

## SHORT COMMUNICATION

## Extensive Erythema and Hyperkeratosis on the Extremities and Lumbar Area as an Unusual Manifestation of Nagashima-type Palmoplantar Keratosis

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Nagashima-type palmoplantar keratosis (NPPK; OMIM 615598) is the most common palmoplantar keratoderma (PPK) in East Asia. It has autosomal recessive inheritance (1, 2). Recently, homozygous or compound heterozygous loss-of-function mutations in *SERPINB7*, encoding a member of the serine protease inhibitor superfamily, were identified as a cause of NPPK (1–5). NPPK is clinically characterized by well-demarcated erythema with mild to moderate hyperkeratosis over the whole of the palms and soles, extending to the dorsal surfaces of the hands and feet, inner wrists, ankles and the Achilles tendon area (1–3). The elbows and knees are often affected (1–3). NPPK is also characterized by the white, spongy change of affected areas upon exposure to water (2). *SERPINB7* is expressed in the epidermis, not only of the palmoplantar regions, but also of other body areas

(1, 2). Even so, the lesions have been considered to be limited to only these specific areas. We report here a case of NPPK showing more widespread involvement of the extremities and the lumbar area than reported previously.

## CASE REPORT

An 18-year-old Japanese male presented with bilateral, well-demarcated erythematous hyperkeratotic lesions on his extremities and lumbar area. The non-pruritic lesions had been apparent since early childhood. His mother reportedly showed similar lesions limited to the hands and feet, although she was unavailable for clinical examination. There were no consanguineous marriages in this family. Physical examination revealed diffuse erythema with mild hyperkeratosis on the palms and soles that extended to the dorsal surfaces of the hands and feet (Fig. 1a–d), inner wrists, ankles, the Achilles tendon area, elbows and knees. Notably, similar lesions were

observed on the central lumbar area and cubital fossae (Fig. 1e). Moreover, slightly hyperkeratotic reddish papules were noted on the forearms, thighs, popliteal fossae and lower legs (Fig. 1f–h). He also reported palmoplantar hyperhidrosis and a whitish change in all the reddish hyperkeratotic areas after bathing. Histology of lesional skin sampled from his palm, lower leg, and cubital fossa showed hyperkeratosis, acanthosis, hypergranulosis and parakeratosis in the lower layers of the stratum corneum (Fig. S1a–c<sup>1</sup>). From these clinicopathological findings, a diagnosis of NPPK was highly suspected. However, the involvement of the non-palmoplantar areas was unusual and atypical for NPPK. Moreover, the cutaneous phenotype appeared to be inherited in an autosomal dominant fashion in this family, whereas NPPK is an autosomal recessively inherited disorder (Fig. S2a<sup>1</sup>). To confirm the diagnosis, we performed mutation analysis. Genomic DNA of the patient and his parents was extracted from peripheral blood using the QIAamp DNA Blood Maxi Kit (Qiagen, Germantown, MD, USA) or saliva using the Oragene DNA Self-Collection Kit (DNA Genotek, Kanata, ON, Canada), respectively. This study was approved by the institutional review board. We amplified all exons and exon-intron boundaries of *SERPINB7* (RefSeq: NM\_001040147.2) by PCR using previously described primers (2). The PCR products were then sequenced using an ABI 3130xl Genetic Analyzer (Applied



Fig. 1. Features of the proband. (a–d) Well-demarcated, diffuse erythema with mild hyperkeratosis on the palms and soles extend to the dorsal surfaces of the hands and feet, inner wrists and ankles. (e) Slightly hyperkeratotic erythema is noted at the centre of the lumbar area. (f) Scaly erythema on the elbows and tiny reddish papules on the forearms and (g, h) thighs and lower legs.

Biosystems). This led to the identification of a homozygous nonsense mutation c.796C>T (p.(Arg266Ter)) in the patient and his mother, whereas his father was heterozygous for that mutation (Fig. S2a, b<sup>1</sup>). Although we also sequenced all exons and exon-intron boundaries of *SLURP1*, *GJB3*, *GJB4*, *LOR*, *KRT1* and *AQP5* (primer sequences are available upon request), no pathogenic mutations were detected in the patient (data not shown). Taken together, the diagnosis of NPPK was made. Topical use of 10% salicylic acid and vitamin D3 produced little improvement.

## DISCUSSION

In this study, we identified a homozygous nonsense mutation in *SERPINB7* that led to a diagnosis of NPPK. NPPK clinically shows “transgrediens”, which refers to the extension of hyperkeratosis beyond the volar margins of the palmoplantar skin, and typically affects the palms, soles, dorsal surfaces of the hands and feet, inner wrists, ankles and Achilles tendon area (1, 2). However, the distribution of the skin lesions was rather unusual in the present case, since hyperkeratotic erythema and/or papules were noted not only on these areas but also on the lumbar area, cubital and popliteal fossae, forearms, thighs and lower legs. Notably, the histology of lesional skin sampled from the lower leg and cubital fossa showed similar findings to those of skin sampled from the palm, which are commonly seen in NPPK (3). Mutation analysis of genes responsible for PPK with possible involvement of non-palmoplantar skin, including *SLURP1*, *GJB3*, *GJB4*, *LOR*, *KRT1* and *AQP5* revealed no pathogenic mutations in the patient. Moreover, he reported a whitish spongy change in the lesional skin even on the atypical affected areas after bathing (Fig. S3<sup>1</sup>). Taken together, we consider that erythema and hyperkeratosis on the non-palmoplantar areas are not a coincidental finding, but are part of the clinical features of NPPK, although the involvement of such regions has not been reported in patients with NPPK. Since *SERPINB7* is ubiquitously expressed in the epidermis (2, 6), one would predict that NPPK can affect any part of the body skin. Indeed, hyperkeratotic lesions on the ears and toenail dystrophy have been reported as atypical manifestations of NPPK (7, 8). These findings also support our hypothesis that NPPK can show more extensive manifestations than reported previously.

The pathomechanism of NPPK lesions usually restricted to specific areas remains unknown. Notably, frequent involvement of the knees and elbows in NPPK suggests that chronic exposure to mechanical stress might play a role in the development of NPPK lesions (1, 2). However, our patient had no special habits relevant to chronic mechanical stress on the extremities and

lumbar area. Considering that the mutation c.796C>T is the most common mutation in NPPK (1–4) and that patients with this mutation have never been reported to show similar phenotypes to our case, it is also difficult to explain the widespread manifestations in light of the genotype/phenotype correlation. The existence of as-yet unknown modifier genes or environmental factors might explain the unusual manifestations in our patient.

It is also notable that the present parent–unrelated family showed pseudodominance, a situation in which an autosomal recessive condition occurs in individuals in 2 or more generations of a family and the inheritance mimics an autosomal dominant pattern (3). To date, only one family with NPPK has been reported to exhibit such inheritance (3). In the Japanese population, the nonsense mutation c.796C>T is carried by 22 out of 2,298 alleles, according to the Human Genetic Variation Database Version 1.42 (<http://www.genome.med.kyoto-u.ac.jp/SnpDB>) (9), or by 2 out of 178 alleles, according to the 1000 Genomes Browser Version 3.4. Therefore, the mutant allele frequency is estimated to be 0.010. With the high null allele frequency, families with NPPK can show pseudodominance. Thus, this study provides further evidence for pseudodominant inheritance in NPPK, which will contribute to more accurate genetic testing and counselling of the disease.

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