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Case and Review

Nagashima-Type Palmoplantar Keratosis with Compound Heterozygous Mutations in SERPINB7

Chankiat Songsantiphap[a] Jirat Suwanwatana[a] Chupong Ittiwut[b]
Pravit Asawanonda[a] Pawinee Rerknimitr[a] Vorasuk Shotelersuk[b, c]

[a]Division of Dermatology, Department of Medicine, Faculty of Medicine, Skin and Allergy Research Unit, Chulalongkorn University, Bangkok, Thailand; [b]Center of Excellence for Medical Genomics, Medical Genomics Cluster, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; [c]Excellence Center for Genomics and Precision Medicine, King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok, Thailand

Keywords
Nagashima type · Palmoplantar keratosis · SERPINB7 · Compound heterozygosity

Abstract
Nagashima-type palmoplantar keratosis (NPPK) is a diffuse, non-syndromic (isolated), autosomal recessive palmoplantar keratoderma (PPK) with transgredients. It is characterized by non-progressive mild to moderate transgredient PPK. The mutation in *SERPINB7* is reported to underlie the condition. Though many case reports/series have demonstrated various mutations in *SERPINB7*, the genotype-phenotype correlation in this disorder is still lacking. We herein report two brothers with NPPK. Both patients were found to be compound heterozygous for c.796C>T and c.650_653delCTGT in the *SERPINB7* gene. We then summarize the previously reported cases of different mutations in *SERPINB7* along with their clinical phenotypes in an attempt to shed some light on this correlation. Further investigations and systematic data collection are still needed to clarify this issue.

KARGER

Pawinee Rerknimitr
Division of Dermatology, Department of Medicine, Faculty of Medicine
Skin and Allergy Research Unit, Chulalongkorn University
1873 Rama IV Road, Pathumwan, Bangkok 10330 (Thailand)
Pawinee.r@chula.ac.th

Introduction

Palmoplantar keratoderma (PPK) is defined as an excessive epidermal thickening of the palms and soles, which can be an acquired or hereditary disorder. Due to the high heterogeneity of phenotypes and genotypes, the entity can be divided into non-syndromic (which is then further divided into isolated and complex types) and syndromic form [1].

Herein, we report the case of non-syndromic (isolated) PPK, Nagashima-type (NPPK), with demonstration of useful cardinal features for guiding the diagnosis. Whole exome sequencing successfully identified the causative mutations. The review of different mutations in causative gene in NPPK is also depicted here.

Case Report

A 22-year-old Thai man had presented with bilateral reddish, hyperkeratotic skin on the palms and soles since he was 3 years old. Neither pain nor itch was observed. The lesion would occasionally peel off resulting in maceration, erosion, and tenderness. When he went swimming or diving, white spongy lesions would develop on his palms only to resolve a few hours later. He also complained of excessive sweating on both palms and soles.

Skin examination showed symmetrical, well-demarcated diffuse erythema and hyperkeratosis over the palms and soles, extending to the dorsal hands, fingers, toes, and Achilles tendons (shown in Fig. 1a, e–g). Similar lesions were also observed on both elbows and knees. The lesions have remained stable since childhood and no other lesions have extended beyond those areas mentioned above. Moreover, the iodine starch test and water immersion of his palms were done and exhibited positive results (Fig. 1a–d). Notably, other physical examinations were within normal limits. His younger brother reportedly had similar clinical features and course. However, he was unavailable for physical examination. The pedigree of the patient is shown in Figure 2.

According to the clinical manifestation, the provisional diagnosis was NPPK. To confirm the diagnosis, the tetrad-whole exome sequencing (WES) using blood samples of the affected siblings and their parents was performed with previously described methods [2]. Both patients were found to be compound heterozygous for c.796C>T (p.R266*, rs1553630472) and c.650_653delCTGT (p.S217Lfs*7) in the *SERPINB7* gene.

The single nucleotide substitution at the position 796 from C to T, c.796C>T (GRCh37: chr18:61471522C>T, https://www.ncbi.nlm.nih.gov/clinvar/variation/521466/), changes amino acid arginine at residue 266 to a termination codon. It was inherited from their mother and was found heterozygously in 24 of 4,330 alleles (2,165 individuals; allele frequency of 0.006) in our in-house Thai exome database. This mutation has been found to occur in East Asian ancestry. Its mRNA was shown to be degraded by nonsense-mediated mRNA decay [3].

The 4-base pair deletion c.650_653delCTGT (chr18:61468152_61468155delCTGT [GRCh37]; p.S217Lfs*7) causes a frameshift resulting in a change of amino acid residue 217 from serine to leucine and stop seven codons later. It was inherited from their father and found heterozygously in 16 of 4,330 alleles (2,165 individuals; allele frequency of 0.004) in our in-house Thai exome database.

The compound heterozygous mutations were previously reported in a male patient (Table 1) with tinea pedis and hyperhidrosis by Yin et al. [4].

In our patient, supportive treatments were given including moisturizer and occasionally topical low-potency corticosteroid for maceration and tenderness.

Discussion

Our patients presented with non-syndromic (isolated) PPK that exhibits striking features including diffuse erythema, transgredience (extending beyond the palms and soles) into the fingers, toes, and Achilles tendons, lesions being found on other body sites especially the elbows and knees, hyperhidrosis, and a non-progressive nature. These cardinal manifestations fit well with the diagnosis of NPPK [5].

NPPK is characterized by non-progressive mild to moderate transgredient PPK. The disorder is inherited in an autosomal recessive manner. However, in Asian populations, due to the high frequency of the mutant alleles, the occurrence of pseudodominant inheritance can be observed [6]. The onset of the disease is in infancy (from birth to 3 years of age). White spongy skin changes when the affected hands and feet are immersed into the water are frequent. Although the complications of NPPK are commonly less severe, which includes hyperhidrosis and tinea pedis [1], the development of an acral lentiginous melanoma in the long-term follow-up has also been reported [7, 8].

NPPK has mainly been reported in Asia, especially in Japan and China. A recent study showed that mutations in the serine protease inhibitor, clade B, member 70 (*SERPINB7*) gene was causative of the disease. *SERPINB7* is expressed in the stratum corneum and stratum granulosum, which encodes a member of serine protease inhibitor superfamily that may be responsible for protecting cells from protease-mediated injury. Deficiency in its protease inhibitory function is likely the cause of the clinical manifestations in NPPK. Moreover, *SERPINB7* may have a role in inhibiting mechanical stress-induced protease-mediated cellular damage, which explained the location of the lesion usually confined to mechanical stress areas including palms, soles, knees, and elbows [9]. Interestingly, the phenotype of NPPK can be masked or modified by other common conditions such as atopic dermatitis [10] or X-linked ichthyosis [11].

To our knowledge, 13 different *SERPINB7* mutations have been reported as depicted in Table 1 [4, 6, 9, 12–18]. The highly prevalent c.796C>T nonsense mutation has been found using a single nucleotide polymorphism analysis to have a common ancestry (a founder effect) [15]. So far, all reported cases of NPPK have been from patients with homozygous or two compound heterozygous mutations of *SERPINB7*. Heterozygous carriers of a single mutation, for example parents of affected individuals, have never been found to have clinical manifestations of NPPK. Kubo et al. [9] reported that loss of functional SERPINB7 was involved in induced overactivation of intracorneocyte proteases specifically in the affected skin area, especially in induced degradation of the stratum granulosum and the stratum corneum. In our case, whole exome sequencing revealed two compound heterozygous mutations of *SERPINB7* composed of c.796C>T and c.650_653delCTGT mutation. While c.796C>T is a recurrent pathogenic mutation found in most NPPK, the c.650_653delCTGT has only been reported in a single patient [4].

The treatment of NPPK is usually supportive, which aims to reduce the hyperkeratosis by using topical keratolytic agents such as urea, salicylic and retinoic acid, or topical vitamin D3. The outcomes of these treatments are not very impressive. Due to the high frequency of c.796C>T nonsense mutation of *SERPINB7* in the keratinocytes, the nonsense readthrough-enhancing drug such as topical aminoglycoside, especially gentamicin, is currently a promising potential therapy in reduction of hyperkeratosis in the patient with NPPK [3]. However, further studies are needed to prove the safety and efficacy of this treatment.

Conclusion

NPPK is a mild, non-syndromic (isolated) PPK found more commonly in Asian population. The cardinal features, especially diffuse palmoplantar erythema and transgredience, are critically helpful for clinical diagnosis. Homozygous and compound heterozygous mutations of *SERPINB7* play a major role in the disease pathogenesis. Although many reports demonstrate various mutations in this gene, further investigations and systematic data collection are still needed to find genotype-phenotype correlation of this disease.

Statement of Ethics

Written informed consent was signed from the patient for the publication of his case report including the clinical images. This study was conducted in adherence to the consensus of the Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

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Author Contributions

C.S.: investigation, formal analysis, writing – original draft preparation. J.S.: investigation, resources. C.I.: investigation, formal analysis, writing – review and editing. P.A.: writing – review and editing. P.R.: conceptualization, methodology, writing – reviewing and editing. V.S.: conceptualization, formal analysis, writing – review and editing, funding acquisition. All authors provided essential feedback and approved the final manuscript.

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 May;32(5):704–19.
2 Shotelersuk V, Kamolvisit W, Rojvachiranonda N, Suphapeetiporn K, Porntaveetus T, Shotelersuk V. Severe craniofrontonasal syndrome in a male patient mosaic for a novel nonsense mutation in EFNB1. Eur J Med Genet. 2020 Jun;63(6):103924.
3 Ohguchi Y, Nomura T, Suzuki S, Takeda M, Miyauchi T, Mizuno O, et al. Gentamicin-Induced Readthrough and Nonsense-Mediated mRNA Decay of SERPINB7 Nonsense Mutant Transcripts. J Invest Dermatol. 2018 Apr;138(4):836–43.
4 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 Aug;134(8):2269–72.
5 Nomura T. Possible cases of Nagashima-type palmoplantar keratosis? Comment on the article by Guo et al. Clin Exp Dermatol. 2016 Apr;41(3):320.
6 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 Oct;171(4):847–53.
7 Kogame T, Kaku Y, Endo Y, Yamashita C, Horiguchi A, Kubo A, et al. A follow-up report of acral melanoma in a patient with Nagashima-type palmoplantar keratosis: validation of SERPINB7 mutation and local recurrence. Eur J Dermatol. 2018 Aug;28(4):519–20.
8 Korekawa A, Akasaka E, Rokunohe D, Fukui T, Kaneko T, Sawamura D, et al. Nagashima-type palmoplantar keratoderma and malignant melanoma in Japanese patients. Br J Dermatol. 2019 Feb;180(2):415–6.
9 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 Nov;93(5):945–56.
10 Yamauchi A, Kubo A, Ono N, Shiohama A, Tsuruta D, Fukai K. Three cases of Nagashima-type palmoplantar keratosis associated with atopic dermatitis: A diagnostic pitfall. J Dermatol. 2018 May;45(5):e112–3.
11 Matsudate Y, Niki M, Hida Y, Kubo Y. Coexistence of X-linked ichthyosis and Nagashima-type palmoplantar keratosis: A case report. J Dermatol. 2019 Feb;46(2):e54–5.
12 Zhang J, Zhang G, Ni C, Cheng R, Liang J, Li M, et al. Nagashima-type palmoplantar keratosis in a Chinese Han population. Mol Med Rep. 2016 Nov;14(5):4049–54.
13 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 Jul;44(7):e146–e147.
14 Nakajima K, Ishiguro M, Shiohama A, Kubo A, Sano S. Novel frame-shift mutation in SERPINB7 in a Japanese patient with Nagashima-type palmoplantar keratosis. J Dermatol. 2017 Jul;44(7):841–3.
15 Shiohama A, Sasaki T, Sato S, Sakabe J, Ito T, Isoda H, et al. Identification and Characterization of a Recessive Missense Mutation p.P277L in SERPINB7 in Nagashima-Type Palmoplantar Keratosis. J Invest Dermatol. 2016 Jan;136(1):325–8.
16 On HR, Lee SE, Nomura T, Miyauchi T, Suzuki S, Shimizu H, et al. Identification of SERPINB7 mutations in Korean patients with Nagashima-type palmoplantar keratosis. J Dermatol. 2017 Jul;44(7):840–1.
17 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. 2019 Nov;S0190-9622(19)33004-X.
18 Hua S, Miao X, Mao W, Hua L, Chen J, Li B. A novel frameshift SERPINB7 mutation in a Chinese case with Nagashima-type palmoplantar keratosis: case report and review of the literature. Clin Exp Dermatol. 2018 Dec;43(8):953–5.

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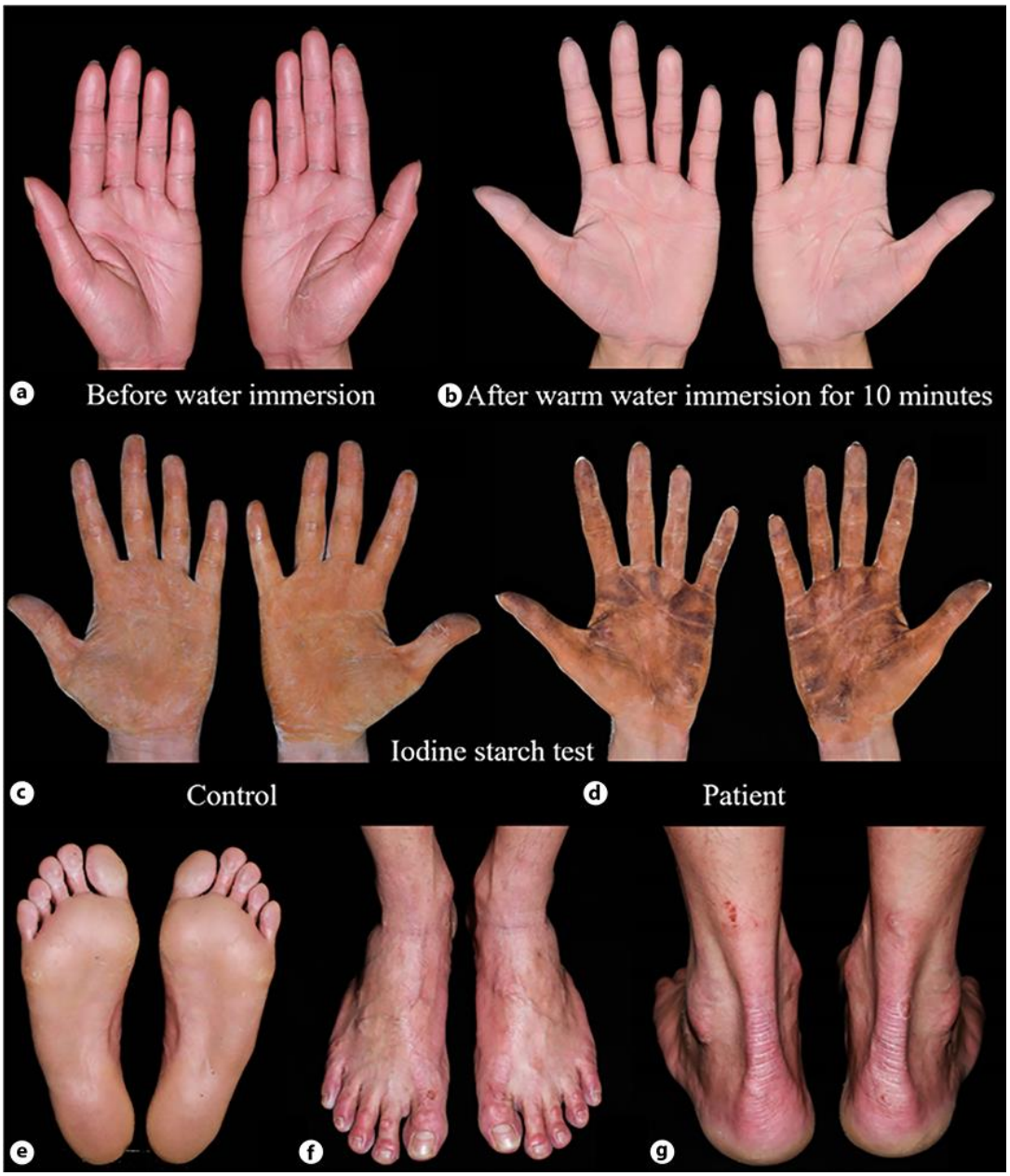

Fig. 1. Clinical features of the proband, water immersion, and iodine starch test. **a**, **e–g** Bilateral symmetrical, well-demarcated diffuse erythema and hyperkeratosis over the palms and soles, extending to the dorsal toes and Achilles tendons. **b** After immersing in warm water for 10 min, white spongy lesions developed on the palms. **c**, **d** Iodine starch test was done on his palms and showed positive result (**d**) after 5 min when compared to the control (**c**).

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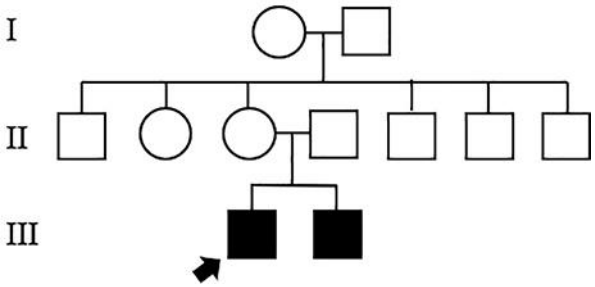

Fig. 2. The pedigree of the patient. His younger brother had a similar lesion as our patient, while other members in his family were not affected.

Table 1. Summary of previously reported different *SERPINB7* mutations

Mutations	Amino acid changes	Allele frequencies in gnomAD	Patients, *n*		Ethnicity	Clinical features in addition to PPK	Ref.
			homo-zygous	hetero-zygous			
c.122_127delTGGTCC	p.Leu41_Val42del	ND	–	1	Chinese	No elbow and knee involvement; no hyperhidrosis	12
c.218_219del12ins12	p.Gln73Leufs*17	ND	–	11	Japanese	Mostly affecting the knee, no elbow involvement; hyperhidrosis; white spongy lesions	6, 9, 13, 15
c.271delC	p.His91Thrfs*9	ND	–	1	Chinese	No elbow and knee involvement	18
c.336+2T>G	NA	1/237984	–	1	Chinese	No data	9
c.382C>T	p.Arg128*	1/251188	–	1	Japanese	Hyperhidrosis; white spongy lesions; no dermatophyte	13
c.455G>T	p.Gly152Val	13/199854	–	2	Chinese	Few affecting the elbows; no hyperhidrosis and dermatophyte infection	4, 12
c.455-1G>A	p.Gly152Valfs*21	5/195598	–	6	Japanese	Few affecting the elbows more than knees; few have hyperhidrosis	6, 9, 15, 18
c.522_523insT	p.Val175Cysfs*46	50/250304	1	4	Chinese Korean	No elbow and knee involvement; white spongy lesions; hyperhidrosis; dermatophyte infection	4, 12, 16, 18
c.636delG	p.Lys213Serfs*12	1/251170	–	1	Japanese	White spongy lesions	14
c.650_653delCTGT	p.Ser217Leufs*7	19/251256	–	1	Chinese	Hyperhidrosis; dermatophyte infection	4
c.796C>T	p.Arg266*	134/243522	19	32	Chinese Japanese Korean	Affecting the elbows and knees; hyperhidrosis; dermatophyte infection; white spongy lesions; mild pruritus	4, 6, 9, 12–16
c.830C>T	p.Pro277Leu	ND	–	5	Japanese	No data	15
c.1136G>A	p.Cys379Tyr	156/242598	3	4	Finnish	No elbow and knee involvement; white spongy lesions; hyperhidrosis; dermatophyte infection	17

NA, not applicable; ND, not detected.