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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.

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Diffuse and focal palmoplantar keratoderma can be caused by a keratin 6c mutation

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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. 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*.

The palmoplantar keratodermas (PPKs) are a large group of genodermatoses comprising nearly 60 genetically distinct diseases.[1] They are characterized by clinical and histological hyperkeratosis on the palms and soles in association 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.[2] The hyperkeratotic lesions, under which blistering frequently occurs, are often extremely painful, resulting in restricted mobility.[3] 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.[3] 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.[1] 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.

Case and methods

The proband (Fig. 1a, II-3), a 26-year-old Japanese male ironworker, 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 hyperkeratotic plaques 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 hyperkeratotic plaques, which had been present since her first decade (Fig. 1e), although the palms were not involved. Some of the plaques were associated with clavi (Fig. 1e, arrows) and were painful with walking. Her 5-year-old son (III-1) had no palmoplantar lesions. Mycological examination showed no fungal infection of the proband's soles. Neither patient had abnormal nails, while hyperhidrosis of the soles

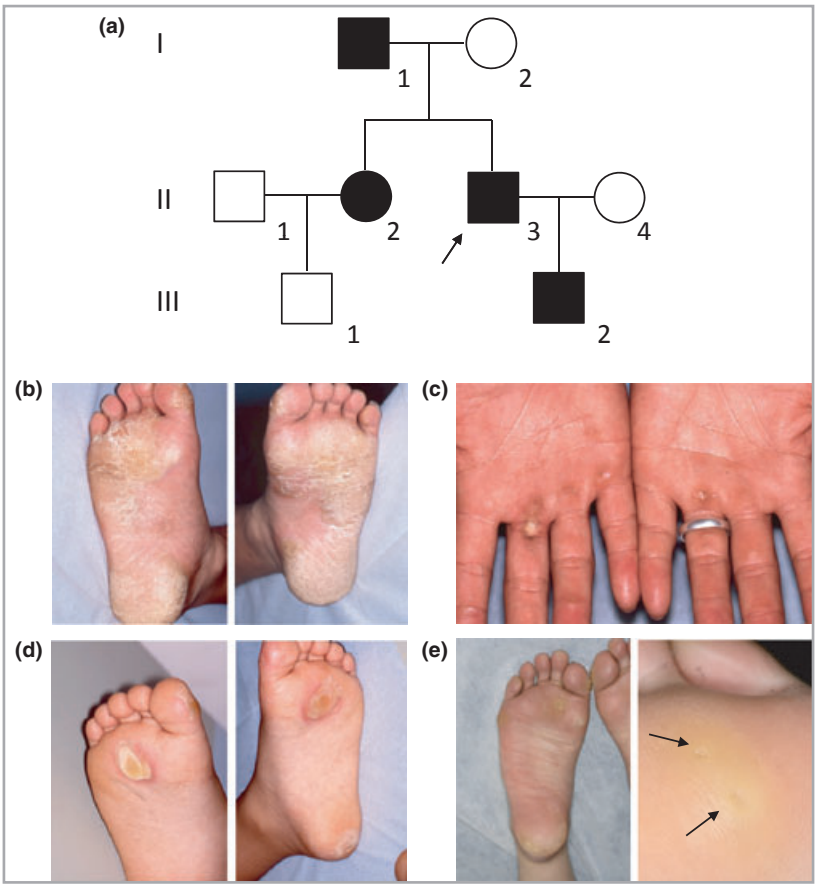

Fig 1. (a) Pedigree of a Japanese PPK family. Autosomal dominant inheritance is suggested. Arrow indicates the proband. (b–e) Clinical presentation of the proband (b, c), the son III-2 (d), and the elder sister II-2 (e). Clavus formation is indicated by arrows.

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 nonepidermolytic 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

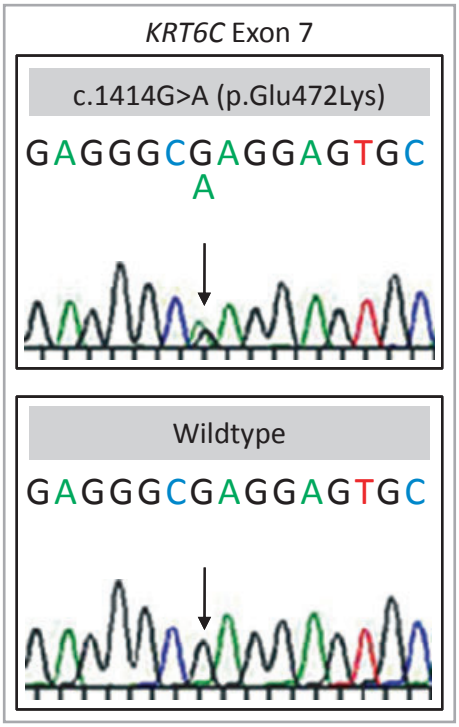

Fig 2. Sequencing results of *KRT6C*. Heterozygous c.1414G>A of the proband (upper panel) and wild-type of asymptomatic individual III-1 (lower panel).

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).[4] Sequencing of all coding regions and splicing sites of *KRT6A*, *KRT6B*, *KRT16* and *KRT17*[5] 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.[1] 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.[4] 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.[1] Mutational analysis of *KRT6C* may clarify the pathogenesis of palmoplantar hyperkeratoses with unknown aetiology.

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