

Familial Mediterranean Fever in 2 Japanese Families

KOJI SHINOZAKI, KAZUNAGA AGEMATSU, KOZO YASUI, HARUO NAGUMO, HAJIME NAITOH, KUNIAKI NAGANUMA, and ATSUSHI KOMIYAMA

ABSTRACT. We describe 3 Japanese patients in 2 families with familial Mediterranean fever (FMF) as determined by gene analysis. FMF is an ethnically related, genetic disease, occurring commonly in some Mediterranean populations. The FMF gene (MEFV) mutation found in our patients is M694I. The patients may be remote from East Asian extraction. (J Rheumatol 2002;29:1324–5)

Key Indexing Terms:

FAMILIAL MEDITERRANEAN FEVER

SEQUENCE ANALYSIS

FAR EAST

Familial Mediterranean fever (FMF) is an autosomal recessive disease that affects populations of non-Ashkenazi Jews, Armenians, Turks, and Arabs¹. FMF is characterized by periodic attacks of fever accompanied by serosal, synovial, or cutaneous inflammation². Renal amyloidosis is a dreadful manifestation of the disease^{1,2}. Daily oral colchicine is known to prevent both acute attacks and development of amyloidosis³. Recently, the gene responsible for FMF was identified; it has 10 exons coding a 781-amino-acid protein known as pyrin/marenostrin^{4,5}.

FMF has been reported only anecdotally in East Asians. The present is the first report of 2 Japanese families with the point mutation of pyrin/marenostrin.

CASE REPORTS

Materials and methods. After informed consent was obtained, DNA was extracted from peripheral blood leukocytes of the patients and their parents by standard techniques. For analysis ~100 ng of genomic DNA template was used in polymerase chain reaction. Oligonucleotides used to amplify exon 10 were: Forward, 5'-GAGGTGGAGGTTGGAGACAA-3'; Reverse, 5'-TCCTCCTCTGAAATCCATGG-3'. Sequencing reactions were carried out using ABI prism dye terminator cycle sequencing kit, and the products were analyzed on an ABI prism 310 DNA sequencer.

Family 1. A 15-year-old girl presented with periodic attacks of fever and abdominal pain, chest pain, and arthralgia (Patient 1). From age 1 year, she developed fever of up to 40°C about once a week that lasted from half to an entire day. From age 3 years, the febrile attacks occurred about once a month, lasting for 2 days, and her ankle and knee joints became swollen and reddish. At age 13 years, she began to complain of abdominal pain, chest pain, and/or arthralgia accompanied by the febrile attacks that forced her to rest in bed. Her abdominal pain once became so severe that a physician at another hospital suspected acute appendicitis. When she experienced chest pain, her breathing became shallow and rapid. Chest and

abdominal imaging (computed tomography scans and x-ray films), electrocardiogram, echocardiography, and digestive tract endoscopy failed to detect any abnormalities. The laboratory tests showed normal neutrophil count (5300–8000/ml), and increased C-reactive protein (CRP, 5–11 mg/dl) and erythrocyte sedimentation rate (54–74 mm/h). Nonsteroidal antiinflammatory drugs were administered without any clinical effect. The patient's elder sister also suffered from periodic febrile attacks during childhood, but attacks were milder (Patient 2). The patient's parents never had periodic febrile attacks. Consanguineous marriage was not noted in this family.

After the diagnosis of FMF was made, Patient 1 began colchicine treatment and has been maintained taking 1 mg/day of colchicine, with good therapeutic response. She has had no attacks of FMF for the last 6 months. Patient 2 declined colchicine treatment because her symptoms have been mild.

Family 2. Patient 3 was a 19-year-old woman. At age 9 years she had febrile attacks above 38°C once monthly. Each febrile attack lasted for about 2 days and was accompanied by chest or back pain. The results of clinical tests at the time of febrile attacks showed increased CRP level (8–12 mg/dl) and erythrocyte sedimentation rate (27–64 mm/h), but no elevated leukocyte count. Although infection, malignant tumor, or collagen disease was suspected no such diagnoses were confirmed. We followed her with symptomatic treatment. The patient continued to experience febrile attacks, accompanied by chest or abdominal pain, every month or two. These attacks forced her to rest in bed, and adrenocortical hormones and analgesics were administered to alleviate the pain. Her family history was unremarkable, and there was no history of consanguineous marriage. She was diagnosed as having FMF, but has declined treatment with colchicine despite discussions about the need to take medication.

There is no relation between Family 1 and 2, and there are no Mediterranean ancestors in these families.

Results. Since the "hot spot" of mutations was reported to be in exon 10, we performed sequence analysis of the region^{4,5}. It revealed that Patients 1 and 2 are homozygous for a mutation M694I, which is already known in FMF⁵. The parents in Family 1, Patient 3, and her mother are heterozygous for the same mutation (Figure 1). In Family 2, we failed to detect another mutation in the other allele in areas other than the hot spot.

DISCUSSION

Although FMF is common among people in the Mediterranean region, it is rare in the rest of the world. In areas where FMF is not common, it is very difficult to diagnose FMF; patients with this disease are often misdiagnosed as having collagen disease, infection, or acute abdomen, and thus are treated unsuccessfully. Although a few published

From the Department of Pediatrics, Graduate School of Medicine, Shinshu University, Matsumoto, Japan.

K. Shinozaki, MD; K. Agematsu, MD, PhD; K. Yasui, MD, PhD; H. Nagumo, MD, PhD; H. Naitoh, MD, PhD; K. Naganuma, MD, PhD; A. Komiyama, MD, PhD.

Address reprint requests to Dr. K. Agematsu, Department of Pediatrics, Graduate School of Medicine, Shinshu University, Asahi 3-1-1, Matsumoto 390-8621, Japan. E-mail: agemats@gipac.shinshu-u.ac.jp

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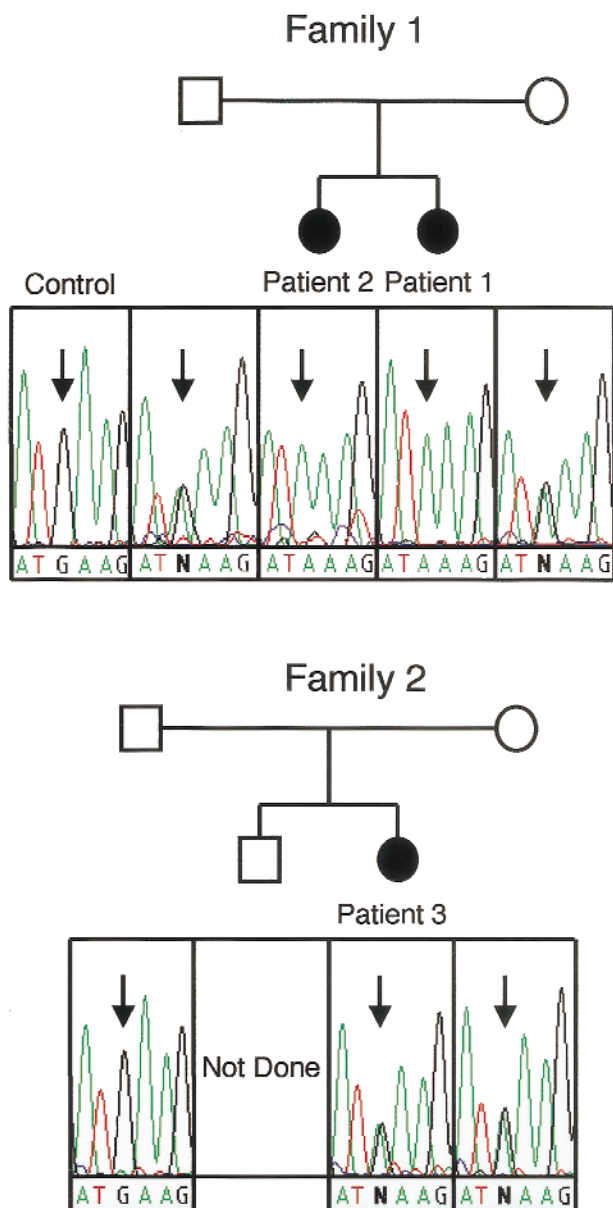


Figure 1. Pedigrees and DNA sequence electropherograms demonstrating the M694I mutation. On the pedigree diagram, closed symbols represent affected family members. The panel below the symbol shows the DNA sequence electropherogram. Arrows indicate "hot spots" of mutations.

reports of FMF can be found in Japanese, there are no reports with a confirmed genetic mutation^{6,7}. Japan has been a racially homogenous nation for a long time, and contacts with foreigners and immigration have been very limited

until recently. The occurrence of the M694I mutation in our Japanese patients suggests that this mutation is likely to occur, or that these patients share a common ancestor with the people in the Mediterranean. In any event, FMF may latently exist in Japanese and probably in East Asians. Further studies are expected to disclose the distribution of FMF in East Asians. In this respect, of interest is the incidence of Behçet's disease, which is common in some Mediterranean races, and is also fairly high among Japanese. The finding that these rare diseases occur in 2 such distinct populations probably reflects the possibility of the genetic relation between FMF and Behçet's disease^{8,9}.

Although our Japanese sisters (Patient 1 and 2) had the same genetic mutation, they did not exhibit the same symptoms, indicating wide variation of clinical features of FMF. Although we failed to detect another mutation in the other allele in Patient 3, we made a diagnosis of FMF on the basis of typical clinical course and relatively common M694I mutation. FMF occurs during childhood in many cases, and some patients develop amyloidosis followed by nephrotic syndrome or even renal failure, unless adequately treated. Thus, even in areas of the world where FMF is rare, pediatricians should suspect FMF in children or adolescents experiencing periodic attacks of fever.

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