is reported to be inhibited by pyrin [17]. Consistent with this, our results indicated that WT pyrin suppresses IL-8 secretion from SW982 cells (Fig. 2). However, unexpectedly, both ASC and caspase-1 were at undetectable levels in SW982 cells (Fig. 3), suggesting that inflammasome may have been dispensable in the mechanism of suppression of IL-8 secretion from SW982 cells in our experiment (Fig. 3).

To investigate whether pyrin can suppress IL-8 secretion from another cell line, THP-1, monocytic leukemia cells, we generated stable THP-1 cells stably expressing WT pyrin or mutant pyrin proteins such as E148Q, M694V, or vector control. We found that pyrin can suppress IL-8 secretion from THP-1 cells as well as IL-1β and TNF-α (Fig. 4). Because pyrin was reported to inhibit ASC-related inflammasome signaling [15, 16], suppression of IL-1β and TNF-α secretion from THP-1 cells may be inflammasome-dependent. Considering the results from SW982 and THP-1, we speculate that pyrin may contribute to the suppression of IL-8 secretion by an inflammasome-independent pathway.

What kind of signaling pathway does pyrin affect? We performed Western blotting analyses for the p38, ERK, and NF-κB pathways of SW982 cells. Interestingly, we found that p38 and ERK were spontaneously phosphorylated (Fig. 5a, b) and just ERK was less phosphorylated when WT pyrin was ectopically expressed in SW982 cells (Fig. 5b). We also found that NF-κB p65 was not phosphorylated (Fig. 5c). Thus, we speculate that pyrin affects at least the ERK pathway independently of inflammasome.

Notably, peripheral blood mononuclear cells from FMF patients exhibit higher IL-8 secretion than those from healthy volunteers, even when plated on a culture dish (Fig. 6a, b), suggesting that only mechanical stress may affect clinical manifestations of FMF patients.

The most frequent mutation of FMF patients in Middle Eastern countries is reported to be M694V, which is associated with arthritis and severe clinical manifestations [25], whereas no M694V mutation was found among Japanese FMF patients [6–9]. Japanese FMF patients exhibit atypical clinical manifestations, and approximately half of FMF patients exhibit E148Q/M694I compound heterozygosity, E148Q heterozygosity, or M694I homozygosity [9]. As for the clinical significance of our results in correlation with the above description, pyrin-M694V hardly suppressed IL-8 secretion from SW982 and THP-1 cells (Figs. 2, 4, respectively), whereas E148Q, M694I, and E148Q+M694I still had the ability to suppress IL-8 secretion from SW982 cells (Fig. 2).

In conclusion, our data demonstrate that FMF-related mutated pyrin proteins have a low ability to suppress IL-8 secretion from SW982 cells independently of inflammasome. Common mutations in Japanese FMF patients of E148Q, M694I, and E148Q/M694I result in retention of the power to suppress IL-8 secretion from SW982 cells, rather than the M694V mutation, which may explain why atypical clinical manifestations are common in Japanese FMF populations.

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REVIEW ARTICLE

Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) in Japan: a review of the literature

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Abstract Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is a dominantly inherited autoinflammatory syndrome that is characterized by recurrent episodes of fever attacks associated with rashes, abdominal pain, myalgia, conjunctivitis, chest pain, and arthralgia. Some patients have severe abdominal pain leading to abdominal surgery. Most reported cases of TRAPS involve patients of European ancestry, but there have been nine reports of patients with TRAPS in Japan. Here, we review these nine case reports. Reported *TNFRSF1A* gene mutations in these nine index patients were C70S, T61I, C70G, C30Y, C30R, N101K, and N25D. Fever (100 %) was seen in all 23 cases. Most patients developed rash (erythema) (84.6 %) and arthralgia (73.3 %), and half suffered from myalgia (54.5 %) and abdominal pain (50.0 %). Although one-half of the patients suffered from abdominal pain, none underwent surgery. In contrast, only a small percentage of patients suffered from chest pain (20.0 %), conjunctivitis (20.0 %), and headache (10.0 %). Almost all cases (95.7 %) concerned patients whose relatives suffered from periodic fever. These findings suggest that the clinical features of Japanese TRAPS patients may be milder than those of patients in Western countries.

Keywords TRAPS · Autoinflammatory disease · *TNFRSF1A* gene mutation · Japan

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Introduction

Tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS), formerly known as Familial Hibernian Fever [1], is an inherited autoinflammatory syndrome that is caused by mutations in the TNF receptor type 1 (*TNFRSF1A*), the gene encoding for the 55-kDa receptor for TNF [2–6]. The *TNFRSF1A* gene mutations were first thought to be associated with a deregulation of the shedding of TNFRSF1A [2], and in 2006 Lobito and colleagues [7] reported that the mutations may spontaneously induce alternative signaling, independent of binding TNF-α. Recently, the concerted pro-inflammatory action of cell-surface wild-type and accumulated intracellular mutant TNF receptors has been reported [8]. Since TRAPS was first proposed as a genetic diagnosis, only those patients with demonstrable TNF receptor mutations should be included as having TRAPS [2–6].

More than 100 different mutations have been reported for patients with TRAPS in INFEVERS, a mutational database accessible on the World Wide Web at http://fmf.igh.cnrs.fr/infevers. However, a few *TNFRSF1A* gene mutations are also found in about 1 % of the general population [9]. The *TNFRSF1A* gene mutations that are present in unaffected individuals are considered to be low-penetrance gene mutations [10].

TRAPS is characterized by recurrent episodes of fever attacks associated with rash, abdominal pain, myalgia, conjunctivitis, chest pain, and arthralgia [2–6]. Hull and colleagues [3] reported the clinical characteristics of 50 genetically confirmed American TRAPS patients (i.e., 47 of European ancestry, 2 Puerto Ricans, and 1 African American). Common symptoms associated with periodic fever were myalgia (98.0 %), conjunctivitis/periorbital edema (90.0 %), abdominal pain (88.0 %), rash (86.0 %), arthralgia (84.0 %), and pleuritis (54.0 %). Among these 50 patients, 26 (52.0 %) had abdominal pain which led to abdominal surgery. Pelagatti and colleagues [11] reported the clinical profiles of 11 Italian patients with TRAPS, noting that the recurrent fever attacks were associated with abdominal pain (81.8 %), arthralgia (63.6 %), myalgia (63.6 %), rash (54.4 %), headache (54.4 %), chest pain/pleuritis (27.2 %), and conjunctivitis (9.0 %). Although these authors reported that arthralgia (63.6 %) was frequently associated with periodic fever, arthritis (27.2 %) was less common [11].

TRAPS was originally described as occurring among Irish and Scottish descendants [1], and most reported patients with TRAPS are of Northern European ancestry [2–6], although any ethnic group may be afflicted in this disease [2–6].

We have reported Japanese TRAPS families with the C70G mutation [12] and C30R mutation [13] of the *TNFRSF1A* gene. However, including our reports [12, 13], there have been only nine reported cases of patients with genetically confirmed TRAPS in Japan [12–20]. Moreover, to our knowledge, no TRAPS patients have been reported in East Asian countries, with the exception of Japan. In order to clarify the characteristics of TRAPS in the East Asian population, as well as to explore the modified diagnostic criteria for Japanese TRAPS patients, we reviewed the published case reports on Japanese patients with genetically confirmed TRAPS.

Japanese patients with TRAPS

Table 1 presents a summary of the reported cases of Japanese patients with TRAPS and information on their families [12–20]. Seven different mutations of the *TNFRSF1A* gene were reported in these nine Japanese patients with TRAPS: C70S (T295A) [14], T61I (C269T) [15, 20], C70G (T295G) [12], C30Y (G176A) [16, 19], C30R (T175C) [13], N101K (C390G) [17], and N25D (A160G) [18].

All mutations reported among these Japanese patients are located in the exon regions. Among the nine reports of gene mutations of *TNFRSF1A*, six reports demonstrated that family members also had gene mutations as well as clinical symptoms [12–16, 20]. One report showed that family members had episodes of periodic fever [18, 19], but no genetic analysis was performed [18, 19]. Another paper reported that a patient with TRAPS had no family history of the disease [17].

Three of the nine index cases (30.0 %) and six of 23 patients (26.1 %) had been misdiagnosed as having juvenile idiopathic arthritis (JIA) or adult onset Still's disease prior to the diagnosis of TRAPS being established [13, 16, 19] (see remarks in Table 1). All of these patients had a family history of periodic fever [13, 16, 19].

As shown in Table 2, fever was observed in all Japanese index cases [12–20]. Almost 90 % of all index patients developed rash (erythema) [12–18, 20], and nearly 80 % suffered from arthralgia [12, 14–19]; only half suffered from myalgia (55.6 %) [15, 16, 18–20]. In contrast, only a small percentage of Japanese index cases suffered from abdominal pain (33.3 %) [16, 19, 20], chest pain (22.2 %) [16, 19], conjunctivitis (22.2 %) [14, 15], and headache (11.1 %) [18].

In almost 70 % of the Japanese index cases, fever and rash improved after glucocorticoid therapy (66.7 %) [13–17, 19]. With the exception of two index cases who had no chance to use glucocorticoid [12, 18], fever and rash improved after glucocorticoid therapy in 6 out of 9 Japanese index cases with TRAPS (77.8 %) [13–17, 19]. All Japanese index cases but one (88.9 %) had patients with periodic fever occurring among their relatives [12–16, 18–20].

Table 2 also presents the summary of the clinical symptoms of Japanese index cases and TRAPS patients in their families [12–20]. Fever was seen in all cases [12–20], and most patients presented with rash (erythema) (84.6 %) [12–18, 20] and arthralgia (73.3 %) [12–19], and half suffered from myalgia (54.5 %) [15, 16, 18–20] and abdominal pain (50.0 %) [15, 16, 19, 20]. Although half of the Japanese TRAPS patients suffered from abdominal pain, none underwent surgery [15, 16, 19, 20]. In contrast, only a small percentage of patients suffered from chest pain (20.0 %) [16, 19], conjunctivitis (20.0 %) [14, 15], and headache (10.0 %) [17]. Among the ten patients who received glucocorticoid therapy, 80 % were responsive [13–17, 19]. All cases but one (95.7 %) had relatives who suffered from periodic fever attacks [12–16, 18–20].

Discussion

Hereditary periodic fevers are a group of inherited systemic disorders characterized by episodes of fever with localized inflammation that often affects serosal membranes, joints, and skin [4]. The clinical features of periodic fevers are episodes of fever and localized inflammation, which can include abdominal pain, pleuritic chest pain, arthritis or

Table 1 Reported cases of Japanese patients with TRAPS and their families

References	Age (years) and sex	Kinship	Age at onset (years)	*TNFRSF1A* gene mutation	Fever	Abdominal pain	Myalgia	Rash (erythema)	Conjunctivitis (periorbital edema)	Chest pain (pleuritis)	Arthralgia	Other symptoms	Response to glucocorticoids	Remarks
Kusuhara et al. [14]	14F	Proband	0 (2 months)	C70S (T295A)	Positive	Negative	Negative	Positive	Positive	Negative	Positive	Negative	Responder	Her 17-year-old sister was a mutation carrier with C70S (T295A)
	48F	Mother	Childhood	C70S (T295A)	Positive	NA	NA	NA	NA	NA	NA	NA	NA	Similar symptoms were observed as the proband
	45M	Maternal uncle	NA	Not examined	NA	NA	NA	NA	NA	NA	NA	NA	NA	Similar symptoms were observed as the proband
	Deceased (85F)	Maternal great grandmother	NA	Not examined	NA	NA	NA	NA	NA	NA	NA	NA	NA	Similar symptoms were observed as the proband
	Deceased (57M)	Maternal grandfather	NA	Not examined	NA	NA	NA	NA	NA	NA	NA	NA	NA	Similar symptoms were observed as the proband
Ida et al. [15]	27F	Proband	6 or 7	T61I (C269T)	Positive	Negative	Positive	Positive	Positive	Negative	Positive	Negative	Responder	She was diagnosed with SLE at the age of 21 years. Mother, 3 sisters, 2 brothers, and 1 nephew were mutation carriers with T61I (C269T)
	18F	Niece	NA	T61I (C269T)	Positive	Positive	NA	Positive	NA	NA	Negative	NA	NA	Established the diagnosis of TRAPS but did not fulfil the criteria for SLE
	6M	Nephew	NA	T61I (C269T)	Positive	Positive	NA	Negative	NA	NA	Negative	NA	NA	Established the diagnosis of TRAPS but did not fulfil the criteria for SLE
	4F	Niece	NA	T61I (C269T)	Positive	Positive	NA	Positive	NA	NA	Positive	NA	NA	Established the diagnosis of TRAPS but did not fulfil the criteria for SLE
Horiuchi et al. [12]	32M	Proband	Childhood	C70G (T295G)	Positive	Negative	Negative	Positive	Negative	Negative	Positive	Negative	No chance to use	
	87M	Grandfather	NA	C70G (T295G)	NA	NA	NA	NA	NA	NA	NA	NA	NA	Similar symptoms were observed as the proband
	55M	Father	NA	C70G (T295G)	NA	NA	NA	NA	NA	NA	NA	NA	NA	Similar symptoms were observed as the proband
	33M	Brother	NA	Not examined	NA	NA	NA	NA	NA	NA	NA	NA	NA	Similar symptoms were observed as the proband

Table 1 continued

References	Age (years) and sex	Kinship	Age at onset (years)	*TNFRSF1A* gene mutation	Fever	Abdominal pain	Myalgia	Rash (erythema)	Conjunctivitis (periorbital edema)	Chest pain (pleuritis)	Arthralgia	Other symptoms	Response to glucocorticoids	Remarks
Manki et al. [16]	10M	Proband	0 (6 months)	C30Y (G176A)	Positive	Positive	Positive	Positive	Negative	Positive	Positive	Negative	Responder	He was misdiagnosed as systemic JIA based on the ILAR criteria (prolonged spike-fever, skin rash, arthritis, and pericarditis) at 3 years of age
	7F	Sister	3	C30Y (G176A)	Positive	Positive	NA	NA	NA	NA	Positive	NA	Responder	She was suspected of having systemic JIA at 3 years of age although the clinical symptoms did not fulfill the ILAR criteria
	38M	Mother	28	Not examined	Positive	NA	Positive	NA	NA	NA	Positive	NA	NA	She had recurrent fever, arthralgia, and myalgia after the delivery of a daughter
Takagi et al. [13]	36F	Proband	22	C30R (T175C)	Positive	Negative	Negative	Positive	Negative	Negative	Negative	Negative	Responder	She had experienced periodic high-grade fever after the birth of her elder son. Fever was often accompanied with skin rash and lymphadenopathy. She was diagnosed as having adult onset Still's disease before the diagnosis of TRAPS
	11M	Son	0 (7 months)	C30R (T175C)	Positive	Negative	Negative	Positive	Negative	Negative	Positive	Negative	Responder	Tentatively diagnosed as having JIA before the diagnosis of TRAPS
	9M	Son	3	C30R (T175C)	Positive	NA	NA	NA	NA	NA	NA	NA	Non-responder	Tentatively diagnosed as having JIA before the diagnosis of TRAPS. Fever did not respond to either corticosteroid or non-steroidal anti-inflammatory drugs, but disappeared for several months independent of treatment
Nakamura et al. [17]	17F	Proband	17	N101K (C390G)	Positive	Negative	Negative	Positive	Negative	Negative	Positive	Negative	Responder	Sporadic case. No family history of TRAPS was described

Table 1 continued

References	Age (years) and sex	Kinship	Age at onset (years)	*TNFRSF1A* gene mutation	Fever	Abdominal pain	Myalgia	Rash (erythema)	Conjunctivitis (periorbital edema)	Chest pain (pleuritis)	Arthralgia	Other symptoms	Response to glucocorticoids	Remarks
Nakamura and Tokura [18]	29F	Proband	29	N25D (A160G[a])	Positive	Negative	Positive	Positive	Negative	Negative	Positive	Positive[b]	No chance to use	Her son had fever one to three times a month since he was 2 months old. Her grandfather also had episodes of periodic fever for a long time
Kai et al. [19]	21F	Proband	Childhood	C30Y (G176A)	Positive	Positive	Positive	Negative	Negative	Positive	Positive	Negative	Responder	She was misdiagnosed as systemic JIA at 11 years of age. Her newborn baby had unexplained fever and the plan was to examine gene mutations related to TRAPS. Her father had died with amyloidosis
Ohmori et al. [20]	16F	Proband	15	T61I (C269T)	Positive	Positive	Positive	Positive	Negative	Negative	Negative	Positive[c]	Non-responder	Oral prednisolone (20 mg/day) could not reduce inflammation but anti-TNF antibody and infliximab did so. Her mother and grandfather were diagnosed as TRAPS patients with similar episodes of inflammation and T61I mutation

TRAPS tumor necrosis factor receptor-associated periodic syndrome, *F* female, *M* male, *NA* not available, *TNFRSF1A* TNF receptor superfamily 1A, *SLE* systemic lupus erythematosus, *JIA* juvenile idiopathic arthritis, *ILAR* International League Against Rheumatism

[a] Changed from A73G [14] to A160G according to a mutational database accessible on the World Wide Web at http://fmf.igh.cnrs.fr/infevers

[b] Headache

[c] Dyspnea, localized edema

Table 2 Summary of clinical symptoms of Japanese TRAPS patients

Patients with TRAPS	Female sex (%)	Age at onset (years)	*TNFRSF1A* gene mutation (%)	Fever	Abdominal pain	Myalgia	Rash (erythema)	Conjunctivitis (periorbital edema)	Chest pain (pleuritis)	Arthralgia	Headache	Response to glucocorticoids	Family history of periodic fever
Index cases [12–20]	$n = 9$	$n = 9$	$n = 9$	$n = 9$	$n = 9$	$n = 9$	$n = 9$	$n = 9$	$n = 9$	$n = 9$	$n = 9$	$n = 9$	$n = 9$
	7 (77.8 %)	0 (2 months) to 29	9 (100 %)	9 (100 %)	3 (33.3 %)	5 (55.6 %)	8 (88.9 %)	2 (22.2 %)	2 (22.2 %)	7 (77.8 %)	1 (11.1 %)	6 (66.7 %)[b]	8 (88.9 %)
Index cases and patients in their family [12–20]	$n = 23$	$n = 14$	$n = 23$	$n = 17$	$n = 14$	$n = 11$	$n = 13$	$n = 10$	$n = 10$	$n = 15$	$n = 10$	$n = 12$	$n = 23$
	12 (52.2 %)	0 (2 months) to 29	18 (78.3 %)[a]	17 (100 %)	7 (50.0 %)	6 (54.5 %)	11 (84.6 %)	2 (20.0 %)	2 (20.0 %)	11 (73.3 %)	1 (10.0 %)	8 (66.7 %)[c]	22 (95.7 %)

[a] 7 of 9 patients (77.8 %) who received glucocorticoids were responders

[b] 5 family members were diagnosed as having TRAPS with clinical symptoms and family histories

[c] 8 of 10 patients (80.0 %) who received glucocorticoids were responders

arthralgia, myalgia, rashes (erythematous macular rash), and conjunctivitis [3, 4]. Periodic fevers can be characterized according to their mode of inheritance—recessively or dominantly inherited [3, 4], with familial Mediterranean fever (FMF) and hyperimmunoglobulinemia D with periodic fever syndrome (HIDS) composing the group of recessively inherited periodic fevers and TRAPS, familial cold autoinflammatory syndrome (FCAS), Muckle–Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease [NOMID; which is also known as chronic infantile neurological cutaneous and articular syndrome (CINCA)] composing the group of dominantly inherited periodic fevers [3, 4].

TRAPS, a dominantly inherited periodic fever [2–6], can be clinically distinguished from other hereditary periodic fevers by a number of characteristics: (1) recurrent attacks that often last >5 days and sometimes several weeks; (2) localized myalgia that is often associated with an overlying macular rash, which together display a centrifugal migratory pattern; (3) conjunctivitis and/or periorbital edema; (4) attenuation of symptoms with glucocorticoid but not with colchicine; (5) an autosomal-dominant mode of inheritance [21].

More than 100 different mutations have been reported for patients with TRAPS in INFEVERS, a mutational database accessible on the World Wide Web at http://fmf.igh.cnrs.fr/infevers. Of the seven mutations identified in the reported cases of Japanese TRAPS, five (C70S [14], T61I [15, 20], C70G [12], N101K [17], N25D [18]) have been reported only in Japan, while the remaining two (C30Y [16, 19], C30R [13]) have also been reported in Western countries. Since there are only 18 genetically confirmed TRAPS patients in Japan [12–20], further studies should be carried out to search for additional mutations among Japanese patients with TRAPS.

In our review of the nine case reports on Japanese TRAPS patients, eight index cases have family histories with periodic fever [12–16, 18–20], while there is only one sporadic case of TRAPS [17]. Ida and colleagues [15], who reported the T61I variant in TRAPS patients associated with systemic lupus erythematosus (SLE), reported that this variant was detected in five of 60 SLE patients (8.3 %) and five of the 120 healthy Japanese individuals in their study (4.2 %). They could not detect any significant difference in the proportion of this variant between the SLE patients and the healthy controls [15]. In addition, Horiuchi and colleagues [12], who reported on TRAPS patients with the C70G *TNFRSF1A* gene mutation, also reported that they identified the T61I variant in one of the 100 healthy Japanese volunteers in their study (1.0 %) [12]. In contrast, Aksentijevich and colleagues [9] also reported the presence of P46L and R92Q *TNFRSF1A* gene variants in TRAPS patients, which were also found in about 1 % of the U.S.

population. In particular, the R92Q mutation is supposed to be a low-penetration mutation that is associated with a milder disease course [11]. Assuming that these three substitutions confer susceptibility to autoinflammatory disease, the penetrance (i.e., the probability of having a disease if a person has a mutation) must be low because the frequency of TRAPS does not reach 1 % of the general population. The T61I, P46L, and R92Q mutations are generally considered to be low-penetrance *TNFRSF1A* gene variants because they are present in symptomatic patients as well as unaffected individuals [10].

The functional significance of T61I on *TNFRSF1A*, which augments TNF signaling, has been reported in Japan. The T61I variant has been associated with a defect in *TNFRSF1A* shedding in peripheral blood mononuclear cells [12]. However, other Japanese investigators did not find any effect on *TNFRSF1A* shedding in the monocytes collected from their patients carrying T61I [15]. In a specific cell population, such as lymphocytes, T61I may be related to the pathogenesis of TRAPS. As the T61I variation has not been reported in Caucasian patients with TRAPS, the clinical and functional importance of T61I variation needs to be clarified within the Japanese population.

There have been many sporadic cases of TRAPS in the absence of the *TNFRSF1A* gene mutation in both Japan [5] and Western countries [9]. However, we cannot eliminate the possibility sporadic cases without any gene mutation, which have been reported in the literature, had a novel gene mutation, as Nakamura and colleagues reported [18]. Since TRAPS was first proposed as a genetic diagnosis, only those patients with demonstrable TNF receptor mutations should have been included as being cases of TRAPS [2–6]. Further studies are recommended to argue this issue.

A review of the literature compiling 153 TRAPS patients from all over the world demonstrated that the most frequent symptom associated with fever is abdominal pain (77 %), which can occasionally lead to surgery in 33 % of TRAPS patients [10]. Other common clinical symptoms reported in this review are myalgia (63.5 %), rash (55.2 %), arthralgia (51 %), ocular involvement (48.8 %), and pleuritis (32 %) [10]. Arthralgia is more frequent than arthritis in TRAPS patients [4]. Chronic arthritis of the type seen in FMF has not been observed in TRAPS [4], and characteristic migratory myalgia and rashes, which distinguish TRAPS from FMF, typically occur as a localized area of cramping muscle pain with warmth and tenderness to palpation and an overlying erythematous, blanchable rash [4].

In our review of nine reports on Japanese TRAPS patients, the common clinical symptoms associated with fever were rash (erythema) (84.6 %), arthralgia (73.3 %), myalgia (54.5 %), and abdominal pain (50.0 %). Although half of the Japanese TRAPS patients suffered from abdominal pain, they had no history of abdominal surgery [15, 16, 19, 20]. In contrast, only small percentage of Japanese TRAPS patients suffered from chest pain (20.0 %), conjunctivitis (20.0 %), and headache (10.0 %). These findings suggest that the clinical symptoms of TRAPS may be milder in Japanese patients than in Caucasian ones, which is similar to the presentation of other inherited autoinflammatory syndromes, such as FMF [22] and HIDS [23]. The difference of the disease-causing mutations, the genetics or environmental background may be responsible for the discrepancies in the results. Further research is required before definitive conclusions can be drawn.

Since colchicine is ineffective in preventing the fever attacks, glucocorticoid can be used to treat the attacks of TRAPS, but patients will require escalating dosages over time [4–6]. Etanercept, an anti-TNF agent, is recommended for chronic therapy to prevent attacks [4–6]. Interleukin 1β blockade may be effective in cases resistant to anti-TNF therapy [24]. In our review of the Japanese literature, fever and rash improved after the administration of glucocorticoid in all patients [13–17, 19, 20], with the exception of the two patients who did not receive corticosteroid therapy [12, 18].

In our review of the Japanese literature, three of the nine index cases (30.0 %) and six of the 23 patients (26.1 %) had been misdiagnosed as having JIA or adult onset Still's disease prior to the diagnosis of TRAPS being established [13, 16, 19]. All of these patients had a family history of periodic fever [13, 16, 19]. Since glucocorticoid attenuates the clinical symptoms of TRAPS patients [21], patients misdiagnosed as having JIA or adult onset Still's disease may experience an improvement in their clinical symptoms with glucocorticoid therapy. There may be more TRAPS patients misdiagnosed as having JIA or adult Still's disease in Japan. Thus, an important issue should be whether Japanese patients diagnosed with JIA or adult onset Still's disease are actually TRAPS patients, especially if there is a family history of periodic fever.

There are a number of limitations to our review. First, the number of reported Japanese TRAPS patients is very small. In addition, insufficient clinical information was available for some of the family member patients of the index cases. Second, although all index cases are genetically confirmed TRAPS patients, some family members of index cases have been diagnosed as having TRAPS with clinical symptoms and this has been identified in their family history (i.e., kinship of index cases). Third, we cannot provide the answer to whether the differences between Japanese and Western TRAPS is dependent on the difference in the disease-causing mutations, genetics, or environmental background. Further studies are recommended to provide this answer.

The major strength of this review is that it demonstrates that clinical symptoms are milder in Japanese TRAPS patients than in TRAPS patients in Western countries. Compared with their counterparts, Japanese patients are less likely to suffer from severe abdominal pain, and none of the patients in this review had a medical history of abdominal surgery.

In conclusion, our review of the Japanese literature possibly suggests that the clinical features of Japanese patients with TRAPS are milder than those of TRAPS patients in Western countries. We have launched a national survey of TRAPS patients in Japan [6] and are investigating the modified diagnostic criteria for Japanese patients with TRAPS.

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Conflict of interest None.

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