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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.
Cutaneous Biology

Keratin 17 mutation in pachyonychia congenita type 2 with early onset sebaceous cysts

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Summary

Background Pachyonychia congenita (PC) is a group of autosomal dominant ectodermal dysplasias caused by mutations in four differentiation-specific keratin genes. Two major clinical subtypes of PC have been generally recognized. Symmetrically thickened fingernails and toenails are the defining characteristic of PC type 2 (PC-2) with onset at infancy. Pilosebaceous cysts are the best hallmark of PC-2, but they usually occur at puberty.

Objectives To report a Chinese pedigree of PC-2 with unusually early onset sebaceous cysts and to explore the genetic mutation and its phenotype.

Methods Exon 1 of keratin 17 was amplified by polymerase chain reaction (PCR) from genomic DNA from the three patients in the pedigree, the proband, his half-sister and his younger son, two unaffected members in the pedigree and 50 unrelated and unaffected people. PCR products were directly sequenced to detect the mutation.

Results Direct sequencing of the PCR products revealed a heterozygous 275A → G mutation in all three affected members. This mutation predicts the substitution of asparagine by serine in codon 92 (N92S) located in the 1A domain of keratin 17.

Conclusions Mutation in the 1A domain of keratin 17 underlies the affected members’ phenotype. PC-2 with early onset sebaceous cysts and late-onset thickened fingernails and toenails. The onset of the cysts is very early in some people within this family and the age at onset of thickened fingernails and toenails is variable within the family, implying the existence of modifying factors.

Key words: ectodermal dysplasia, genodermatosis, intermediate filaments, nail dystrophy, pachyonychia congenita

Keratins are structural proteins expressed in all epithelial cells. They form heteropolymeric 10-nm intermediate filaments composed of specific pairs of type I and type II keratin subunits, which are coexpressed in a tissue- and differentiation-specific fashion.1 The keratin intermediate filaments have been shown to be the primary stress-bearing structure within epithelial cells. Structural failure caused by keratin mutations can manifest as blistering and/or hyperkeratosis of the affected tissue. Each keratin polypeptide possesses a 310-amino acid residue α-helical rod domain that consists of four helical segments named 1A, 1B, 2A and 2B. The sequences at the beginning of the helix 1A and at the end of the helix 2B are highly conserved and are the most critical for the assembly of the intermediate filaments in vivo and in vitro.2–5 Most of the reported keratin mutations in skin diseases are in the highly conserved helix boundary motifs.6

Pachyonychia congenita (PC) is a group of hereditary, autosomal dominant ectodermal dysplasias, the main feature being hypertrophic nail dystrophy. In terms of certain additional abnormalities specific to each subtype, two major clinical subtypes of PC have been generally recognized. In PC type 1 (PC-1), oral leucokeratosis, palmoplantar keratoderma and follicular keratosis may be observed. PC type 2 (PC-2, Jackson–Lawler syndrome; MIM 167210) has the same
features as PC-1 (Jadassohn–Lewandowsky syndrome; MIM 167200), with additional features of natal teeth and pilosebaceous cysts.\(^7\) Natal teeth are sometimes but not always present, but the presence of pilosebaceous cysts is indispensable to the diagnosis of PC-2. As the cysts normally only appear at puberty, PC-2 is difficult to distinguish from PC-1 in childhood. PC is caused by mutations in four differentiation-specific keratin genes. Specifically, PC-1 is the result of mutations in keratin K6a\(^8,9\) and K16\(^10,11\). In contrast, PC-2 results from mutations in K6b\(^12\) and K17\(^10,13,14\).

In classical PC-2, thickening of the nails usually begins within the first months of life. Clinical observation of some patients with the onset of the characteristic nail changes of PC during the second and third decades of life has been reported in the literature.\(^15\) Pilosebaceous cysts usually only appear at puberty, but onset at the age of 5 years has been reported recently.\(^16\) We report a Chinese pedigree of PC-2 with unusually early onset sebaceous cysts and late-onset thickened nails. Mutation in the 1A domain of keratin 17 underlies the affected members’ phenotype.

**Subjects and methods**

The Human Medical and Ethical Committee of Xi’an Jiaotong University approved the investigation presented here, and all study subjects gave informed consent. We studied a Chinese pedigree of PC-2 (Fig. 1) from Shaanxi Province. The proband in this pedigree developed pinhead-sized yellowish cystic nodules in the head, face, and neck from 1 year of age. These nodules gradually grew larger and more extensive, mainly in the head and face (Fig. 2a), groin and axillae. The size of these cysts varied from 0·1 to 3 cm in diameter. When punctured, the cysts discharged yellowish, oily material. At age 14 years, focal areas of the plantar skin became hyperkeratotic and thick (Fig. 2b). At 15–16 years of age, all fingernails and toenails were found to be thickened and discoloured (Fig. 2c). The nail plates were as thick as 0·4–0·6 cm. The proband’s mother (deceased) had similar but less severe manifestations. No implicit age at onset of cysts and hypertrrophic nails of the proband’s mother were recalled by the proband. His half-sister (having same mother as the proband but a different father) developed cysts at age 5 years and thickened nails at 7–8 years of age, but her plantar skin was only mildly hyperkeratotic. Her phenotypic severity was the mildest of the affected members of the pedigree. The proband’s younger son, whose fingernails and toenails were found to be thickened at age 4 years, had pinhead-sized cysts at 2 years of age. There were four affected members among 26 people in the pedigree. No natal teeth or leucokeratosis of mucous membranes were found in this pedigree.

A biopsy of the dorsal skin of the proband was routinely processed for haematoxylin and eosin staining. Five millilitres of peripheral blood was obtained...
from the proband, his half-sister and his younger son, two unaffected members in the pedigree (his elder son and his niece) and 50 unrelated and unaffected people. Genomic DNA was extracted with a whole blood genomic DNA extraction kit (Sino-American Biotechnology Company, Shangai, China) and used as a template for the polymerase chain reaction (PCR)-mediated amplification of exon 1 of the keratin 17 gene. The primers (K17p8 and K17p10) and PCR conditions are described in the literature.10 Sequence analyses were performed using Big Dye terminator technology on an ABI 377 genetic analyser (Perkin-Elmer)-Cetus Instruments, Norwalk, CT, U.S.A. Sequences were compared with those of two unaffected and 50 unrelated and unaffected samples.

**Results**

Cysts from the dorsal skin of the proband were examined pathologically. These cysts often contained yellowish, oily material. Each cyst was located in the dermis. The cyst wall was folded, and consisted of several layers of squamous epithelial cells, with flattened sebaceous lobules within or close to the wall. There was a layer of eosinophilic keratinized substance inside the wall. No granular layer was present. There were a few keratinized cells and much sebum within the cyst (Fig. 2d).

Primers K17p8 and K17p10 successfully amplified the expected 978-bp DNA fragments from genomic DNA from all of the blood samples. Direct sequencing of the PCR products revealed a heterozygous 275A→G mutation in all three affected members (Fig. 3a). This mutation predicts the substitution of asparagine by serine in codon 92 (N92S) located in the 1A domain of keratin 17. No such mutation was found in the two unaffected and 50 unrelated controls (Fig. 3b). Sequencing of PCR products from 50 unrelated and unaffected controls excluded the polymorphism.

**Discussion**

Based on clinical features, PC is mainly subdivided into two types. PC-1 is characterized by: (i) the distinctive and excessive thickening of all nails; (ii) palmar and plantar hyperkeratosis; (iii) follicular keratosis of the skin, especially on the knees and elbows; (iv) palmar and plantar hyperhidrosis; (v) leucokeratosis of the mucous membranes; and (vi) onset at infancy. Besides the above features, PC-2 has the additional features of natal teeth and pilosebaceous cysts. The affected members in the pedigree presented here not only had thickened fingernails and toenails, palmar and plantar hyperkeratosis, but also significant multiple sebaceous cysts, which allowed the categorization of their disease as PC-2. However, the proband developed pinhead-sized cysts from age 1 year, an unusually early age for onset of this feature, as the onset of cysts at the age of 1 year has not been seen in any of the many families with PC-2 reported in the literature. Onset of cysts in a 5-year-old patient with PC-2 has recently been reported by a Japanese researcher.16 In this pedigree, it was difficult to distinguish PC-2 from steatocystoma multiplex before the onset of thickened nails.

To date, all the mutations in the K17 gene from PC-2 or steatocystoma multiplex families have been in exon 1 encoding the highly conserved sequences of helix 1A.17–19 where any substitution or deletion would be expected to lead to a distortion of the α-helical structure at the beginning of the 1A domain. As far as we know, 14 mutations have been reported. The mutation in the pedigree presented here is N92S, which is the most frequent mutation reported in the literature. Recently, Connors et al. reported the first case of PC-1 with delayed-onset thickened nails at 6 years of age, with a mutation located in the 2B domain of K16.20 They speculated that delayed-onset pachyonychia might be determined by the site and type of mutation. On the other hand, as pointed out by Munro, it is premature to conclude from a single case that late onset of nail dystrophy is due to the site of the mutation.21 and more pedigrees of PC tarda need to be studied.20,21 In the pedigree we report here, we were able to demonstrate that the affected members were heterozygous for the N92S mutation, which is the most commonly reported mutation for PC-2. That the onset of PC-2 symptoms,
i.e. the cysts, is very early in some people within this pedigree and that the age at onset of thickened nails is variable within the pedigree, imply the existence of other modifying factors. As we know, one major factor contributing to the formation of acne lesions is androgenic stimulation of sebaceous glands. The occurrence of androgen secretion at the onset of puberty explains the usual onset of acne at that age. As the sebaceous cysts of PC-2 normally only appear at puberty, we wonder whether androgen as a modifying factor plays a role in the pathogenesis of sebaceous cysts. At present, we do not know which other factors may be involved. It is possible that modifier genes may promote or delay the onset of symptoms. A non-mutually exclusive possibility is that environmental factors may influence the age of disease presentation. Therefore, our results suggest that the site and type of keratin mutation is not the sole determinant of the age at onset of thickened nails, at least for PC-2. In addition, our results do not rule out the possibility that the age at onset of PC-1 is determined by the site and type of mutation.

In conclusion, we have presented a Chinese pedigree of PC-2 with unusually early onset of cysts and late onset of thickened fingernails and toenails; the cause is an N92S mutation in K17, which has previously been described to cause PC-2 or steatocystoma multiplex. The variation of this pedigree’s phenotype suggests the existence of other modifying factors.

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References