Atypical phenotype without fever in a Japanese family with an autosomal dominant transmission of familial Mediterranean fever due to heterozygous MEFV Thr577Asn mutations

Sir.

Familial Mediterranean fever (FMF) is an inherited autoinflammatory disease caused by mutations in the Mediterranean fever (MEFV) gene. Although FMF is classically transmitted by autosomal recessive transmission, rare cases of dominant transmission have been reported (1-3). Herein, we report a rare case of a Japanese family with an autosomal dominant transmission of FMF due to heterozygous Thr577Asn (T577N) mutations in the exon 8 of MEFV. A 55-year-old Japanese man had been experiencing recurrent attacks of chest pain and arthritis without fever lasting for 3-4 days since 15 years of age. His laboratory findings showed high C-reactive protein and serum amyloid A levels during these attacks, leading to a suspicion of FMF. After treatment with 1.0-mg/day colchicine, no further attacks were observed. He was finally diagnosed with FMF according to the Tel Hashomer criteria (4). Because his family members had similar, common recurrent symptoms, genetic analyses for MEFV, MVK, TNFRSF1A, NLRP3, PSTPIP1, NLRP12, TNFAIP3, IL1RN, IL36RN and CARD14 were performed in the proband using targeted next-generation sequencing, revealing homozygous E148Q, heterozygous L110P variant and T577N mutation in MEFV. In addition, MEFV was analysed in all family members using targeted next-generation sequencing, further confirming the detected mutations using direct sequencing. All family members with heterozygous MEFV T577N mutations demonstrated recurrent chest pain and/or arthritis without fever, whereas his daughter, who had the heterozygous MEFV Glu148Gln (E148Q) variant, only exhibited recurrent abdominal pain and arthritis with high fever (Fig. 1 A, B). All family members with clinical symptoms showed good response to colchicine and were finally diagnosed with FMF. Both the proband and his daughter were diagnosed with Henoch-Schönlein purpura (HSP) in their childhood. In addition, both the proband and his mother had a history of non-bacterial osteomyelitis in their wrists. Although the genetic characteristics of patients with FMF in Japan include a lower percentage of MEFV exon 10 mutations with a high penetrance and percentage of MEFV exon 2 mutations and low penetrance than those of patients with FMF in Western countries (5), previous reports suggested that the manifestations of FMF are primarily attributed to the difference in the mutational pattern in MEFV (5-7). Thr577 amino acid exists in the coiled-coil domain, followed by the B30.2 domain of pyrin; mutations at this amino acid residue are extremely rare (8). Recently, all members with both homozygous Glu148Gln (E148Q) and heterozygous MEFV T577N mutations/variants in a Japanese family were reported to inherit autoinflammatory disorders characterised by recurrent chest pain without fever (3). However, it remains unclear which mutation/variant of T577N or E148Q contributes to these inheritable and clinical characteristics. In our cases, all family members with heterozygous MEFV T577N mutations experienced recurrent chest pain and/or arthritis without fever (Table I). While only one family member with only heterozygous MEFV exon 2 variants experienced recurrent abdominal pain and high fever, these symptoms were completely different from those of other family members with heterozygous MEFV T577N mutations. These findings suggest different clinical characteristics and genetic penetrance between MEFV mutation/variant of T577N and exon 2. Thus, MEFV T577N mutations may contribute to atypical phenotype presenting without fever and may cause autosomal dominant transmission due to extremely high penetrance. In addition, although some reports have dem-

Fig. 1. (A) Direct sequencing of MEFV exon 8. Red arrow indicates heterozygous MEFV T577N mutations among some members of the Japanese family. (B) Pedigree of the Japanese family. Squares and circles indicate male and female family members, respectively. Diagonal lines indicate deceased individuals. Black arrow indicates the proband. MEFV generic analyses were performed in all members indicated using asterisks, and mutations with amino acid substitution detected using genetic analyses are shown below squares or circles. Mentioned shapes filled with black colour represent members with recurrent clinical symptoms and the details and onset age of these symptoms are also shown below the shapes.
onstrated a comparatively high prevalence of MEFV mutations among patients with HSP (9) and non-bacterial osteomyelitis as a complication of FMF (10), high frequencies of previous HSP and non-bacterial osteomyelitis were noted in our cases and may be caused by MEFV T577N mutations.

When some members in family have recurrent FMF-related symptoms, even without fever, the existence of MEFV T577N mutations should be considered and MEFV genetic analyses should be performed.

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