Hereditary Periodic Fever Syndromes in Japan

Key words: hereditary periodic fever syndromes, familial Mediterranean fever (FMF), tumor necrosis factor receptor-associated periodic syndrome (TRAPS), mutation, pyrin

Hereditary periodic fever syndromes are hereditary inflammatory disorders with recurrent fever, and consist of a unique group of diseases, such as familial Mediterranean fever (FMF), hyperimmunoglobulinemia D with periodic fever syndrome (HIDS), pyogenic sterile arthritis, pyoderma gangrenosum, an acne (PAPA), Muckle-Wells syndrome (MWS), familial cold autoinflammatory syndrome (FCAS), neonatal onset multisystem inflammatory disorder/chronic infantile neurological cutaneous and articular syndrome (NOMID/CINCA), Blau syndrome, and tumor necrosis factor receptor-associated periodic syndrome (TRAPS) (1–3). Susceptibility genes for FMF, HIDS, PAPA, Blau syndrome, and TRAPS were reported to MEFV, MVK, CD2BP1/PSIP1, CARD15/NOD2, and TNFRSF1A, respectively (2, 4, 5).

Although MWS, FCAS, and NOMID/CINCA were previously described as distinct clinical entities, CIAS1 was recently identified as a susceptible gene for these syndromes (6).

FMF is the autosomal recessive disorder observed most frequently in Jewish, Armenian, Arab, Turkish, and Italian, and interestingly, the inheritance of FMF sometimes shows an autosomal dominant or pseudodominant pattern (7). Febrile attacks last one to three days and present with or without abdominal pain, chest pain, skin rash, and arthritis (1, 8). FMF is caused by mutations in MEFV, a 10-exon gene encoded on the short arm of chromosome 16. MEFV codes for pyrin (or marenostrin), a 781 amino acid protein that is predominantly expressed in polymorphonuclear leukocytes (PMNs) and cytokine-activated monocytes. Pyrin inhibits the binding of cryopyrin and ASC (apoptosis-associated speck-like protein containing a card). As cryopyrin-ASC complexes increase NF-kB signaling and mediate caspase-1 activation, pyrin plays an anti-inflammatory role and its dysfunction results in increment of autoinflammatory responses (4).

More than 80 MEFV mutations were reported (INFEVERS; http://fmf.igh.cnrs.fr/infevers/index.html) and most mutations are located in a C-terminal B30.2 domain of pyrin but its function remains unknown (4).

FMF was thought to be a rare disease in Japan until quite recently. Although a few cases were diagnosed by MEFV gene analysis, there has been a proliferation of individual FMF case reports from Japan (9–14). In this issue, Nakamura et al report a 34-year-old Japanese female FMF patient with heterozygous E148Q/M694I mutation (15). Interestingly, E148Q heterozygous mutation seems to enhance the FMF clinical symptoms of M694I heterozygous phenotype in her pedigree analysis (15).

The role of E148Q in FMF is controversial (16–18). As there is a high prevalence of E148Q in normal controls (3–10%), especially in the Japanese population (16%) (19) and no significant differences between the FMF group and control group in the E148Q rate, E148Q is thought to be a benign polymorphism and not a disease-causing mutation. However, this case lead us to consider that E148Q has a phenotypic effect in a compound heterozygote with a severe mutation (ie. M694).

Colchicine is the standard drug for FMF therapy (1, 8). Colchicine effectively prevents acute attacks and amyloidosis by modulating cytokine production derived from PMN, inhibiting leukocyte chemotaxis, changing the expression of adhesion molecules on the vascular endothelium and PMN, and preventing the extracellular assembly of amyloid subunits into mature amyloid fibrils (8). Due to the adverse effects of colchicines, like diarrhea, pancytopenia, myopathy, and rash, physicians have discontinued giving it to FMF patients. Many other drugs for FMF, such as interferon alpha, thalidomide, reserpine, prazosin hydrochloride (20), and herbal medicine (19) have been reported to date (8).

Because of the side effects, Nakamura et al tried to use azelastine, an anti-allergic drug in this patient rather than colchicine, and azelastine successfully reduced the frequency and degree of the attacks (15). As it is similar to colchicine in function that it inhibits neutrophil chemotaxis and has less adverse effects, azelastine may be one of the promising drugs for FMF.

Recently Japanese physicians have recognized hereditary periodic fever syndromes as one of the differential diagnoses of unknown fever in Japanese patients. In addition to FMF, recently there were three reports of Japanese TRAPS patients and pedigrees (21–23). Since the clinical symptoms and the location of mutations in the patients with Japanese hereditary periodic fever syndromes might differ from those in patients from other countries, it is important for us to accumulate clinical cases to elucidate the mechanisms of hereditary periodic fever syndromes.
References