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SHORT REPORT

A novel *SERPINA12* variant and first European patients with diffuse palmoplantar keratoderma

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Abstract

Background: Hereditary palmoplantar keratodermas (hPPKs) comprise a heterogeneous group of skin disorders characterized by persistent palmoplantar hyperkeratosis. Loss-of-function variants in a serine peptidase inhibitor, *SERPINA12*, have recently been implicated in autosomal recessive diffuse hPPK. The disorder appears to share similarities with another hPPK associated with protease overactivity, namely Nagashima-type PPK (NPPK) caused by biallelic variants in *SERPINB7*.

Objectives: The aim of this study was to enhance the understanding of the clinical and genetic characteristics of serine protease-related hPPKs caused by variants in *SERPINA12* and *SERPINB7*.

Methods: Whole-exome sequencing (WES) was performed for hPPK patients. Haplotype analysis was completed for the patients with identified recessive *SERPINA12* variants and their available family members. In addition, the current literature of *SERPINA12*- and *SERPINB7*-related hPPKs was summarized.

Results: The phenotype of *SERPINA12*-related hPPK was confirmed by reporting three new *SERPINA12* patients, the first of European origin. A novel *SERPINA12* c.1100G>A p.(Gly367Glu) missense variant was identified confirming that the variant spectrum of *SERPINA12* include both truncating and missense variants. The previously reported *SERPINA12* c.631C>T p.(Arg211*) was indicated enriched in the Finnish population due to a plausible founder effect. In addition, *SERPINA12* hPPK patients were shown to share a similar phenotype to patients with recessive variants in *SERPINB7*. The shared phenotype included diffuse transgradient PPK since birth or early childhood and frequent palmoplantar hyperhidrosis, aquagenic whitening and additional hyperkeratotic lesions in non-palmoplantar areas. *SERPINA12* and *SERPINB7* hPPK patients cannot be distinguished without genetic analysis.

Conclusions: Recessive variants in *SERPINA12* and *SERPINB7* leading to protease overactivity and hPPK produce a similar phenotype, indistinguishable without genetic analysis. *SERPINA12* variants should be assessed also in non-Asian patients with diffuse transgradient PPK. Understanding the role of serine protease inhibitors will provide insights into the complex proteolytic network in epidermal homeostasis.

INTRODUCTION

Hereditary palmoplantar keratodermas (hPPKs) comprise a heterogeneous group of skin disorders characterized by hyperkeratosis of palms and soles.[1] Loss-of-function variants in a serine peptidase inhibitor *SERPINA12* have been implicated in autosomal recessive hPPK with diffuse palmoplantar erythema and hyperkeratosis expanding transgrediently and to the Achilles tendon area.[2,3] Additional features include palmoplantar hyperhidrosis, aquagenic whitening (hyperkeratotic areas turn white and spongy upon water exposure) and skin peeling.[2,3] To date, six *SERPINA12* variants have been reported in eight patients, none of European origin.[2,3]

SERPINA12-related hPPK shares similarities with Nagashima-type PPK (NPPK), which is an autosomal recessive diffuse hPPK caused by *SERPINB7* variants leading to protease overactivity.[4,5]

In this study, we confirm the phenotype of *SERPINA12*-related hPPK through three new patients and report a novel *SERPINA12* variant. In addition, we summarize the current literature of *SERPINA12*- and *SERPINB7*-related hPPKs. We aim to enhance the understanding of the clinical and genetic characteristics of serine protease-related hPPKs.

MATERIALS AND METHODS

The study was approved by the Coordinating Ethical Review Board of the Helsinki and Uusimaa Hospital District, Helsinki, Finland. Three patients with biallelic *SERPINA12* variants were identified by whole exome sequencing (WES). Haplotype analysis was performed using genotype data from a genome-wide array. In addition, a systematic literature search was performed. The detailed description of the materials and methods is found in Appendix S1.

RESULTS

Three new *SERPINA12* hPPK patients

We found biallelic *SERPINA12* variants in three nonconsanguineous Finnish patients. They all carried also a heterozygous *SERPINB7* c.1136G>A p.(Cys379Tyr) variant, which most likely does not affect the patients' phenotypes, as NPPK is inherited autosomal recessively (Appendix S1, Table S1).

Patient I was a 24-year-old woman with diffuse PPK since birth. PPK extended to the dorsum of the fingers and toes, the Achilles tendon region and the inner wrists (Figure 1, Table 1). She had aquagenic whitening, palmoplantar skin peeling, hyperhidrosis and repeated dermatophyte infections. Plantar skin histology showed epidermal acanthosis and hyperkeratosis. WES revealed a homozygous variant *SERPINA12* c.631C>T p.(Arg211*) (NM_001382267.1). Sanger sequencing confirmed her unaffected father and mother heterozygous carriers of the variant.

Patient II was a 63-year-old man with diffuse PPK since birth extending to the dorsum of the hands and feet, the inner wrists and the Achilles tendon area (Figure 1, Table 1). He had palmoplantar hyperhidrosis, aquagenic whitening and skin peeling, but no fungal infections. Occasionally, he had facial erythema, slight facial skin peeling and eczema on the legs and the dorsum of the hands and feet. Palmar skin histology revealed acanthosis and orthohyperkeratosis. WES identified homozygosity for the *SERPINA12* c.631C>T p.(Arg211*) variant.

Patient III was a 15-year-old girl with diffuse PPK since birth. Progressive transgrediens was noted on the inner wrists, dorsum of the hands and feet and the Achilles tendon area (Figure 1, Table 1). She had palmoplantar skin peeling, aquagenic whitening and hyperhidrosis. Yellowish discoloration and onycholysis of her I and IV left toenails were noted; otherwise, the nails were normal. Mycological tests from the affected nails were negative, but she had a plantar dermatophyte infection once in her childhood. Plantar skin histopathology revealed hyperkeratosis and acanthosis. WES showed compound heterozygosity for the c.631C>T variant, paternally inherited and a previously unreported maternally inherited missense variant *SERPINA12* c.1100G>A p.(Gly367Glu) (NM_001382267.1). This missense variant is rare: According to the Genome Aggregation Database (GnomAD), there are only 81 heterozygotes of which 64 are of Finnish ethnicity and no homozygotes. The variant is predicted to be deleterious by in silico prediction tools SIFT (Sorting Intolerant from Tolerant),[6] probably damaging by Polyphen (Polymorphism Phenotyping)[7] and destabilizing by SDM (Site Directed Mutator),[8] whereas MutationTaster predicts the variant to be a polymorphism.

A common haplotype of approximately 53 kilobases around the c.631C>T p.(Arg211*) variant shared by all three patients and four heterozygous carrier family members was identified (Table S2). The allele frequency of this variant in the Finnish population is 0.01161 (GnomAD), which is 2.3 times higher than in the total population (0.005120), indicating an enrichment in Finns by a founder effect.

Comparison with previously reported *SERPINA12* and *SERPINB7* hPPK patients

SERPINA12 patients

The previous publications reported biallelic *SERPINA12* variants in eight patients of Chinese, Arab and Indian ethnicity[2,3] (Table 1, Table S3). All had diffuse transgradient PPK with symptoms since birth in the majority (7/8). Most patients reported mild palmoplantar hyperhidrosis.[3] Palmoplantar skin peeling, aquagenic whitening and nonpalmoplantar hyperkeratosis were all reported in two patients and one reported progrediens.[2,3] Similarly, our three

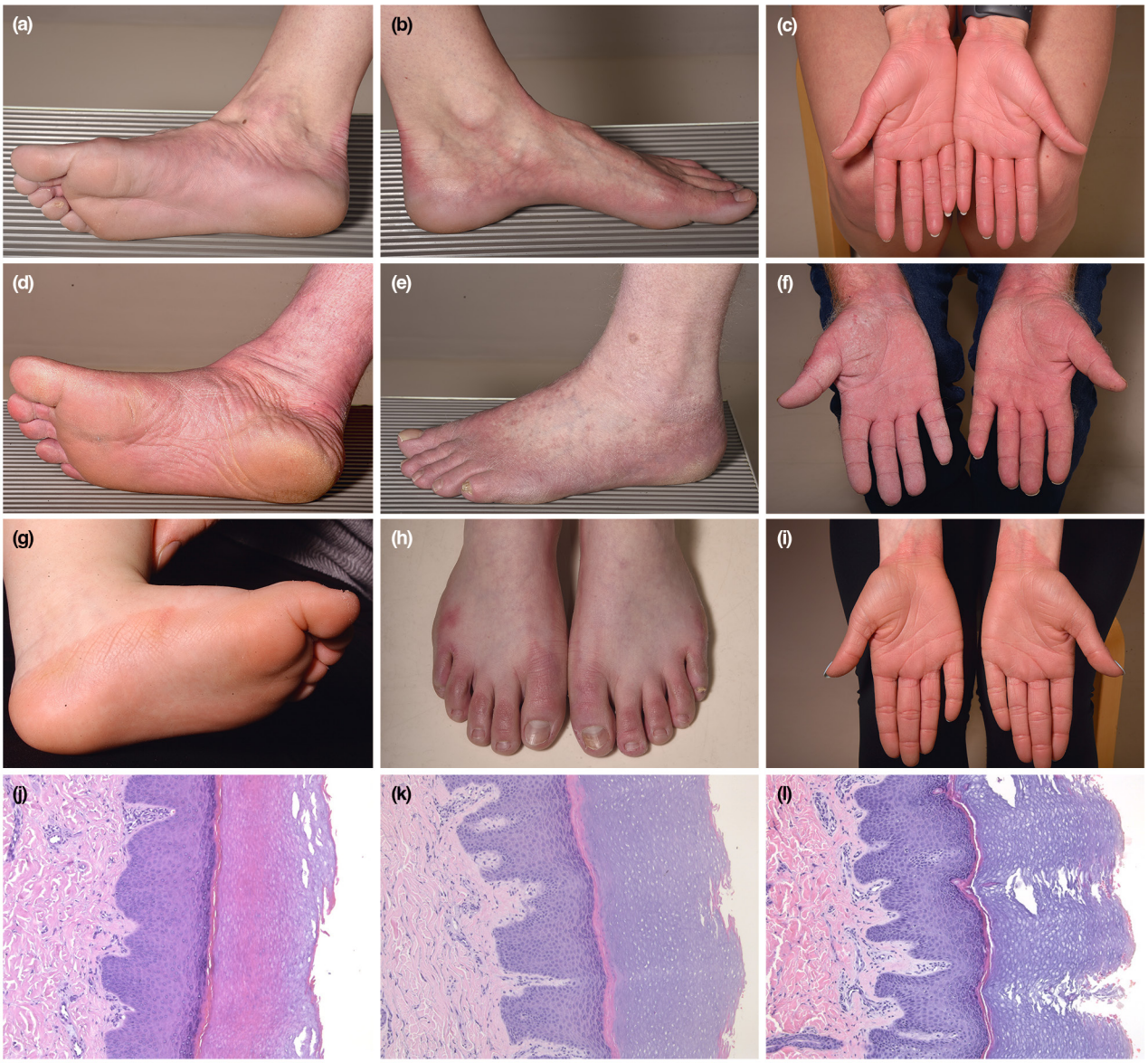

FIGURE 1 Clinical and histological characteristics of the three *SERPINA12* patients. (a–i) Diffuse and transgradient palmoplantar erythema and hyperkeratosis extending from the palms and soles to the dorsum of the hands and feet, the inner wrists and the Achilles tendon area. (a–c) Patient I and (d–f) patient II, both homozygous for *SERPINA12* c.631C>T. (g–i) Patient III, compound heterozygous for *SERPINA12* c.631C>T and c.1100G>A. (g) Diffuse PPK of patient III at age 1 year. (f) Note the aquagenic whitening of patient III's right palm following exposure to water for 5 min. (j, k) Biopsy specimens showing acanthosis with hypergranulosis and keratohyalin granules, and hyperkeratosis. Histopathological features of (j) patient I, (k) patient II and (l) patient III.

SERPINA12 patients had diffuse transgradient PPK since birth, palmoplantar skin peeling, aquagenic whitening and hyperhidrosis. Fungal infections (2/3) and progrediens (1/3) were also noticed.

In all, six *SERPINA12* variants were reported (Figure 2): c.631C>T p.(Arg211*) and c.1051G>T p.(Glu351*) both resulting in premature stop codons, a Chinese founder mutation c.970_971del p.(Ser324Leufs*9), a frameshift variant c.662del p.(Asn221Metfs*2), a missense variant c.656A>G p.(Asp219Gly) and an intronic variant c.635-7A>G predicted to result in a premature termination codon before the reactive centre loop (RCL).[2,3]

SERPINB7 patients

One hundred fourteen patients with biallelic *SERPINB7* variants were reported (Table 1, Table S4). The patients were mostly Japanese (64/110) or Chinese (34/110). All had diffuse PPK with symptoms mainly since birth (26/79) or below the age of 2 years (41/79). Transgrediens, aquagenic whitening and hyperhidrosis were frequent (89/91, 50/56 and 58/76, respectively). Non-palmoplantar hyperkeratotic lesions were noticed in 34 patients. Progrediens was uncommon (1/30). Dermatophyte infections and palmoplantar skin peeling were reported in 13 and five patients, respectively.

TABLE 1 Clinical characteristics of hPPKs caused by biallelic variants in *SERPINA12* and *SERPINB7*.

Gene	*SERPINA12*	*SERPINA12*	*SERPINB7*
Reported	Here	Previously[a]	Previously[a]
Patients	3	8	114
Female	2/3	5/8	54/106, NR 8
Ethnicity	Finnish 3/3	Chinese 6/8	Japanese 64/110
		Arab 1/8	Chinese 34/110
		Indian 1/8	Finnish 4/110
			Korean 3/110
			Arab 2/110
			Thai 2/110
			Vietnamese 1/110
			NR 4
Diffuse PPK	3/3	8/8	114/114
Age of onset			
Birth	3/3	7/8	26/79
<2 years	0/3	1/8	41/79
2–30 years	0/3	0/8	12/79
>30 years	0/3	0/8	0/79
NR	0	0	35
Transgrediens	3/3	8/8	89/91, NR 23
Wrists affected	3/3	8/8	57/61, NR 53
Achilles tendon area affected	3/3	8/8	52/60, NR 54
Palmoplantar skin peeling	3/3	2/2, NR 6	5/5, NR 109
Aquagenic whitening	3/3	2/2, NR 6	50/56, NR 58
Hyperhidrosis	3/3	NR 8[b]	58/76, NR 38
Fungal infections	2/3	NR 8	13/42, NR 72
Progrediens	1/3	1/1, NR 7	1/30, NR 84
Nail dystrophy	1/3	NR 8	3/4, NR 110
Other hyperkeratotic lesions	0/3	2/2, NR 6	34/77, NR 37
Other cutaneous manifestations	Facial erythema and skin peeling 1	Slight skin peeling on the cheeks 1	Atopic dermatitis 11
			MM or MM in situ 6
	Eczema on the extremities 1	NR 7	NR 80

Abbreviations: MM, malignant melanoma; NR, not reported.

[a]References are listed comprehensively in the Tables S3 and S4.

[b]Liu et al.[3] report mild palmar hyperhidrosis in most of the six patients participating in their study.

In all, 17 *SERPINB7* variants were reported (Figure 2, Table S5). The most frequent variant (97 patients) was c.796C>T, p.(Arg266*) proposed to be a founder mutation in Asian populations.[4,9] The second and third most common variants were c.218_219delAGinsTAAACTTTACCT, p.(Gln73Leufs*17) (20 patients) and c.830C>T, p.(Pro277Leu) (12 patients). The remaining 14 variants were infrequent: each found in less than 10 patients who were mostly Japanese, except for four Finnish patients identified with a homozygous c.1136G>A, p.(Cys379Tyr) variant proposed to be a Finnish founder mutation.[10,11]

DISCUSSION

We reported three Finnish patients with biallelic *SERPINA12* variants and confirmed a similar phenotype to the eight recently described *SERPINA12* patients.[2,3] In addition, we showed that biallelic variants in *SERPINA12* and *SERPINB7* share a similar phenotype. The novel *SERPINA12* c.1100G>A p.(Gly367Glu) missense variant increased the number of reported *SERPINA12* variants to seven.

Our patients are the first *SERPINA12* patients of European descent. The previously reported c.631C>T p.(Arg211*)

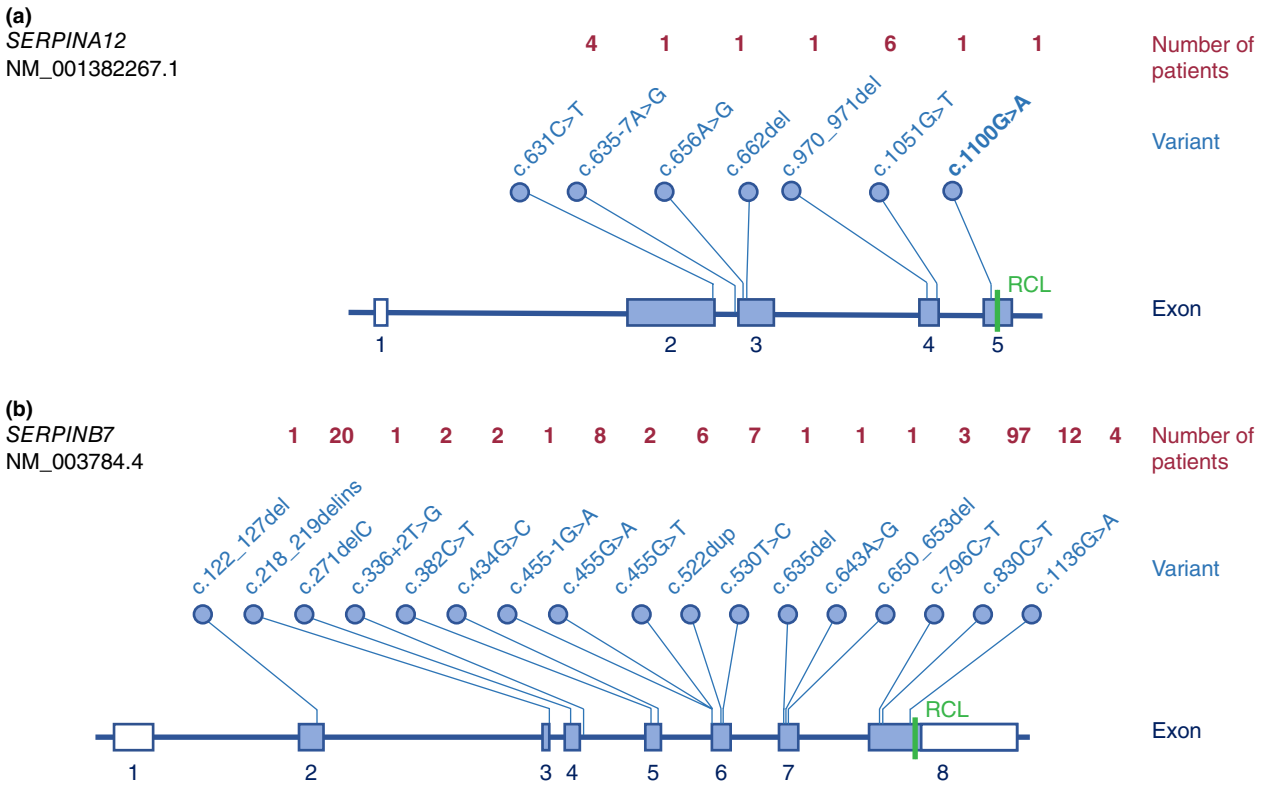

FIGURE 2 Schematic diagrams representing the genomic structure of (a) *SERPINA12* and (b) *SERPINB7*. Untranslated and coding regions are indicated with white and blue boxes, respectively. The line indicates the reactive centre loop (RCL). The number of patients indicates the total amount of patients reported with homozygous or compound heterozygous *SERPINA12* or *SERPINB7* variants. The novel *SERPINA12* c.1100G>A p.(Gly367Glu) missense variant identified in this study is bolded. c.218_219delins refers to the variant c.218_219delAGinsTAAACTTTACCT.

variant was indicated enriched in Finland by a founder effect. The variant was reported also in an Arab patient,[2] suggesting a likely recurring mutational event that, however, cannot be proven as the patient's haplotype data are unavailable. In addition, the results confirm that the variant spectrum of *SERPINA12* include both truncating and missense variants.

Similar clinical features were found in our patients and the previously reported *SERPINA12* and *SERPINB7* patients. Taken together, the findings suggest that *SERPINA12* and *SERPINB7* patients share a similar phenotype including diffuse transgradient PPK since birth or early childhood, frequent palmoplantar hyperhidrosis and aquagenic whitening. Symptoms seldom progress, but especially *SERPINB7* patients may also exhibit non-palmoplantar hyperkeratotic lesions, mainly on knees and elbows. In addition, fungal infections and palmoplantar skin peeling were reported, but especially palmoplantar skin peeling may be underdiagnosed as the data were lacking for the majority. Skin histology in *SERPINA12* patients shows acanthosis with hypergranulosis and keratohyalin granules, and hyperkeratosis, compatible with histological findings with *SERPINB7* variants.[2,4,10,12–16] Similar to *SERPINA12* patients, most *SERPINB7* patients were Asian. Interestingly, both the *SERPINA12*- and *SERPINB7*-related hPPK are indicated enriched in Asian and Finnish populations by founder effects.

SERPINA12 and SERPINB7 belong to a superfamily of functionally diverse serpins sharing a well-conserved tertiary structure with an exposed RCL crucial for their function.[17] The RCL interacts with the protease's active site to inhibit it.[17] The RCL's residues 364–370 are largely conserved among serpins and variants in the region negatively affect the inhibitory activity.[18] The novel Gly367Glu substitution located in the RCL region of SERPINA12 (Figure S1) is a non-conservative amino acid change, and it may negatively affect the inhibitory activity of SERPINA12 in analogy to the other variants of the RCL region.

It is proposed that biallelic variants in *SERPINA12* and *SERPINB7* result in protease overactivity,[2,4] but as the epidermal protease network still remains partly unknown, further studies are needed to clarify their role. Considering the limited number of *SERPINA12* patients, the clinical and molecular picture of *SERPINA12*-related hPPK needs to be refined as more cases are identified. Although the number of *SERPINB7* patients is higher, the literature consists mostly of case reports limiting the accuracy of the described phenotype.

In conclusion, a precise distinction between the two serine protease-related hPPKs cannot be made based on clinical characteristics alone but requires genetic evaluation. *SERPINA12* variants are a recently described cause of diffuse

autosomal recessive hPPK, which should be assessed in patients of various ethnicities.

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CONFLICT OF INTEREST STATEMENT

Dr. Hannula-Jouppi is a clinical advisor at Blueprint Genetics. All the other authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The exome sequencing and haplotype data are not publicly available due to privacy or ethical restrictions. The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The patients in this manuscript have given written informed consent to the publication of their case details.

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REFERENCES

1. Guerra L, Castori M, Didona B, Castiglia D, Zambruno G. Hereditary palmoplantar keratodermas. Part I. Non-syndromic palmoplantar keratodermas: classification, clinical and genetic features. J Eur Acad Dermatol Venereol. 2018;32:704–19.
2. Mohamad J, Sarig O, Malki L, Rabinowitz T, Assaf S, Malovitski K, et al. Loss-of-function variants in *SERPINA12* underlie autosomal recessive palmoplantar keratoderma. J Eur Acad Dermatol Venereol. 2018;32:704–19.
3. Liu Y, Tan Y, Liu J, Song Z, Hu L, Mo R, et al. Novel and founder variants of *SERPINA12* in Chinese patients with autosomal recessive palmoplantar keratoderma. Br J Dermatol. 2022;187:267–70.
4. Kubo A, Shiohama A, Sasaki T, Nakabayashi K, Kawasaki H, Atsugi T, et al. Mutations in *SERPINB7*, encoding a member of the serine protease inhibitor superfamily, cause Nagashima-type palmoplantar keratosis. Am J Hum Genet. 2013;93:945–56.
5. Kubo A. Nagashima-type palmoplantar keratosis: a common Asian type caused by SERPINB7 protease inhibitor deficiency. J Invest Dermatol. 2014;134:2076–9.
6. Sim NL, Kumar P, Hu J, Henikoff S, Schneider G, Ng PC. SIFT web server: predicting effects of amino acid substitutions on proteins. Nucleic Acids Res. 2012;40:W452–7.
7. Adzhubei IA, Schmidt S, Peshkin L, Ramensky VE, Gerasimova A, Bork P, et al. A method and server for predicting damaging missense mutations. Nat Methods. 2010;7:248–9.
8. Worth CL, Preissner R, Blundell TL. SDM - a server for predicting effects of mutations on protein stability and malfunction. Nucleic Acids Res. 2011;39:W215–22.
9. Yin J, Xu G, Wang H, Zhao J, Duo L, Cao X, et al. New and recurrent *SERPINB7* mutations in seven Chinese patients with Nagashima-type palmoplantar keratosis. J Invest Dermatol. 2014;134:2269–72.
10. Hannula-Jouppi K, Harjama L, Einarsdottir E, Elomaa O, Kettunen K, Saarela J, et al. Nagashima-type palmoplantar keratosis in Finland caused by a *SERPINB7* founder mutation. J Am Acad Dermatol. 2020;83:643–5.
11. Harjama L, Karvonen V, Kettunen K, Elomaa O, Einarsdottir E, Heikkilä H, et al. Hereditary palmoplantar keratoderma – phenotypes and mutations in 64 patients. J Eur Acad Dermatol Venereol. 2021;35:1874–80.
12. Hashimoto T, Teye K, Numata S, Suga Y, Hamada T, Ishii N. Detection of *SERPINB7* mutation can distinguish Nagashima-type palmoplantar keratoderma from other keratodermas with palmoplantar lesions. Clin Exp Dermatol. 2017;42:342–5.
13. Mizuno O, Nomura T, Suzuki S, Takeda M, Ohguchi Y, Fujita Y, et al. Highly prevalent *SERPINB7* founder mutation causes pseudodominant inheritance pattern in Nagashima-type palmoplantar keratosis. Br J Dermatol. 2014;171:847–53.
14. Katsuno M, Shiohama A, Aoki S, Kitamura H, Sasaki T, Amagai M, et al. Novel nonsense mutation in *SERPINB7* and the treatment of foot odor in a patient with Nagashima-type palmoplantar keratosis. J Dermatol. 2017;44:e146–7.
15. Nakajima K, Ishiguro M, Shiohama A, Kubo A, Sano S. Novel frameshift mutation in *SERPINB7* in a Japanese patient with Nagashima-type palmoplantar keratosis. J Dermatol. 2017;44:841–3.
16. Li CX, Zhang SQ, Wen J, Chen PJ, Liu QX, Han K, et al. A sporadic case of Nagashima-type palmoplantar keratosis caused by gene mutation in *SERPINB7*. Clin Exp Dermatol. 2016;41:811–3.
17. Heit C, Jackson BC, McAndrews M, Wright MW, Thompson DC, Silverman GA, et al. Update of the human and mouse *SERPIN* gene superfamily. Hum Genomics. 2013;7:22.
18. Pippel J, Kuettner EB, Ulbricht D, Daberger J, Schultz S, Heiker JT, et al. Crystal structure of cleaved vaspin (serpinA12). Biol Chem. 2016;397:111–23.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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