between Japanese and Mediterranean FMF patients may have effects on the difference of phenotype.

Because of atypical symptoms like high fever or abdominal pain, 5 patients with Behçet's disease underwent the *MEFV* gene analysis. All of them clinically met the Tel-Hashomer criteria and were therefore diagnosed as having both FMF and Behçet's disease. However, there was no significant difference between the patients with con-

Table 6. Frequency of symptoms during attack (%) in different races.

	Japanese (80 cases)	Mediterranean populations[2]			
		Turks	Jews	Arabs	Armenians
Fever	98.8	93	100	100	100
Peritonitis	55.0	94	95	82	96
Pleuritis	61.3	31	40	43	87
Arthritis	27.5	47	77	37	37
Erysipelas-like erythema	10.0	21	46	3	8

comitant Behçet's disease and the patients with FMF alone in terms of the clinical severity of FMF symptoms.

With regard to age at disease onset, 90% of FMF patients experience their first attacks before the age of 20 years and the percentage of patients with onset at age over 30 is less than 5% in the Mediterranean area[2,3]. In Japanese patients, 63.8% of patients experienced their first attack before age 20 and 11.3% of patients after age 30, indicating that FMF onset in Japanese patients was much later than in Mediterranean patients. The Turkish FMF Study Group reported that the mean period from disease onset to diagnosis of FMF in Turkey was 6.9 ± 7.65 years[28], and there may also be a delay in the diagnosis of FMF in Japanese patients, probably due to the low recognition of this disorder in Japan.

Administration of colchicine is known to be the most effective therapy for FMF to reduce the frequency, duration, and severity of attacks in most patients, and it has commonly been used in doses of 1.0–2.0 mg/day[2]. Moreover, Pras, *et al* noted that 30% of North African Jewish patients needed 2 mg or more of colchicine to control their symptoms[30]. In our study a small dose of colchicine, not over 1.0 mg/day, showed a favorable therapeutic effect in the majority of Japanese patients, so a relatively lower dose of colchicine may control the attacks of FMF symptoms in Japanese as described[21].

Prevalence of reactive systemic AA amyloidosis in Japanese patients with FMF. Although the incidence of reactive systemic AA amyloidosis in Mediterranean FMF patients varies in different ethnic groups, AA amyloidosis occurs very frequently in North African Jews (12.4%–26%), Iraqi Jews (9.5%–15%), Ashkenazi Jews (11%), Arabs (12%), Armenians (24%), and Turks (12.9%)[28,30-32]. On the other hand, the prevalence of AA amyloidosis in our study was quite low. Of 80 patients, only one male patient[10] had AA amyloidosis, which had been detected 3 years before the *MEFV* gene mutation (M694I) was identified. At the time he was diagnosed as having amyloidosis, he did not receive treatment with colchicine. However, in 21 out of 80 FMF patients who had not been treated with colchicine, to date no patient has had AA amyloidosis. Thus, the prevalence of AA amyloidosis associated with FMF in Japanese would appear to be lower than in Mediterranean patients, regardless of treatment with colchicine.

Genotype of MEFV gene in Japanese patients with FMF. The characteristics of the genotype of the *MEFV* mutations in Japanese patients were that almost all patients were homozygous, heterozygous, compound heterozygous, and/or complex allele for L110P, E148Q, and/or M694I. The correlation between the *MEFV* genotype and phenotype (severity of the disease) in FMF has been well discussed. The C-terminal B30.2 domain of pyrin encoded by exon 10 is known to play an important role in its function, interacting directly with caspase-1 to modulate interleukin 1ß production[33]. In addition, the methionine residue in codon 694 makes a crucial contribution to the function of pyrin[34]. Thus, the mutations in codon 694 are considered to produce severe symptoms with early onset and high frequency of attacks and the necessity of a high dose of colchicine to prevent attacks[2]. In particular, the M694V mutation is regarded as a significant risk factor for secondarily developing amyloidosis[3,7,35]. However, in our study none of the 80 patients carried this mutation. While the M694I mutation was the one most frequently found in Japanese patients, the majority of the patients were compound heterozygous or complex allele for M694I and other mutations producing a relatively milder phenotype such as E148Q and/or L110P, or heterozygous for M694I alone. In addition, numbers of Japanese patients were compound heterozygous or complex allele for E148Q and L110P, so the characteristics of Japanese patients such as late onset and low prevalence of AA amyloidosis would be associated with differences of *MEFV* genotype compared with Mediterranean patients.

It remains controversial whether the E148Q mutation is a disease-causing mutation or a simple polymorphism because of high allele frequency in healthy controls[36-39]. However, it has been reported that most homozygote or compound heterozygote patients associated with other *MEFV* mutations are symptomatic[40,41], and it has also been noted that the allele frequency of E148Q is significantly higher among patients with AA amyloidosis and chronic fever of unknown origin[41]. Moreover, the E148Q mutation was described as producing a milder FMF phenotype with low penetrance[2,6]. While in our study 5 healthy controls were proved to be homozygous for E148Q, the allele frequency of E148Q in patients with FMF was significantly higher than in healthy individuals. Hence we also consider that this mutation can cause FMF, especially when patients are compound heterozygous for E148Q and other *MEFV* mutations or homozygous for E148Q[14].

The L110P mutation was first reported in 2000[42], and to date, several patients have been reported to be compound heterozygote with other mutations even in Japan[19,21]. In our study, 30 out of the 80 patients carried L110P as heterozygote with other mutations, and among these, 28 were compound heterozygous or complex allele for L110P and E148Q. Moreover, there was a significant difference in the frequency between FMF and healthy populations. Therefore, it is considered that L110P can also be associated with the onset of FMF.

Although it is true that *MEFV* gene analysis is needed to establish a definite diagnosis in suspected cases of FMF, *MEFV* mutations are not always found on both alleles even in typical FMF patients[7]. Therefore, diagnosis based on the clinical diagnostic criteria, family history, and the patient's response to colchicine treatment is of great importance in this disorder.

Our study indicates that the clinical presentations and the

MEFV genotype of Japanese patients with FMF seem to be different from those of Mediterranean patients, and our survey suggests that there will be a large number of FMF patients even in Japan.

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