

Striate Palmoplantar Keratoderma Showing Transgrediens in a Patient Harboring Heterozygous Nonsense Mutations in Both *DSG1* and *SERPINB7*

Ryo FUKAURA^{1,2}, Takuya TAKEICHI¹, Yusuke OKUNO^{3,4}, Daiei KOJIMA⁴, Michihiro KONO¹, Kazumitsu SUGIURA⁵, Yasushi SUGA⁶ and Masashi AKIYAMA^{1*}

Departments of ¹Dermatology and ⁴Pediatrics, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan, ²UCL Medical School, University College London, UK, ³Center for Advanced Medicine and Clinical Research, Nagoya University Hospital, Nagoya, ⁵Department of Dermatology, Fujita Health University School of Medicine, Toyoake, and ⁶Department of Dermatology, Juntendo University Urayasu Hospital, Urayasu, Japan. *E-mail: makiyama@med.nagoya-u.ac.jp

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Palmoplantar keratoderma (PPK) is a group of inherited skin disorders characterized by thickening of the skin on the palms and soles, often leading to pain. Classification has largely been clinical, but recently, causative genes for the various PPKs have been found, resulting in a need for a genetic classification of PPK (1). The most common type in the Japanese population is Nagashima-type PPK (NPPK) (2). This autosomal recessive condition is caused by a mutation in *SERPINB7*. The *SERPINB7* protein is found in the stratum corneum of the skin, and its main function is to regulate intercellular protease activity (3). The clinical features of NPPK include diffuse hyperkeratosis associated with erythema on the palms and soles and, in addition, on the dorsal aspects, known as transgrediens (2). Another type of PPK, striate PPK (SPPK), is autosomal dominant. The clinical features include strips of hyperkeratosis running longitudinally along the hands and fingers, and generalized hyperkeratosis on the soles of the feet. A mutation in any of 3 genes is reported to be an underlying cause: desmoglein 1 (*DSG1*), desmoplakin (*DSP*) and keratin 1 (*KRT1*) (4). Not only are these desmosomal proteins essential in maintaining the structure and integrity of the skin, but they are also essential to cell turnover (5). *DSP* mutations have been shown to increase skin proliferation,

leading to hyperkeratosis, and the same effect has been predicted with *DSG1* mutations (1), although the exact mechanism has not been fully clarified despite *DSG1* being involved in various skin disorders (6, 7). To date, there have been no reports of a patient with genetic mutations for 2 types of PPK. Here, we describe such a Japanese male.

CASE REPORT

A 36-year-old man presented with longstanding pain and hyperkeratotic palms. He had presented with corns on his palms in adolescence, which developed easily after sports. It was when he started working as a farmer that he noticed pain and “stripe-like” hyperkeratosis on his palms, and circular areas of hyperkeratosis on the soles (Fig. 1A and B). He also had abnormalities on the dorsal aspects of the hands: poorly demarcated areas of erythema and maceration (Fig. 1C). No lesions were found on the dorsa of the feet. Although there were no white spongy changes after water immersion, as has been reported for some cases of NPPK, his palms were abnormally moist and malodorous compared with a healthy subject. The stripe-like pattern of hyperkeratosis on this patient’s palms appeared to be a classical example of SPPK. However, the continuation of the lesions to the dorsal aspects, and a change in the lesions from hyperkeratosis to erythema were atypical. Instead, these seemed to resemble transgrediens reported in NPPK (2). Other than a sister who has atopic dermatitis, he has no family history of hyperkeratosis or other skin disorders.

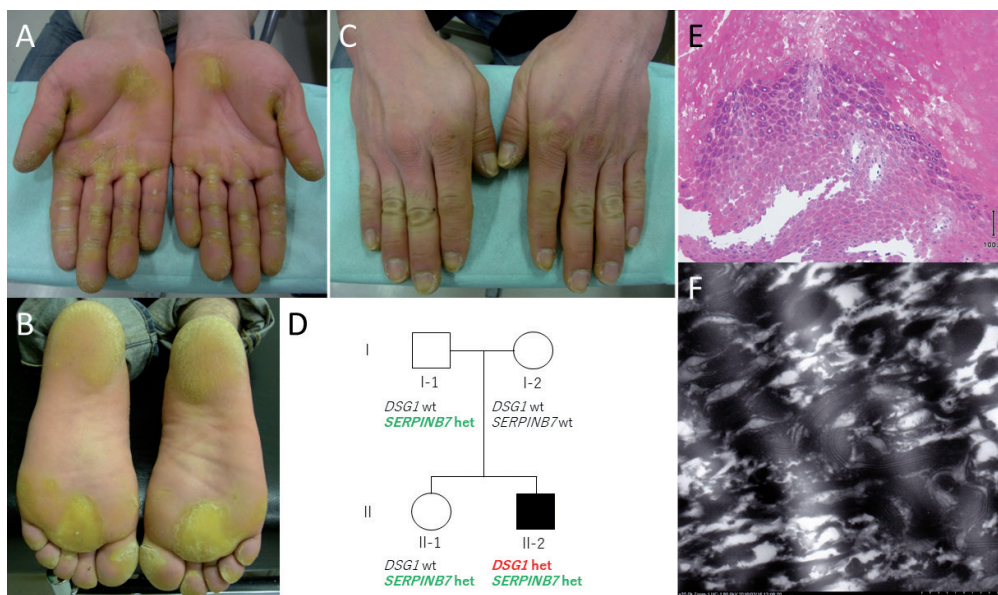


Fig. 1. Clinical and histological features of the patient. (A) Palms showing typical longitudinal hyperkeratotic lesions on the fingers. (B) Plantar aspects showing diffuse areas of hyperkeratosis. (C) Dorsal aspects of the hands, showing generalized erythema. (D) Pedigree of the family showing genotypes for the mutations in *DSG1* and *SERPINB7*. wt: wild type, het: heterozygote. (E) Skin biopsy sample from the sole shows keratohyalin granules of various sizes, and acantholysis. Scale bar: 100 μ m. (F) Electron microscopy clearly shows a highly electron-dense line. Magnification: $\times 20,000$.

Informed consent and ethical approval were obtained, and all research conformed to the principles of the Declaration of Helsinki. Given the wide range of differentials and the variety of genes these conditions cover, we opted to perform whole-exome sequencing (WES) to determine the causative gene. This showed that not only did the patient have a heterozygous mutation c.655C>T (p.R219*) in the *DSG1* (*DSG1*: NM_001942), but he was also heterozygous for a mutation c.796C>T (p.R266*) on the *SERPINB7* (*SERPINB7*: NM_001040147) (3). The WES data excluded pathogenic mutations in other PPK-causative genes, including *KRT1* and *DSP*. His father and sister were carriers for the *SERPINB7* variant, while his mother showed a wild-type genotype (Fig. 1D). All relatives demonstrated a wild-type *DSG1* variant.

Histologically, parts of the basal layer and the stratum spinosum are missing; however, we observed size irregularities in the keratohyalin granules, and acantholysis, possibly due to reduced epithelial intercellular cohesion, which is thought to result from the *DSG1* mutation (Fig. 1E) (1, 8). Electron microscopy revealed, within the hyperkeratotic regions, thickening of the desmosomal intermediate zone, giving the appearance of a highly electron-dense line (Fig. 1F). Clinically, we initially suspected *KRT1* mutation-induced SPPK with a V2 frameshift, which has been reported to cause SPPK (9). Histologically, it was necessary to consider a *DSG1* mutation, as there have been reports of this mutation leading to acantholysis (10).

DISCUSSION

It is not clear in the presented case if transgrediens appeared because the *SERPINB7* mutation directly caused the phenotype, or whether the *SERPINB7* mutation had a modifying effect on *DSG1* that coincidentally manifested as transgrediens on this occasion. In any case, our results suggest that simultaneous disruption of the skin by 2 different genes may create an overlap in symptoms of their respective disorders. Thus, there is a possibility that a heterozygous *SERPINB7* mutation may be considered as a modifying factor for patients with *DSG1* mutation-positive SPPK, although we cannot exclude the possibility that the *SERPINB7* mutation had no effect on the phenotype in the heterozygous state. Indeed, the present *SERPINB7* mutation c.796C>T (p.R266*) might be entirely coincidental given the high prevalence of this particular mutation in the Japanese population (see below). In addition, the protein string interactions suggest a possible link between *DSG1* and *SERPINA4* (one of the Serpin family members), but not *SERPINB7* (11).

Another noteworthy point is that the 2 mutations were found by chance. Had we taken the usual protocol and tested only for *DSG1* by Sanger sequencing on the suspicion of SPPK from the patient's symptoms, the result would have been positive. It is likely then that we would have terminated any further investigations and initiated management for standard SPPK. On the other hand, had we only tested for *SERPINB7*, based on transgrediens demonstrated by the patient, the result would have shown heterozygosity. Although heterozygous *SERPINB7* mutation carriers have not been reported to be symptomatic of NPPK, it is probable we would have assumed that the symptoms were due to another related mutation that was

difficult to pick up by Sanger sequencing, and we would have searched in vain for a large deletion, an intronic mutation or a promoter site mutation. It was only because we opted to perform WES that we were able to visualize both mutations. We feel this may provide another angle from which to consider the genetic aetiology of PPKs. Undetected, unsearched-for modifying mutations in other PPK-causative genes, such as *SERPINB7* in the present case, may be present in some previously reported, genetically defined, PPK cases. Indeed, the carrier rate of the present *SERPINB7* mutant allele, c.796C>T, is estimated as 0.9% from both our screening data in the Japanese population (data not shown) and HGVD (Human Genome Variation Database (<http://www.genome.med.kyoto-u.ac.jp/SnpDB/index.html>)).

In summary, we reported a patient presenting with autosomal dominant SPPK caused by the *DSG1* mutation and a previously reported *SERPINB7* mutation, the causative gene of autosomal recessive NPPK.

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