Nagashima-Type Palmoplantar Keratosis with Uncommon Homozygous Frameshift Mutations in *SERPINB7*

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ABSTRACT:

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Nagashima-type palmoplantar keratosis (NPPK, MIM6155998) is a non-epidermolytic, non-progressive, non-syndromic (isolated), diffuse palmoplantar keratosis inherited by autosomal recessive

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pattern. It is characterized by diffuse, erythematous palmoplantar hyperkeratosis that extends to the dorsal surfaces of hands, feet, inner wrists, ankles, and Achilles tendon area. Loss-of-function mutations in *SERPINB7* have been identified as a cause of NPPK. Here, we report a Chinese male with NPPK, confirmed as having one basepair duplication at nucleotide 522 (c.522dupT), likely homozygous variant, which created a shift in the reading frame and expected to result in a prematurely truncated protein (p.Val175Cysfs*46) in *SERPINB7*. We review the genomic structure of *SERPINB7* and all probable mutations.

Key words: Nagashima type, palmoplantar keratosis, *SERPINB7*, autosomal recessive

Introduction

Nagashima-type palmoplantar keratosis (NPPK) is characterized by non-epidermolytic, non-progressive, well-demarcated erythematous, diffuse, and mild-to-moderate palmoplantar non-epidermolysis hyperkeratosis that extends beyond the palmar and/or plantar skin to involve the dorsal surfaces of hands and feet, inner wrists, ankles, and the Achilles tendon areas. Elbows and knees are also often affected. No associated features were found in NPPK. The association of palmoplantar hyperhidrosis and/or dermatophytosis are commonly seen in NPPK. The palms and soles of NPPK patients show a whitish spongy appearance within 10 minutes of water exposure specifically in the erythematous hyperkeratotic area[1]. Clinically, spongy appearance after soaking in water is also seen in PPK type Bothnia (OMIM # 600231), a disease common in Sweden but inherited in an autosomal dominant fashion. In the far east, however, it was shown to be the autosomal recessive Nagashima type instead. Malignant transformation was not found[2].

NPPK is inherited in an autosomal recessive fashion[1] caused by biallelic loss-of-function mutations in the serine protease inhibitor, clade B, member 70 (*SERPINB7*). The onset of disease mostly within the first year of life. NPPK is common in East Asian populations. The prevalence rate is 1.2/10,000 and 3.1/10,000 in Japanese and Chinese, respectively. The prevalence rate of NPPK in non-Asian populations is estimated to be extremely low (～0.5/100,000,000)[2,3]. There was no sexual predilection and not affected by seasonal change.

We report a case of NPPK, non-epidermolytic, non-syndromic (isolated) PPK who had typical clinical features. Whole-exome sequencing identified the causative uncommon mutation, c.522dupT (p.Val175Cysfs*46). We compare our patient's phenotypes with other previous reported patients with the same (c.522dupT) and common (c.796C>T) mutations to find the difference of clinical features.

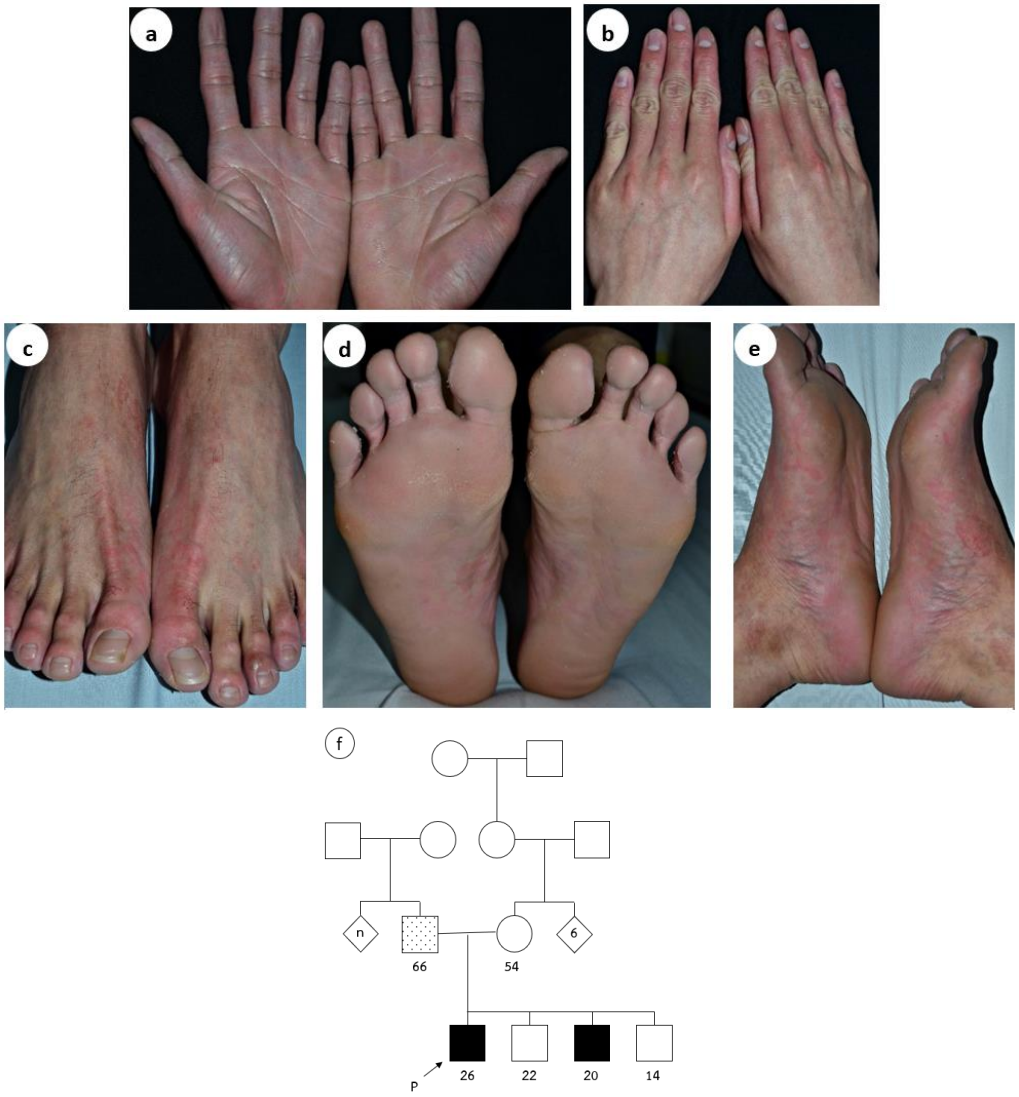

Figure 1 Clinical features of proband. (a-e) Symmetrical, well-demarcated diffuse erythema and hyperkeratosis over the palms and soles, extending to the dorsal hands, fingers, toes, and Achilles tendons. (f) Patient's family pedigree.

Case presentation

A 28-year-old Chinese male displayed bilateral thickening skin on the palms and soles since he was born. Skin lesions progressed slowly and there was neither pain nor itch. He had no complaint about 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. Scattered skin macerations were seen on palms and soles. There was no elbow/knee involvement and no nail abnormalities (Figure 1a-e). Potassium hydroxide (KOH) skin scraping was also negative. Iodine starch test and water immersion of palms were not done. Other complete physical examinations were within normal limits. He has 3 brothers, one of them reportedly had similar clinical features and course. However, his brother was unavailable for physical examination and genetic evaluation. The skin biopsy was not done because patient refused.

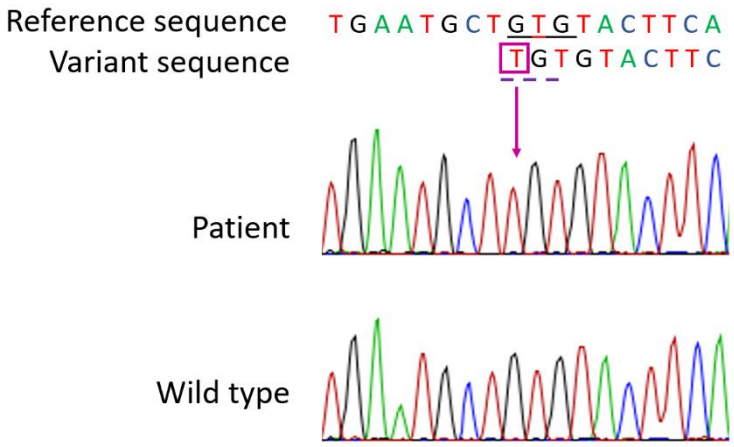

Figure 2 Sanger sequencing of our patient compared with a wild type sequence show a homozygous c.522dupT frameshift mutation in exon 6 of *SERPINB7* gene (box indicates insT nucleotide, underline indicates the reference codon and dotted line indicates the variance codon)

So, differential diagnosis in this patient were NPPK and Bothnia-type PPK due to diffuse transgrediens PPK without associated features. However, it is still a possibility to be epidermolytic PPK since we lack histopathology evidence. Genomic DNA was extracted from peripheral blood leukocytes of our patient, and was prepared as an Illumina sequencing library, and in the exome capture step. The sequencing libraries were enriched by SureSelect Human All Exon V5 Kit. The captured libraries were sequenced using Illumina HiSeq 4000. Singleton-WES analysis was made by using 147 genes list of palmoplantar hyperkeratosis (HP:0000972) in The human phenotype ontology, and all SNVs and Indels were filtered by the following filtering criteria: (1) located in exons or flanking introns of the gene related to phenotype, (2) not synonymous, (3)

less than 1% of minor allele frequency in the database of Genome Aggregation Database (GnomAD), 1000 Genomes Project Consortium, and in-house database of 2,000 Thai exomes, (4) if the variant is a missense; predicted to be damaging by silico predictive algorithms programs.

Whole-exome sequencing (WES) demonstrated that the patient harbored a frameshift mutation in *SERPINB7*, c.522dupT (p.Val175Cysfs*46), confirming that the diagnosis was NPPK. In this patient, c.522dupT (p.Val175Cysfs*46) is likely a homozygous mutation (Figure 2), however, hemizygous variant in deletion in another allele was still possible, given we were unable to have parental blood test done to demonstrate a heterozygous carrier in both parents or to perform deletion/duplication analysis. Some recent literatures identified either homozygous or compound heterozygous variant of c.522dupT (p.Val175Cysfs*46) as underlying genetic defect in NPPK[4-7].

In our patient, supportive treatment with 10% urea cream and genetic counseling were given. However, we cannot evaluate the clinical response because the patient was lost to follow-up.

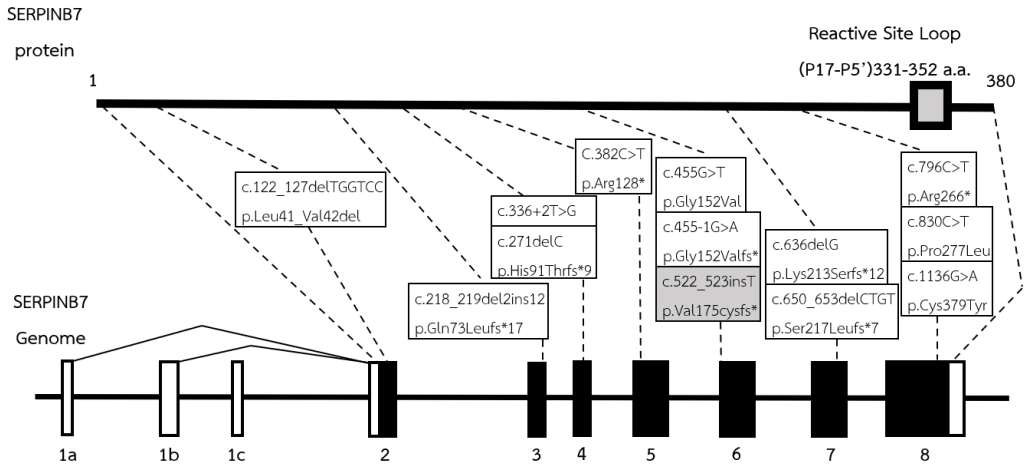

Figure 3 Schematic presentation of genomic structure of *SERPINB7*, reactive site loop of protease inhibitory activity of *SERPINB7* protein, and summarized location of NPPK-causing mutations

Discussion

In our patient, NPPK, Nagashima type was confirmed by identifying mutation in *SERPINB7*, while other types of PPK could be excluded by not seen any pathogenic variants in other 146 genes associated with PPK.

NPPK, Nagashima type was initially described in Japanese literature in 1977 and identified the

underlying genetic defect in 2013[2]. Biallelic loss-of-function mutations in the serine protease inhibitor, clade B, member 70 (*SERPINB7*) gene was causative of the disease. *SERPINB7* is located on chromosome 18q21.3, forming a cluster of clade-B serpin genes. *SERPINB7* is expressed in the stratum corneum and stratum granulosum, and is responsible for protecting cells from exogenous and endogenous protease-mediated injury[4]. *SERPINB7* consists of eight exons, with three distinct transcription start sites (exons 1a–c; Figure 3). The start codon is located within exon 2, and the termination codon within exon 8 (Figure 3). The *SERPINB7* transcript encodes a 380 amino-acid protein. Reactive site loop of *SERPINB7*, (P17-P5') 331-352 a.a, form a covalent bond with target proteases to activate protease-inhibitory function. Therefore, all the mutations result in a complete loss of the protease inhibitory activity of *SERPINB7*[2].

To date, 13 distinct *SERPINB7* mutations have been reported and we identified the positions of each mutation in the genomic structure of *SERPINB7* (Figure 3). c.796C>T (p.Arg266*) nonsense mutation in the last exon of the *SERPINB7* is the hotspot mutation of NPPK, either homozygous or compound heterozygous, which is identified in at least 70% of Chinese and Japanese NPPK patients[1,4,5].

Table 1 Summary of previously reported of c.522dupT (p.Val175Cysfs*46) in *SERPINB7* mutation

Patient	Gender/ Age(years)	Onset age	Ethnicity	Allele 1		Allele 2		Additional clinical features	Year	Ref
				Mutations	Amino-acid change	Mutations	Amino-acid change			
1	Male/30	4 years	Chinese	c.522-523insT	p.Val175Cysfs*46	c.522-523insT	p.Val175Cysfs*46	Onychomycosis, tinea pedis, hyperhidrosis	2014	4
2	Female/2	1 week	Chinese	c.796C>T	p.Arg266*	c.522dupT	p.Val175Cysfs*46	-	2016	5
3	Female/51	-	Chinese	c.796C>T	p.Arg266*	c.522dupT	p.Val175Cysfs*46	-	2017	5
4	-	-	Korean	c.796C>T	p.Arg266*	c.522-523insT	p.Val175Cysfs*46	-	2017	6
5	Male/6	After birth	Chinese	c.522dupT	p.Val175Cysfs*46	c.271delC	p.His91Thrfs*9	No elbow and knee involvement	2018	7
6	Male/28	After birth	Chinese	c.522dupT	p.Val175Cysfs*46	c.522dupT†	p.Val175Cysfs*46†	No elbow and knee involvement	Our case	

† Hemizygous variant in deletion in another allele was still possible

In our case, homozygous frameshift mutation of C.522dupT in exon 6 was identified. This uncommon variant was previously reported from China and Korea. Our patient is Chinese as well.

The allele frequency of this variant was found in 55 out of 281,686 alleles (1:5,121) in GnomAD (https://gnomad.broadinstitute.org) and 15 out of 4,328 alleles (1:288) in ThaiExome population (https://genomicsthailand.com). When we use these numbers to calculate the mutation-specific disease prevalence, it shows at least 1:82,000 in Asian and 1:26,224,641 worldwide with homozygous NPPK resulting from c.522dupT.

There is no conclusive phenotype-genotype association with this rare variant. Only 1 case of homozygous mutation and 4 cases of compound heterozygous c.522dupT (p.Val175Cysfs*46) mutation have been reported so far in the population (Table 1)[4-7]. Onychomycosis, tinea pedis, hyperhidrosis were described, but these features are also commonly seen in various NPPK genotypes

To date, there are no satisfactory treatments for NPPK. Treatment mainly aims to minimize hyperkeratosis with topical keratolytic agents such as urea, salicylic acid, and adapalene, however reports have not shown satisfactory improvement. Recently, topical gentamicin was used for patients with NPPK compared with petrolatum and showed a preliminary curative effect[8].

Conclusion

NPPK is a non-severe, non-progressive, non-syndromic (isolated) diffuse transgrediens PPK with autosomal recessive trait caused by a mutation in *SERPINB7*. We discovered an uncommon, likely homozygous *SERPINB7* variant, c.522dupT (p.Val175Cysfs*46). Our report demonstrates the beneficial of genetic test to confirm the definite diagnosis, which is more comfortable and less invasive investigation. Further investigations and case collections are needed to discover effective treatment and genotype-phenotype association.

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