

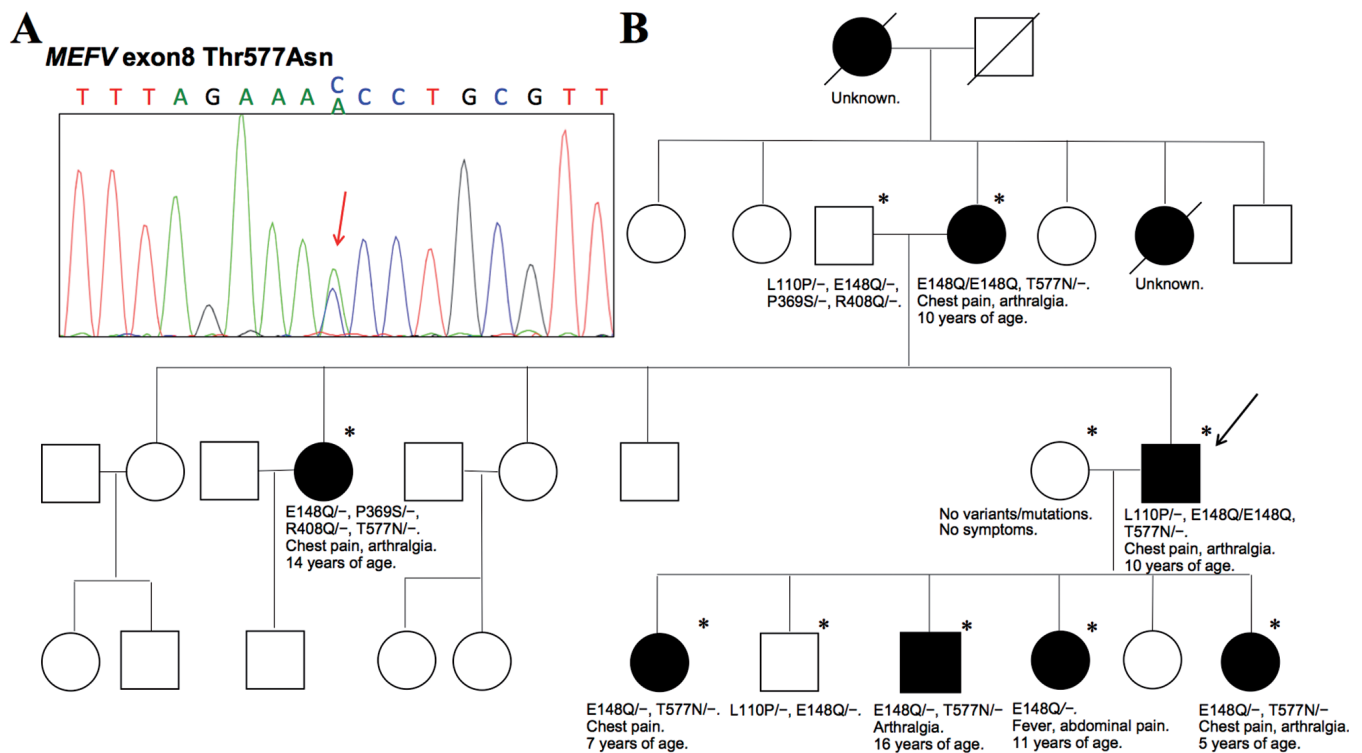
# Atypical phenotype without fever in a Japanese family with an autosomal dominant transmission of familial Mediterranean fever due to heterozygous *MEFV* Thr577Asn mutations

Sirs,  
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. Aforementioned 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.

# Letters to the Editors

**Table 1.** Characteristics of typical FMF cases, previous reports with heterozygous MEFV T577N mutations and present case.

Characteristics	Typical FMF	Previous reports		Proband	Mother	Sister	Present cases			
		Stoffels <i>et al.</i> (1)	Nakaseko <i>et al.</i> (3)				Eldest daughter	Third daughter	Eldest son	Fourth daughter
Types of MEFV mutations/variants	Great variety	Heterozygous T577N	Homozygous E148Q Heterozygous T577N	Heterozygous L110P Homozygous E148Q Heterozygous T577N	Homozygous E148Q Heterozygous T577N	Heterozygous E148Q P369S Heterozygous R408Q Heterozygous T577N	Heterozygous E148Q T577N	Heterozygous E148Q	Heterozygous E148Q T577N	Heterozygous E148Q T 5 7 7 N
Inheritance	Autosomal recessive	Autosomal dominant	Autosomal dominant probable	Autosomal dominant						
Age at onset (years)	Superiority of young-onset	6, 10	3, 5, 16	10	10	14	5	11	16	7
Fever	++	++	–	–	–	–	–	+	–	–
Chest pain	+	++	++	++	++	++	++	–	++	–
Abdominal pain	++	++	±	–	–	–	–	+	–	–
Arthralgia	+	++	–	++	++	++	++	+	–	+
Skin lesions	+	+	–	–	–	–	–	–	–	–
Duration of the attacks	1–3 days	Days to weeks	Days to months	3–4 days	1–2 days	1–2 days	3–4 days	3–4 days	2–3 days	2–3 days
Good response to colchicine	++	++	++	++	++	++	++	++	++	++
History of HSP	±	NA	NA	+	–	–	+	–	–	–

FMF: familial Mediterranean fever; MEFV: Mediterranean fever; HSP: Henoch-Schönlein purpura; NA: not available

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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