Pachyonychia Congenita Project

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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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Identification of a recurrent mutation in keratin 6a in a patient with overlapping clinical features of pachyonychia congenita types 1 and 2

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Summary

Pachyonychia congenita is characterized by hypertrophic nail dystrophy and associated ectodermal features. PC-1 subtype is associated with mutations in keratins 6a or 16, whereas PC-2 subtype is linked to mutations in keratins 6b or 17. The correlation between the mutated gene and the type of PC has generally been consistent. In this report, we describe a case with overlapping clinical features of PC-1 and PC-2 in which a mutation in K6a was identified.

Report

Pachyonychia congenita (PC) is a group of autosomal dominantly inherited diseases characterized by nail dystrophy and various features of ectodermal dysplasia. The most widely used classification divides PC into two clinical subtypes. Jadassohn–Lewandowsky type or PC-1 (OMIM no. 167200) presents with nail dystrophy accompanied by palmoplantar keratoderma, follicular keratosis and oral leukokeratosis.[1] By contrast, the Jackson–Lawler type or PC-2 (OMIM no.167210) is characterized by nail dystrophy associated with palmoplantar keratoderma, natal teeth, and pili torti.[2] An important element of PC-2 is the presence of pilosebaceous cysts arising from the hair follicle infundibulum (epidermoid cysts and eruptive vellus hair cysts) or from the sebaceous duct epithelium (steatocystomas). In fact, the presence of pilosebaceous cysts has been noted to be the most useful distinguishing feature of PC-2.[3]

In recent years the genetic basis of PC has been elucidated. Mutations in keratins 6a (K6a) and 16 (K16) have been associated with PC-1, and PC-2 has been linked to mutations in keratins 6b (K6b) and 17 (K17).[4–6] The correlation between the mutated gene and the type of PC has generally been consistent. However, in this report we describe a case with overlapping clinical features of PC-1 and PC-2 in which a mutation in K6a was identified. Of interest, this recurrent mutation, N171del, has been previously reported in individuals exhibiting PC-1 phenotype.

The pedigree of the family described here is shown in Fig. 1a. The proband is a 41-year-old-man with skin manifestations of PC since birth. He presented with hyperkeratotic dystrophic toenails and scarred nail beds on his hands due to surgical removal of the fingernails at age 12 (Fig. 1d). Focal palmar keratosis and severe diffuse plantar keratoderma were noted. The patient also had scattered follicular keratoses on the elbows, knees, and buttocks as well as oral leukokeratosis. In addition, multiple soft, yellow papules and nodules, histologically confirmed as steatocystomas, were noted on the patient's anterior neck and upper chest (Fig. 1e). Pili torti and corneal dyskeratosis were not present, and the patient denied a history of natal teeth.

After informed consent, genomic DNA was extracted from the patient's peripheral blood lymphocytes. The 1A helix initiation regions of K6a, K16, and K17 were amplified by PCR using previously described primers.[4,7] PCR products were sequenced using an Applied Biosystem 310 automated sequencing system. In addition, a skin biopsy was obtained from the patient's palm, and

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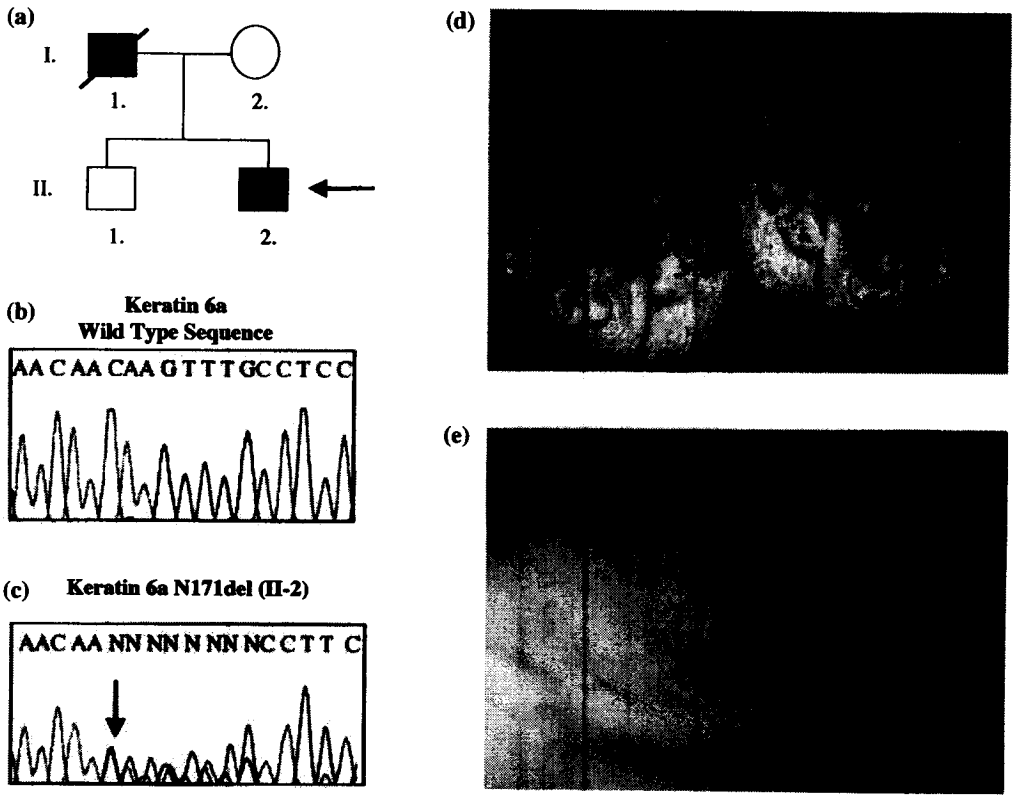

Figure 1 Clinical data and sequence analysis of 1 A helix initiation motif of K6a. (a) Pedigree of the family. (b) Wild-type sequence of K6a. (c) Proband's K6a sequence, illustrating a heterozygous three base pair deletion of AAC at codon 171. (d) Plantar and subungual hyperkeratosis. (e) Multiple soft, yellow papules and nodules (some indicated by arrows) are observed on the proband's upper chest and anterior neck.

the keratinocytes were cultured. Total RNA was isolated by using TRIzol reagent, as described by the manufacturer (Life Technologies), and the cDNA was synthesized by reverse transcription using random primers. The K6a cDNA was amplified by PCR and the 1A region was directly sequenced.

Automated sequencing of genomic DNA revealed no mutations in the 1A regions of K16 and K17. The K6a sequence showed a three base pair deletion (AAC) at codon 171, resulting in the deletion of an asparagine (Asn) residue from the amino acid sequence (Fig. 1b and c). Direct sequencing of the K6a cDNA obtained from the skin biopsy revealed the same N171del mutation, confirming the results.

Keratins are characterized by the presence of a highly conserved central rod domain consisting of four alpha-helical regions (1A, 1B, 2A, and 2B). The helix boundary motifs are mutational hotspots for all keratin disorders, and most PC mutations reported to date occurred in these regions. The N171del mutation in K6a is located at the helix initiation domain and has been reported in six other cases.[3,5,7] This mutation is consistent with DNA polymerase slippage during replication of three tandem CAA repeats in exon 1. It is predicted to be disruptive to intermediate filament assembly and its recurrence highlights the helix boundary motifs as mutational hotspots for keratin diseases. Of interest, all of the previously reported cases with the N171 del mutation exhibited PC-1 phenotype. Our patient has clinical features of both PC-1 and PC-2. Nail dystrophy and palmoplantar keratoderma seen in this patient can be observed in both PC types. Follicular keratosis and oral leukokeratosis are usually associated with PC-1, and the steatocystomas are typically observed in PC-2. Similarly, identical mutations producing distinct effects in different individuals have been observed in PC, suggesting clinical heterogeneity. For example, the R94C mutation in K17 has been reported to present with steatocytomas or nail dystrophy in different families.[8] However, the correlation between the clinical syndrome (PC-1 or PC-2) and the pair of genes involved (K6a/K16 or K6b/K17) has so far

been highly consistent. This case demonstrates the rare occurrence of a clinical overlap between PC-1 and PC-2.

Pilosebaceous cysts have been identified as a key diagnostic feature of PC-2 that distinguishes this subtype from PC-1. The presence of these cysts has been explained by the tissue-specific expression of keratin genes. K6b and K17 are expressed at higher levels in the pilosebaceous unit than K6a and K16, explaining the pilosebaceous cysts in PC-2. By contrast, K6a and K16 are more widely expressed in oral epithelia, explaining the greater predominance of oral leukokeratosis in PC-1.[3] As K6a is also expressed in the hair follicles, it is possible that mutation of this gene can lead to cysts, as seen in our patient.

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