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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.
Novel and recurrent keratin 6A (KRT6A) mutations in Chinese patients with pachyonychia congenita type 1

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Pachyonychia congenita (PC) is a rare autosomal dominant disorder caused by keratin gene mutations. PC clinically presents with hypertrophic nail dystrophy, hyponychial keratosis, painful palmoplantar keratoderma and other ectodermal features. The PC classification accepted worldwide includes two clinical subtypes: the Jadassohn–Lewandowsky or PC type 1 (PC-1; OMIM 167200) and the Jackson–Lawler or PC-2 variant (OMIM 167210). PC-1 is characterized by nail dystrophy

Fig 1. (a) Four pachyonychia congenita type 1 (PC-1) pedigrees: families 1–4 (F1–F4). (b) The clinical presentation of sporadic patient SP4 with PC-1: hypertrophic nails, palmoplantar keratoderma, follicular hyperkeratosis and oral leucokeratosis. Asterisks in each pedigree indicate those who were examined and sequenced in this study.

Table 1 Phenotypic and genotypic data for the sporadic patients (SP1–4) and families (F1–F4) with pachyonychia congenita (PC)

<table>
<thead>
<tr>
<th>Patients</th>
<th>Province</th>
<th>PC</th>
<th>PPK</th>
<th>OL</th>
<th>FH</th>
<th>Hoarseness</th>
<th>Hyperhidrosis</th>
<th>KP</th>
<th>AC</th>
<th>Mutation (domain)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SP1 Hunan</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>KRT6A Asn171Lys (1A)</td>
</tr>
<tr>
<td>SP2 Anhui</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>KRT6A Phe174Ser (1A)</td>
</tr>
<tr>
<td>SP3 Shandong</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>KRT6A Asn171Lys (1A)</td>
</tr>
<tr>
<td>SP4 Sichuan</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>KRT6A Asn171Lys (1A)</td>
</tr>
<tr>
<td>F1 Shandong</td>
<td>1/1</td>
<td>1/1</td>
<td>1/1</td>
<td>1/1</td>
<td>0/1</td>
<td>1/1</td>
<td>0/1</td>
<td>0/1</td>
<td>0/1</td>
<td>KRT6A Glu166Pro (1A)</td>
</tr>
<tr>
<td>F2 Shandong</td>
<td>2/2</td>
<td>2/2</td>
<td>0/2</td>
<td>0/2</td>
<td>0/2</td>
<td>2/2</td>
<td>0/2</td>
<td>0/2</td>
<td>0/2</td>
<td>KRT6A Ile178Asn (1A)</td>
</tr>
<tr>
<td>F3 Anhui</td>
<td>3/3</td>
<td>3/3</td>
<td>3/3</td>
<td>0/3</td>
<td>0/3</td>
<td>3/3</td>
<td>0/3</td>
<td>0/3</td>
<td>0/3</td>
<td>KRT6A Ala463Pro (2B)</td>
</tr>
<tr>
<td>F4 Hebei</td>
<td>5/5</td>
<td>5/5</td>
<td>5/5</td>
<td>5/5</td>
<td>0/5</td>
<td>5/5</td>
<td>0/5</td>
<td>0/5</td>
<td>0/5</td>
<td>KRT6A Tyr465His (2B)</td>
</tr>
</tbody>
</table>

PPK, palmoplantar keratoderma; OL, oral leucokeratosis; FH, follicular hyperkeratosis; KP, keratosis pilaris; AC, angular cheilitis; +, phenotype present; −, lack of phenotype. The denominator indicates the number of examined patients and the numerator indicates the number having the phenotype of the examined patients in one family. The three novel mutations are indicated in bold.
associated with painful, focal, palmoplantar keratoderma, follicular keratoses and oral leucokeratosis.

Steatocystomas and natal teeth are findings associated with PC-2 but not typically with PC-1. It is known that keratin proteins share a similar structural motif consisting of a highly conserved central helical rod domain. Each keratin polypeptide possesses an amino acid sequence of 310 residues and an \( \alpha \)-helical rod domain composed of four helical segments named 1A, 1B, 2A and 2B, respectively.\(^1\) It has been reported that all the known keratin mutations in patients with PC-1 are limited to within the conserved helix boundary motifs of either the beginning of 1A or the end of the 2B domain which are encoded by exons 1 and 6 of the keratin 16 gene (KRT16) and exons 1 and 7 of the keratin 6A gene (KRT6A), respectively.\(^3\)\(^-\)\(^5\) So far, over 33 mutations in KRT6A/KRT16 have been identified in independently ascertained families with PC-1 (http://www.interfil.org). Here we report three novel mutations and four recurrent missense mutations within the hotspot regions of KRT6A detected in Chinese patients with PC-1.

Cases and methods

Eleven affected patients and six unaffected members of four families (Fig. 1a) and four sporadic patients together with five unaffected parents from five provinces in China were studied. The study was approved by the ethics committee of the Anhui Medical University. Consensus diagnosis of PC-1 was performed by two experienced dermatologists based on clinical and histopathological findings. All the subjects with sporadic PC were examined. However, as seen in Figure 1a and Table 1, not all the affected subjects in the families gave informed consent to have their skin examined and their blood analysed. Their phenotypic status was ascertained from descriptions by the probands. Clinical features of the patients are summarized in Table 1.\(^6\) Figure 1b shows the typical clinical manifestations of PC-1 as seen in sporadic patient 4, including hypertrophic nails, palmoplantar keratoderma, follicular hyperkeratosis and oral leucokeratosis. After informed consent was obtained, peripheral blood samples from the 15 patients and the 11 unaffected family members as well as 100 additional unrelated population-matched controls were prepared. Blood DNA was extracted using a DNA extraction kit (Promega, Madison, WI, U.S.A.). A long-range polymerase chain reaction (PCR) was performed using primers reported elsewhere to avoid any potential amplifications of KRT6A\(\tilde{}\)KRT16 pseudogenes, followed by a conventional nested PCR.\(^3\) Nest PCR primers used for specific amplification of the mutation hotspot regions of KRT6A/KRT16 were designed by PRIMER 5.0 software (Premier Biosoft, Palo Alto, CA, U.S.A.). PCR products were further purified by exonuclease 1 and shrimp alkaline phosphatase and then sequenced on a CEQ 8800 automated sequencer (Beckman Coulter, Fullerton, CA, U.S.A.).

Results and discussion

In this study, seven mutations were identified in the 15 affected patients. Three of the substituted mutations were novel, including KRT6A 497A>C in family 1 (p.Gln166Pro; Fig. 2a), KRT6A 533T>A in family 2 (p.Ile178Asn; Fig. 2b) and KRT6A 1387G>C in family 3 (p.Ala463Pro; Fig. 2c). The other four mutations were recurrent mutations (KRT6A p.Asn171Lys, KRT6A p.Phe174Ser, KRT6A p.Asn172del and KRT6A p.Tyr465-His) in the four sporadic patients and the patients in family 4.

Fig 2. Three novel KRT6A gene mutations in patients of affected families. (a) A heterozygous missense mutation KRT6A 497A>C (Gln166Pro, black arrow) and a single nucleotide polymorphism (KRT6A 495A>G, red arrow) in the proband of family 1. (b) A heterozygous missense mutation KRT6A 533T>A (Ile178Asn, black arrow) in family 2. (c) A heterozygous missense mutation KRT6A 1387G>C (Ala463Pro, black arrow) in family 3.
(Table 1). The frameshift mutation in sporadic patient 4 was a three-base deletion (AAC) at codon 172, resulting in the missing of the Asn residue of the amino acid sequence. None of these mutations was found in either the healthy members of the families or the 100 controls, indicating that these mutations were pathogenic mutations of the KRT6A gene, rather than neutral polymorphisms. Structurally, five of the seven mutations (p.Asn171Lys, p.Phe174Ser, p.Asn172del, p.Gln166Pro and p.Ile178Asn) occurred in the 1A region of KRT6A and the other two mutations (p.Ala463Pro and p.Tyr465His) were within the 2B region of KRT6A, completely consistent with the hypothesis that all the mutations in PC-1 fall within the conserved helix boundary motifs of 1A and 2B.3,5,7,8

Clinically, we found that there were large phenotypic variations among the patients with PC-1 with various mutations and even among the affected subjects within the same families (Table 1). However, for the most part, the variations were in the severity of the phenotype rather than in the presence or absence of the phenotypic features. Because of the small sample size, no firm conclusions can be reached on the correlation between the clinical variations and the specific mutations.

In summary, the sporadic and familial cases of PC-1 reported here have added new information on the clinical and genetic diversity of this condition.

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References


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