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RAPID COMMUNICATION

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# Tumor necrosis factor receptor-associated periodic syndrome with a C30R mutation in a Japanese family

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In 1999, tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS) was described as an autoinflammatory syndrome characterized by periodic fever, rashes, abdominal pain, myalgia, periorbital edema, and arthritis, strongly associated with heterozygous mutations in the gene encoding TNF receptor type 1 (*TNFRSF1A*).[1] Tumor necrosis factor-α exerts its many proinflammatory effects through two distinct receptors: TNFRSF1A (TNFR1, p55/p60-TNFR) and TNFRSF1B (TNFR2, p75/p80-TNFR). TRAPS is associated with substitution of amino acids in the extracellular domain of TNFRSF1A.[1] The *TNFRSF1A* gene mutations were at first thought to be associated with dysregulation of shedding of TNFRSF1A,[1,2] and it was recently reported that the mutations may spontaneously induce the alternative signaling, independent of binding of TNF-α.[3] It is believed that TRAPS is a rare disease in Japanese individuals. Only three families with TRAPS have been reported before 2006: the families had the C70S mutation,[4] T61I mutation,[5] and C30Y mutation.[6] We encountered a TRAPS family with substitution of the 30th amino acid of TNFRSF1A, cysteine to arginine (C30R). The nonsynonymous change resulted from a single-nucleotide mutation, T to C at +7876 bp from the transcription start site of the *TNFRSF1A* gene (NCBI: AY131997) (Fig. 1A), which has never been found in Japanese individuals, although this mutation was reported in an Irish-American family.[1]

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In the present case, the patient family consisted of a woman and her two sons (Fig. 1B). Although the woman had experienced periodic high-grade fever of unknown origin since the birth of her elder son in 1993, her diagnosis was not determined for a long time. Fever was often accompanied by skin rash and lymphadenopathy, but she did not experience arthritis or serositis. Abnormal laboratory findings with leukocytosis and high levels of C-reactive protein (CRP) were always shown during fever attack. However, neither rheumatoid factor (RF) nor antinuclear antibody (ANA) was detected. A diagnosis of adult-onset Still's disease (AOSD) was made in 2004, although the levels of serum ferritin were always lower than 500 ng/ml. Her elder son presented with periodic high-grade fever combined with skin rash and arthralgia several times a year after he was 7 months old. No signs of chronic arthritis, myositis, abdominal pain, conjunctivitis/periorbital edema, or chest pain were observed during the inflammatory attacks. A tentative diagnosis of systemic juvenile idiopathic arthritis (JIA) was made in 1996, and he was treated with aspirin. However, no beneficial effect was observed, and he was then treated with prednisolone (15–20 mg/day), and his fever and rash improved immediately. When the dose of prednisolone was decreased to 5–10 mg/day, high-grade fever recurred every few months. The younger son also had periodic high-grade fever after age 3 years, in 1999, and JIA was tentatively diagnosed in 2000. His fever did not respond to nonsteroidal anti-inflammatory drugs and various immunosuppressive therapies, including corticosteroids, γ-globulin, and methotrexate. However, fever with an increase in acute-phase proteins (CRP, fibrinogen) disappeared for several months independent of treatment.

We suspected that the family members' periodic fever might be due to TRAPS or familial Mediterranean fever, in view of their clinical course and familial history. Genomic DNA was obtained after informed consent was given according to the protocol of the Tokyo Women's Medical University Ethics Committee. DNA sequencing revealed that all three patients had a point mutation of *TNFRSF1A* at +7876 in only one chromosome, leading to substitution of the 30th amino acid in exon 2, as shown Fig. 1A. We also

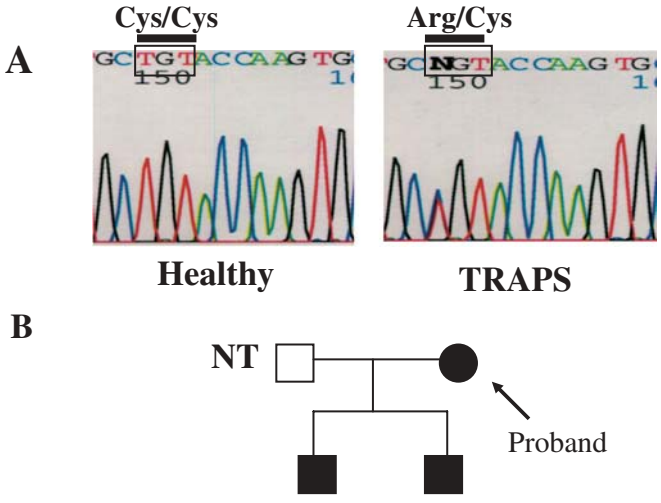


**Fig. 1.** **A** DNA sequence of TNFRSF1A. Representative result for the three patients is shown in the TNF receptor-associated periodic syndrome (*TRAPS*) panel, which indicates a C30R mutation (TGT to CGT). DNA sequence without mutation is shown in the Healthy panel. *Cys*, cysteine; *Arg*, arginine. **B** Family pedigree. Patients are indicated by closed symbols (*square*: male; *circle*: female). *NT*, no genetic analysis performed

measured serum levels of soluble (s) TNFRSF1A in the two boys and in 10 patients with rheumatoid arthritis (RA) (disease control subjects) using an enzyme-liked immunosorbent assay kit (R & D Systems, Minneapolis, MN, USA). Serum samples were prepared when the study subject exhibited active inflammation (serum levels of CRP greater than 2.0 mg/dl). The mean levels of sTNFRSF1A in plasma drawn on two different days were 311.5 pg/ml for the elder son and 435.0 pg/ml for the younger son, whereas the mean level for the 10 patients with RA was 967.5 pg/ml. We diagnosed their disease as TRAPS, with a mutation not previously demonstrated in Japanese individuals.

Although AOSD and systemic JIA (Still's disease) are rare systemic inflammatory disorders of unknown etiology, they are believed to be more frequent than TRAPS in Japanese individuals. However, the TRAPS family in the present report was classified as having AOSD and JIA as the result of fulfilling classification criteria,[7,8] which suggests that the *TNFRSF1A* gene should be considered in the differential diagnosis of AOSD and systemic JIA, especially when the patients have a family history of inflammatory disease.

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