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Letter to the Editor

Updated allele frequencies of *SERPINB7* founder mutations in Asian patients with Nagashima-type palmoplantar keratosis/keratoderma

Letter to the Editor

Nagashima-type palmoplantar keratosis/keratoderma (NPPK, OMIM_#615598) is an autosomal recessive palmoplantar keratoderma (PPK) caused by mutations in *SERPINB7* encoding a member of the serine protease inhibitor superfamily: serpin family B member 7 (SERPINB7) [1]. NPPK is characterized by mild, diffuse, well-demarcated hyperkeratosis with erythema, extending to the dorsal surface of the hands and feet, the inner wrists and the Achilles tendon area (transgrediens) [1]. However, eruptions from NPPK are sometimes overlooked or misdiagnosed as atopic dermatitis, because 15 % of NPPK cases are associated with dermatitis [2].

Thirteen pathogenic mutations in *SERPINB7* have been reported in NPPK: five missense/nonsense mutations, two splice-site mutations, four small-deletion mutations, one small-insertion mutation and one small-indel mutation (The Human Gene Mutation Database; http://www.hgmd.cf.ac.uk/ac/index.php). A common founder mutation, c.796C > T (p.Arg266*), has been reported in the Japanese, Chinese and Korean populations [1]. In 2020, another founder mutation, c.1136 G > A (p.Cys379Tyr), was reported in the Finnish population [3]. We confirmed the high frequency of the *SERPINB7* founder mutation c.796C > T in 10 Japanese families with NPPK [4]. However, the exact frequency of this *SERPINB7* founder mutation in Japanese NPPK patients remains uncertain. In the present study, we performed mutational analyses for *SERPINB7* in a cohort of 14 cases of NPPK from 14 independent families and found six mutations in *SERPINB7*.

Among the 14 patients, five Japanese recurrent mutations in *SERPINB7* were identified: c.218_219del2ins12, c.455−1G > A, c.455 G > T, c.796C > T and c.830C > T. In addition, Case 7 had compound heterozygous mutations, including the novel mutation c.434 G > C (p.Trp145Ser) in exon 5 of *SERPINB7* (Fig. S1a). Clinical details and immunohistochemical results of Case 7 are described in the Supplementary results. Four of the present 14 NPPK patients have atopic dermatitis (Table 1). The AD patients among the present NPPK cases showed AD lesions not only in the regions affected by NPPK, but also in the face, the neck and trunk. We found that three out of the 14 NPPK patients had *FLG* mutations (Table 1). However, there was no significant association between *FLG* mutation and atopic dermatitis phenotype in the NPPK patients (Table 1).

We investigated the numbers of each mutant allele in the present NPPK case series having *SERPINB7* mutations (Table S1). Interestingly, the best-known founder mutation, c.796C > T, accounted for only half of the *SERPINB7* mutant alleles detected in the present study. No obvious genotype/phenotype correlation has been determined and no remarkable differences in clinical severity between patients harboring different mutations have been identified. We investigated all *SERPINB7* mutations reported previously in the literature, including the data in the present NPPK families (Table 2). The allele frequency of the mutation c.796C > T in *SERPINB7* is higher in both the Chinese and Korean NPPK patients than in the Japanese NPPK patients (Table 2). In contrast, the Japanese second- to fourth-most-prevalent *SERPINB7* mutations, c.218_219del2ins12 (p.Gln73Leufs*17), c.830C > T (p.Pro277Leu) and c.455-1G > A (p.Gly152Valfs*21), were not found at all in the Chinese or Korean NPPK patients (Table 2).

It is thought that the mutation c.796C > T leads to a premature termination codon and a lack of the reactive site loop of SERPINB7, resulting in NPPK [5]. Carriers of the *SERPINB7* founder mutant allele c.796C > T are estimated to account for 0.9 % of the Japanese population, based on our screening of that population [6]. The c.796C > T mutation is speculated to be an East Asian founder mutation, because 92 % of Chinese and Korean NPPK families (23/25families) have it (Table 2). Japanese NPPK families with the mutation c.796C > T account for 85.9 % of all Japanese NPPK families reported in the literature (55/64 families), including the present families. The present study revealed that the allele frequency and the carrier rate of the mutation c.796C > T are only 0.535 (15/28 mutant alleles) and 78.6 % (11/14 patients), respectively, in the NPPK case series. In the present study, all 14 patients are from independent families. Thus, the rate of NPPK families with the mutation c.796C > T is 78.6 % among the present Japanese NPPK families (11/14 families). This rate of NPPK families with the most frequent founder mutation c.796C > T among the present 14 NPPK families is slightly lower than those among previously reported Japanese NPPK families and among previously reported East Asian (Japanese, Chinese and Korean) families. This difference might be owed to a geographic effect; most of the present patients were collected from western Japan. In addition, the rates of NPPK families with the most frequent founder mutation, c.796C > T, among Chinese and Korean NPPK patients with *SERPINB7* mutations are higher than that of Japanese NPPK patients, although the difference may be due to a bias caused by the insufficient sample size. The present updated data on the frequency of the founder mutation c.796C > T among NPPK families confirms that the founder mutation is highly

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Table 1
Detailed clinical characteristics and *SERPINB7* genotypes of NPPK patients in the present study.

Case	Age at onset	Age/ Sex	Diffuse mild PPK (palm/ sole)	Erythema (palm/sole)	Itch (palm/ sole)	Transgrediens (hand/foot)	Achilles tendon affected	Wrist affected	Hyperhidrosis	Aquagenic whitening	Fungal infection	Knee/elbow hyperkeratosis	Allele1/Allele2	Atopic dermatitis	*FLG* mutation
Case 1	2 months	1/F	+/+	+/+	+/+	-/+	–	–	–	+	NA	+/+	c.796C > T /c.796C > T	+	c.3221delA_het
Case 2	At birth	17/ M	+/+	+/-	-/-	+/+	–	+	+	+	NA	NA	c.796C > T /c.796C > T	–	–
Case 3	7 years	14/ M	+/+	+/+	NA	+/+	+	+	+	+	NA	+/+	c.796C > T /c.796C > T	–	–
Case 4	1 year	4/F	+/+	+/+	-/-	+/+	+	–	+	+	NA	+/-	c.796C > T /c.796C > T	+	–
Case 5	10 days	6/F	+/+	+/-	+/+	+/+	–	–	+	+	NA	NA	c.796C > T /c.830C > T	–	c.8666_7delinsGA_het
Case 6	Childhood	11/F	+/+	+/+	+/+	+/+	+	+	+	+	–	-/-	c.218_219del2ins12/ c.455-1G > A	–	–
Case 7	Childhood	21/F	+/+	+/+	-/-	+/+	–	+	+	+	–	-/-	c.434 G > C/c.830C > T	+	–
Case 8	1 month	2/M	+/+	+/+	+/+	+/+	–	+	+	NA	–	-/-	c.218_219del2ins12/ c.796C > T	–	–
Case 9	At birth	66/F	+/+	-/-	+/+	+/+	–	+	–	+	NA	NA	c.455 G > T /c.796C > T	–	c.8666_7delinsGA_het
Case 10	At birth	4/M	+/+	+/+	NA	+/+	–	–	+	+	NA	+/+	c.455-1G > A /c.796C > T	+	–
Case 11	At birth	29/F	+/+	+/+	NA	+/+	+	+	+	+	+	+/+	c.455-1G > A /c.796C > T	–	–
Case 12	At birth	43/F	+/+	+/-	NA	+/+	–	+	NA	+	NA	-/-	c.218_219del2ins12/ c.455-1G > A	–	–
Case 13	At birth	2/M	+/+	+/+	+/+	+/+	+	+	+	+	–	+/+	c.218_219del2ins12/ c.796C > T	–	–
Case 14	At birth	4/M	+/+	+/+	-/-	+/+	+	+	–	+	–	-/-	c.218_219del2ins12/ c.796C > T	–	NA

PPK, palmoplantar keratoderma; F, female; M, male; NA, not analyzed.

Table 2
Frequencies of families carrying each reported *SERPINB7* mutation in East Asian NPPK pedigrees reported in the literature, including the present 14 families.

Reported mutation	Number (%) of pedigrees with each *SERPINB7* mutation				references
	Ethnicity				
	Total	Japanese	Chinese	Korean	
c.796C > T (p.Arg266*)	78 (87.6 %)	55 (85.9 %)	20 (90.9 %)	3 (100 %)	Kubo et al. [1], 16 more references
c.218_219del2ins12 (p.Gln73Leufs*17)	19 (21.3 %)	19 (29.6 %)	0	0	Mizuno et al. [4], 6 more references
c.455-1G > A (p.Gly152Valfs*21)	11 (12.3 %)	11 (17.1 %)	0	0	Kubo et al. [1], 4 more references
c.830C > T (p.Pro277Leu)	10 (11.2 %)	10 (15.6 %)	0	0	Shiohama et al. [7], 2 more references
c.455 G > T (p.Gly152Val or aberrant splicing?)	6 (6.74 %)	3 (4.68 %)	3 (13.6 %)	0	Yin et al. (2014), 4 more references
c.522dupT (p.Val175Cysfs*46)	6 (6.74 %)	0	5 (22.7 %)	1 (33.3 %)	Yin et al. (2014), 4 more references
c.336 + 2T > G	2 (2.24 %)	2 (3.12 %)	0	0	Mizuno et al. [4], 1 more reference
c.382C > T (p.Arg128*)	2 (2.24 %)	2 (3.12 %)	0	0	Katsuno et al. [8], 1 more reference
c.434 G > C (p.Trp145Ser) (Our Case)	1 (1.12 %)	1 (1.56 %)	0	0	the present study
c.635delG	1 (1.12 %)	1 (1.56 %)	0	0	Nakajima et al. [9]
c.122_127delTGGTCC	1 (1.12 %)	0	1 (4.54 %)	0	Zhang et al. (2016)
c.271delC (p.His91Thrfs*9)	1 (1.12 %)	0	1 (4.54 %)	0	Hua et al. (2018)
c.650_653delCTGT (p.Ser217Leufs*7)	1 (1.12 %)	0	1 (4.54 %)	0	Yin et al. (2014)
Total families	89	64	22	3	

Refer to supplement for references.

predominant in the Japanese NPPK families with *SERPINB7* mutations.

Interestingly, previous reports demonstrated that the only mutations shared by the Japanese population and the Chinese population are c.796C > T and c.455 G > T. The five mutations including the Japanese second-most-prevalent to fourth-most-prevalent mutations—c.218_219del2ins12 (p.Gln73Leufs*17), c.830C > T (p.Pro277Leu) and c.455-1G > A (p.Gly152Valfs*21)—have been reported only in the Japanese population (Table 2). In contrast, c.122_127delTGGTC, c.271delC, c.522dupT and c.650_653delCTGT have been reported in the Chinese population, but not in the Japanese population.

Clinically, patients with NPPK have hyperkeratotic eruptions not only on the palmoplantar regions, but also on the knees, the elbows and the Achilles tendon areas. Thus, coexisting atopic dermatitis might mask the palmoplantar eruptions associated with NPPK due to SERPINB7 mutations. Indeed, our Case 7 was diagnosed with atopic dermatitis since childhood, and her NPPK was not diagnosed until the age of 21. Studies of greater numbers of NPPK patients are needed to elucidate the association among NPPK, atopic dermatitis and FLG mutations in the future.

In conclusion, the present updated data on the frequency of each *SERPINB7* mutation in the East Asian NPPK families revealed that the other prevalent *SERPINB7* mutations in NPPK families are distinct among the Japanese, Chinese and Korean populations. Additionally, a novel *SERPINB7* mutation, c.434 G > C (p.Trp145Ser), was found in a Japanese NPPK case. Our findings strengthen the current understanding of NPPK and expand the mutational spectrum of *SSERPINB7* mutation, c.434 G > C (p.Trp145Ser), was found in a Japanese NPPK case. Our findings strengthen the current understanding of NPPK and expand the mutational spectrum of *SERPINB7*.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jdermsci.2021.06.002.

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