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We hope that making available the relevant information on Pachyonychia Congenita will be a means of furthering research to find effective therapies and a cure for PC.
Diffuse and focal palmoplantar keratoderma can be caused by a keratin 6c mutation

E. Akasaka, H. Nakano, A. Nakano,* Y. Toyomaki, N. Takiyoshi, D. Rokunohe, Y. Nishikawa, A. Korekawa, Y. Matsuzaki, Y. Mitsuhashi† and D. Sawamura

Department of Dermatology, Hirosaki University Graduate School of Medicine, S Zaifu-cho, Hirosaki 036-8562, Japan
*Department of Dermatology, EST 2 Clinic, Hirosaki, Japan
†Department of Dermatology, Tokyo Medical University, Tokyo, Japan

Correspondence
Hajime Nakano.
E-mail: hnakano@cc.hirosaki-u.ac.jp

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The palmoplantar keratodermas (PPKs) are a large group of genodermatoses comprising nearly 60 genetically distinct diseases. They are characterized by hyperkeratotic lesions on the palms and soles with or without extrapalmoplantar hyperkeratotic lesions. Focal PPK is one of the hallmarks of pachyonychia congenita, a rare autosomal dominant disorder resulting from mutations in the keratin genes KRT6A, KRT6B, KRT16 or KRT17. Recently, in-frame deletion mutations of KRT6C have been identified in three families with focal PPK with slight or no nail changes. We report here a novel KRT6C mutation identified in a Japanese family with PPK with phenotypic heterogeneity, presenting with not only focal but also diffuse hyperkeratosis. The proband had diffuse hyperkeratosis on the soles and small focal hyperkeratoses on the palms, while the two other affected individuals showed focal hyperkeratoses on the soles. All three patients were heterozygotes for c.1414G>A in KRT6C, predicted to result in p.Glu472Lys. These findings strongly suggest that screening of patients with nonepidermolytic diffuse PPK, in whom the pathogenic mutations are yet to be determined, might identify mutations in KRT6C.

Case and methods

The proband (Fig. 1a, II-3), a 26-year-old Japanese male iron-worker, presented with thickened skin on the soles that had developed at around 5 years of age. Diffuse hyperkeratosis with a rough surface was seen on the soles (Fig. 1b). On the palms, small hyperkeratotic plaques were noted (Fig. 1c). Although the hands of the proband’s 4-year-old son (III-2) were not affected, his soles demonstrated focal hyperkeratosis as well as blister formation, which had developed a few days before first visiting the Hirosaki University Hospital (Fig. 1d). The soles of the proband’s 36-year-old sister (II-2) also showed focal hyperkeratoses on the palms, while the two other affected individuals showed focal hyperkeratoses on the soles. All three patients were heterozygotes for c.1414G>A in KRT6C, predicted to result in p.Glu472Lys. These findings strongly suggest that screening of patients with nonepidermolytic diffuse PPK, in whom the pathogenic mutations are yet to be determined, might identify mutations in KRT6C.

1 The palmoplantar keratodermas (PPKs) are a large group of genodermatoses comprising nearly 60 genetically distinct diseases. They are characterized by hyperkeratosis on the palms and soles with or without extrapalmoplantar hyperkeratotic lesions. Among PPKs, a variety of syndromic PPKs are defined by their distinctive extracutaneous involvement. Painful focal PPK is one of the hallmark manifestations of pachyonychia congenita (PC; OMIM #167200, #167210), a rare autosomal dominant disorder resulting from mutations in the keratin genes KRT6A, KRT6B, KRT16 or KRT17, specific for keratinocyte differentiation. The hyperkeratotic lesions, under which blistering frequently occurs, are often extremely painful, resulting in restricted mobility. Palmar lesions can develop due to mechanical trauma. Hypertrophic nail dystrophy is an essential clinical characteristic of PC, and other ectodermal features, including cysts and follicular keratosis, may also be involved. However, in cases of focal PPK with slight or no nail changes, mutational analysis is not usually successful. Recently, in-frame deletion mutations of KRT6C have been identified in three families with focal PPK with slight or no nail changes. We here report a novel KRT6C mutation identified in a Japanese PPK family with phenotypic heterogeneity, presenting with not only focal but also diffuse hyperkeratosis.

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was noted in all three affected individuals. The proband and his sister stated that their father had also developed many calluses on his soles. Biopsy of the proband’s soles demonstrated non-epidermolytic orthohyperkeratosis and acanthosis of the epidermis. A clinical diagnosis of nonepidermolytic focal and diffuse PPK was made.

After obtaining informed consent, mutational analyses were performed using genomic DNA prepared from patients’ peripheral blood leukocytes and an affected family member as described previously.1

**Results and discussion**

Direct sequencing revealed a heterozygous c.1414G>A in exon 7 of KRT6c in the proband (Fig. 2, upper panel). His son and elder sister were also confirmed to have the same nucleotide change, whereas the asymptomatic son of the proband’s elder sister did not (Fig. 2, lower panel), indicating the nucleotide change cosegregated with the disease. Furthermore, c.1414G>A was not detected in 104 unaffected controls, suggesting that the nucleotide change was a pathogenic mutation, not a polymorphism. To our knowledge, c.1414G>A has not been reported previously. The mutation is predicted to result in a substitution of glutamic acid for lysine at amino acid position 472 of the keratin 6c protein, designated as p.Glu472Lys. The Glu472 residue resides in the C-terminus of the 2B domain and is conserved among other type II keratins.

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**Fig 1.** (a) Pedigree of a Japanese PPK family. Autosomal dominant inheritance is suggested. Arrow indicates the proband. (b–e) Clinical presentation of the proband (b, c), the son III-2 (d), and the elder sister II-2 (e). Clavus formation is indicated by arrows.

**Fig 2.** Sequencing results of KRT6C. Heterozygous c.1414G>A of the proband (upper panel) and wild-type of asymptomatic individual III-1 (lower panel).
expressed in epithelia. Moreover, the functional importance of Glu472 in type II keratins is demonstrated by the fact that it is frequently substituted by Lys in a variety of keratin disorders, including PC caused by analogous mutations in KRT6A and KRT6B, respectively (Human Intermediate Filament Database: http://www.interfil.org). Sequencing of all coding regions and splicing sites of KRT6A, KRT6B, KRT16 and KRT17 did not demonstrate any pathogenic mutations in the affected individuals.

Our PPK family exhibited phenotypic heterogeneity; the proband presented with more diffuse hyperkeratosis of the soles compared with focal hyperkeratotic plaques observed on the soles of his affected son and sister. So far, only two in-frame deletion mutations of KRT6C have been described and all affected patients demonstrated focal hyperkeratosis. The proband’s diffuse plantar hyperkeratosis as well as the corns on his palms were thought to have developed at least in part in response to the occupational mechanical stress experienced as an ironworker, although the pathogenetic mechanism of the diffuse hyperkeratosis remains to be determined. Interestingly, PC caused by KRT16 mutations can present as diffuse rather than fully focal plantar hyperkeratotic lesions. However, it is tempting to think that screening of patients with nonepidermolytic diffuse PPK, in whom the pathogenic mutations are yet to be determined, might identify mutations in KRT6C. In addition, KRT6C would be a candidate gene for multiple plantar clavi, especially in familial cases, as some of the hyperkeratotic plaques of the proband’s sister contained clavi inside (Fig. 1e), as demonstrated in the previous report. Mutational analysis of KRT6C may clarify the pathogenesis of palmoplantar hyperkeratoses with unknown aetiology.

References