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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.
Pachyonychia congenita type 2: Keratin 17 mutation in a Japanese case

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Pachyonychia congenita (PC) is an autosomal dominant genodermatosis first described by Muller. Two major subtypes of PC have been described. Jadassohn-Lewandowsky type PC (MIM #167200; PC1) is characterized by onychogryphosis; hyperkeratosis of the palms, soles, knees, and elbows; follicular hyperkeratosis; and leukoplakia of the oral mucous membranes. Jackson-Lawler type PC (MIM #167210; PC2) shows no oral leukoplakia but is characterized by natal teeth and multiple cutaneous cysts and pachyonychia. Histopathologic condition of hyperkeratotic skin shows moderate to marked hyperkeratosis and acanthosis. Ultrastructural analysis of keratinocytes in the stratum spinosum of affected areas shows large tonofibril aggregates without signs of cellular disruption or cell death.

The ultrastructural finding of aggregated keratin filament bundles in keratinocytes is a common feature of keratin diseases such as epidermolysis bullosa simplex, epidermolytic hyperkeratosis, epidermolytic palmoplantar keratoderma, and ichthyosis bullosa of Siemens. In these genetic skin disorders, mutations of keratin genes cause dysfunction of keratin intermediate filaments, leading to blister formation or hyperkeratotic skin lesions. Heterozygous missense mutations of the keratin 16 gene and keratin 17 (K17) gene have been identified in PC1 and PC2, respectively. A heterozygous keratin 6a deletion has also been identified in a PC1 family. In the present study we report a missense mutation within the helix initiation motif of the K17 gene in a sporadic Japanese case of Jackson-Lawler type PC.

PATIENT AND METHODS

Patient

The pedigree examined in this study is shown in Fig. 1. A. The family history of the patient showed no consanguinity and no relatives with similar conditions. The patient is a 24-year-old Japanese man who at birth was covered with white, milia-like cysts (Fig. 1, B) and had two natal teeth. All of his nails were unusually thick from an early age. At 5 or 6 years of age, cysts developed on his face and extremities; the number of cysts gradually increased on his buttocoks, groin, and axillae. At 12 or 13 years of age, these cysts became painful, enlarged, and infected. He underwent numerous surgical procedures for infected cysts in the axillae and was diagnosed with hidradenitis suppurativa. Physical examination at the time of the present study revealed numerous cysts and nodules of various sizes all over the body (Fig. 1, C), pachyonychia on all fingers and toes (Fig. 1, D), pili torti (Fig. 1, E), and callus-like focal plantar keratoderma on the left sole. The mouth, tongue, and teeth were normal. Biopsy specimens of several cysts suggested a diagnosis of steatocystoma multiplex. Immunohistochemistry showed positive staining for K17 in the suprabasal lining cells of the cyst wall (Fig. 1, F).

Reverse transcription–polymerase chain reaction and DNA sequencing

Because K17 has pseudogenes, we performed reverse transcription–polymerase chain reaction to avoid amplifying these genes from genomic DNA. Total RNA was extracted from the patient's steatocystomas because K17 is abundantly expressed in epithelial cells of the cysts (Fig. 1, F). As a control, total RNA was extracted from involved lesions of several patients with psoriasis, because K17 is expressed in abundance in psoriatic lesions. The total RNA was reverse transcribed, and the cDNA encoding the entire rod domain of K17 was amplified by PCR with primers k17p3 and k17p6, as described previously.

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Allele-specific PCR analysis

Allele-specific PCR (AS-PCR) was performed to screen the mutation of subclones containing the 267 base pairs (bp) fragment. The normal allele-specific primer, K17pN (5'-GCCACCATGCAGACCTCAA-3'), and a mutant allele-specific primer, K17pM (5'-GCCACCATGCAGACCTCA-3'), were used as forward primers, and K17p12 (5'-GCCGGATGTTG- GCATTGTC-3') was used as a common reverse primer. AS-PCR was also performed to screen the mutations in genomic DNAs. K17pN and K17pM were used as the forward primers; K17p10 was used as the reverse primer.

RESULTS

Sequence analysis of K17

Direct sequencing of amplified 1032 fragments from the patient's cDNA disclosed an unreadable base in the helix initiation motif of the K17 gene. By subcloning the 267 bp fragment in the helix initiation motif and sequencing some of the positive clones, we identified A to G transition at position 423 in some clones thought to be derived from mutant allele of the patient (Fig. 2, A). This transition results in an asparagine (N) to serine (S) substitution. Other clones showed a normal sequence

thought to be derived from a normal allele. With AS-PCR, we confirmed the existence of 7 mutant clones of 21 positive clones. The 267 bp fragment amplified from psoriatic cDNA showed a normal sequence.

Mutation analysis

Further analysis of the A to G mutation at base pair 423 was undertaken to exclude the possibility that this change occurs in the normal population as a common polymorphism. We used allele-specific primers to assess the presence of this mutation in the DNA of 52 unrelated normal individuals and also in the patient's parents and sister. The 620-bp fragment was amplified with both the normal allele-specific primer (K17pN) and mutant allele-specific primer (K17pM) in the patient's DNA. In DNAs from normal individuals, the patient's parent and sister, the 620-bp fragment was amplified
only by the normal allele-specific primer (Fig. 2, B).

DISCUSSION

In the present study we identified a heterozygous missense mutation within the helix initiation motif of K17 in a Japanese patient with Jackson-Lawler PC (PC-2). In the type I keratin family, the amino acid sequences of the first 15 codons KVT-MQNLNDRLASYL in 1A domain are almost invariant among type I keratins.16,17 A mutation of the K17 gene in a family of PC-2 was initially discovered at position 422 of the K17 genomic sequence, producing an N92D substitution.5 The A to G transition at position 423 in this case occurs at only the base next to the site of the mutation that was determined in a previous report and produces the N92S substitution within the highly conserved helix initiation motif of K17. This mutation has been reported in one familial and three sporadic cases of PC-2.11 Our finding of this mutation in a sporadic case of different ethnic origin supports the thesis that this asparagine (N) codon is a hot spot for the mutation of K17.

Recently, similar types of mutation have been reported in two relatives of familial steatocystoma multiplex. The mutations N92H and R94H of K17 were observed in different family pedigrees.11 These cases were not diagnosed as PC and showed only mild deformity of the nails. The reason that similar underlying genetic lesions lead to manifestations of different clinical phenotypes, with or without pachyonychia, is unclear. As previously speculated, each particular mutation of K17 could lead to a phenotypic variation from typical PC2 to familial steatocystoma multiplex with mild or no nail deformity. In this respect, the mutation N92S in the present case is in agreement with the report by Smith et al.11 and supports the clinical diagnosis of typical PC2. Because K17 does not have a specific coexpressed partner keratin, identification of factors that interact with K17 may solve this problem. Elucidation of a number of mutations of the K17 gene will also enhance our understanding of phenotypic heterogeneity of PC and steatocystoma multiplex.

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REFERENCES