

Mutation analysis in three Chinese pedigrees with palmoplantar keratoderma caused by *SERPINB7* gene mutations

Dear Editor,

Palmoplantar keratoderma (PPK) encompasses a group of keratinising skin disorders characterised by excessive thickening of the epidermis in the palmoplantar regions which may be inherited or acquired. Nagashima-type palmoplantar keratoderma (NPPK, OMIM 615598) is an autosomal

recessive variant of PPK.¹ It is primarily characterised by well-demarcated, transgradient erythema and hyperkeratosis affecting the palms and soles.

Four patients presented at our outpatient department with complaints of rough palms and soles. Their demographic and clinical features are summarised in Table 1. There was no

Table 1: Mutations and Clinical Details of the Subjects

Pedigree ID	Sex	Mutations in <i>SERPINB7</i> gene	Zygotity	Age at diagnosis	Affected areas	Symptoms	Dermoscopic manifestations
Pedigree 1-The proband (II-1)	Female	c.796C>T (p.R266X)	Homozygote	3.5 years	Palms, soles, dorsal feet	Transgradient erythema, hyperkeratosis, scales, hyperhidrosis	Significant scales peeling off on palms
Pedigree 1-The proband's younger sister (II-2)	Female	c.796C>T (p.R266X)	Homozygote	3.5 years	Palms, soles, dorsal feet	Transgradient erythema, hyperkeratosis, scales, hyperhidrosis	Partial disappearance of fingerprints
Pedigree 1-The proband's father (I-1)	Male	c.796C>T (p.R266X)	Heterozygote	-	-	-	-
Pedigree 1-The proband's mother (I-2)	Female	c.796C>T (p.R266X)	Heterozygote	-	-	-	-
Pedigree 2-The proband (II-1)	Male	c.336+2T>G; c.796C>T (p.R266X)	Heterozygote	12 years	Palms, soles, dorsal feet, ankles, achilles tendon	Transgradient erythema, hyperkeratosis, scales, odour, hyperhidrosis, white spongy appearance	Scales peeling off and fissuring on fingers
Pedigree 2-The proband's younger brother (II-2)	Male	-	Wild type	-	-	-	-
Pedigree 2-The proband's father (I-1)	Male	c.336+2T>G	Heterozygote	-	-	-	-
Pedigree 2-The proband's mother (I-2)	Female	c.796C>T (p.R266X)	Heterozygote	-	-	-	-
Pedigree 3-The proband (II-1)	Female	c.455G>T (p.G152V); c.796C>T (p.R266X)	Heterozygote	9 years	Palms, soles	Transgradient erythema, hyperkeratosis, scales, hyperhidrosis, odour, white spongy appearance	Mild scales peeling off on palms
Pedigree 3-The proband's younger sister (II-2)	Female	-	Wild type	-	-	-	-
Pedigree 3-The proband's father (I-1)	Male	c.796C>T (p.R266X)	Heterozygote	-	-	-	-
Pedigree 3-The proband's mother (I-2)	Female	c.455G>T (p.G152V)	Heterozygote	-	-	-	-

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history of consanguinity [Figure S1]. This report summarises the clinical manifestations [Figure 1a-d and Figure S2], dermoscopic findings [Figure S3] and genetic mutations of these four patients from three Chinese pedigrees with NPPK, in order to elucidate the aetiology at the molecular level and provide guidance for future treatment of NPPK.

High-throughput and Sanger sequencing were performed by Shanghai Weihans Biopharmaceutical Technology Co. Ltd. [Table S1]. The sequencing results were analysed and aligned using CodonCode Aligner software. Mutations were identified utilising GATK v3.70 (Genome Analysis Toolkit). Visual sequencing chromatogram was generated using Chromas (Technelysium Pty Ltd.)

Among the 12 subjects, 10 were identified as having either heterozygous or homozygous mutations in the *SERPINB7* gene, while the remaining 2 subjects did not exhibit any mutations. Notably, two patients carrying homozygous mutations (c.796C>T, the founder mutation) and two patients with compound heterozygous mutations (c.796C>T, c.336+2T>G; c.796C>T, c.455G>T) in the *SERPINB7* gene all presented with the NPPK phenotype [Figure 2a-b and Figure S4]. These four cases (II-1, II-2 of pedigree 1, III-1

of pedigree 2 and II-1 of pedigree 3) were diagnosed with NPPK, potentially linked to mutations in the *SERPINB7* gene. No correlation was found between genotype and phenotype across the three pedigrees.

A loss-of-function mutation in the *SERPINB7* gene is implicated in the pathogenesis of NPPK.¹ *SERPINB7* may play a role in the expression of desmin and in the adhesion between keratinocytes. The loss of *SERPINB7* function can damage desmoglein 1 and desmocollin 1, disrupting the adhesion between keratinocytes, leading to a skin peeling phenotype.² Mutations in the *SERPINB7* gene, such as c.796C>T, may result in the formation of premature termination codons (PTCs), leading to a loss of gene expression and protease inhibitory activity in *SERPINB7*. This loss can trigger excessive activation of proteases in the granular layer and stratum corneum, disrupting the integrity structure of the stratum corneum barrier and promoting excessive water penetration which, results in a white, sponge-like appearance.³ Serpins constitute the largest and most widely distributed superfamily of protease inhibitors, typically comprising ≥ 400 amino acids and exhibiting a highly ordered tertiary structure. They exist as a monomeric domain consisting of three β -folds (designated A-C) and



Figure 1a: Well-defined hyperkeratosis on both palms accompanied by scaling of II-1 in pedigree 2.



Figure 1b: White spongy appearance after immersion in water of II-1 in pedigree 2.



Figure 1c: Well-defined hyperkeratosis and erythema on both palms accompanied by scaling of II-2 in pedigree 3.



Figure 1d: White spongy appearance after immersion in water of II-2 in pedigree 3.

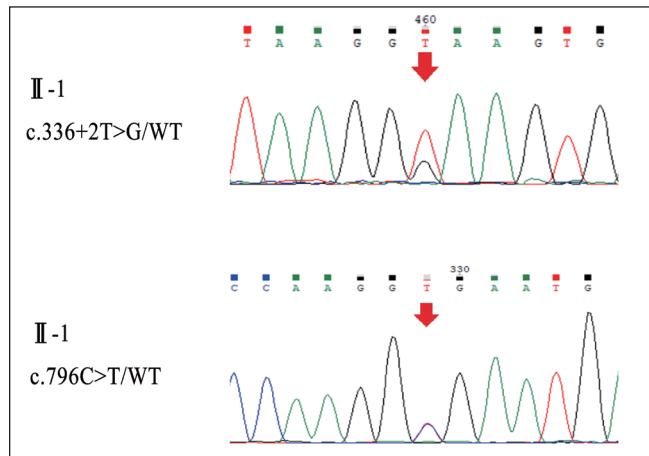


Figure 2a: Sequencing results of the patient II-1 in pedigree 2. Red arrows: The mutation sites.

nine α -helices (designated A-I) which possess highly specific conformational and functional characteristics.⁴ The carboxyl group of the serpin protein (P17-P50, corresponding to amino acid residues 331-352) is referred to as the reactive centre loop (RCL) which is an exposed conformational region that extends above the serpin structure. This region is crucial for docking with the reaction site of the target protease (P1-P1, corresponding to amino acids 347-348), facilitating interactions.⁵ The serpin behaves as a pseudo-substrate for the target protease, exhibiting substrate-like characteristics. When the target protease attempts to cleave the P1-P1' bond, it becomes trapped in a conformational trap, resulting in the formation of a stable 1:1 docking complex with the inhibitor, thereby achieving inhibitory effects. Furthermore, recent findings have identified legumain as a key target protease of *SERPINB7*. The loss of *SERPINB7* function leads to excessive activation of legumain which may disrupt cytoskeletal proteins and damage the skin barrier.⁶

This study confirms that mutations in the *SERPINB7* gene play an important role in NPPK with c.796C>T (the founder mutation) identified as one of the most prevalent mutations. Furthermore, it underscores that compound heterozygous mutations in the *SERPINB7* gene may contribute to the onset of NPPK. Current literature suggests that the topical application of gentamicin cream could be a potential therapy for treating NPPK-related hyperkeratosis. The proposed mechanism involves gentamicin facilitating read-through of PTCs during transcription, resulting in the insertion of random amino acids and the expression of full-length proteins, a process known as nonsense suppression. However, further research is warranted to evaluate the safety and potential for drug resistance associated with this treatment.

Ethical approval: This research/study was approved by the Institutional Review Board at the Ethics Committee of Inner Mongolia Medical University Affiliated Hospital, number Ethics No. S.2019017, dated 2019.06.17.

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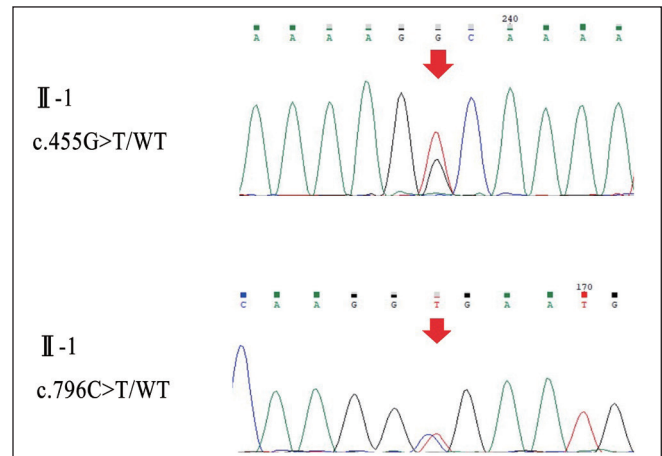


Figure 2b: Sequencing results of the patient II-1 in pedigree 3. Red arrows: The mutation sites.

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