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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 patients with mutations in KRT6A have more extensive disease compared with patients who have mutations in KRT16

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Summary

Background Pachyonychia congenita (PC) is an autosomal dominant, very rare keratin disorder caused by mutations in any of at least four genes (KRT6A, KRT6B, KRT16 or KRT17), which can lead to hypertrophic nail dystrophy and palmoplantar keratoderma, among other manifestations. Classically, patients with mutations in KRT6A and KRT16 have been grouped to the PC-1 subtype (Jadassohn–Lewandowsky type) and KRT6B and KRT17 to PC-2 (Jackson–Lawler type).

Objectives To describe clinical heterogeneity among patients with PC who have genetic mutations in KRT6A and KRT16.

Methods In 2004, the Pachyonychia Congenita Project established the International PC Research Registry (IPCRR) for patients with PC. All patients reporting here underwent genetic testing and responded to a standardized, validated survey about their PC symptoms. We report results from 89 patients with KRT6A mutations and 68 patients with KRT16 mutations.

Results Patients with PC who have KRT6A and KRT16 mutations display distinct phenotypic differences. Patients with PC-K6a experience earlier onset, more extensive nail disease and more substantial disease outside palms and soles, as they reported a higher prevalence of oral leucokeratosis (P < 0.001), cysts (P < 0.001) and follicular hyperkeratosis (P < 0.001) compared with their KRT16 counterparts.

Conclusion Phenotypic differences between patients with KRT6A and KRT16 mutations support adoption of a new classification system based on the mutant gene (PC-6a, PC-16) rather than the PC-1 nomenclature.

Pachyonychia congenita (PC) is an autosomal dominant, rare keratin disorder caused by mutations in any of at least four genes (KRT6A, KRT6B, KRT16 or KRT17) that encode keratin proteins K6a, K6b, K16 and K17, respectively.1 The International PC Research Registry (IPCRR) is a database with information on over 1000 individuals with PC. As of November 2010, this registry included genotype and clinical information for 271 patients with PC. Traditionally, mutations in KRT6A and KRT16 were associated with PC-1 (Jadassohn–Lewandowsky), while KRT6B and KRT17 mutations were associated with PC-2 (Jackson–Lawler). Patients with PC-1 have been reported to have more prominent oral leucokeratosis,2 while patients with PC-2 classically were reported to have cysts and natal teeth.3 However, recent case reports and case series have reported overlapping clinical features of PC-1 and PC-2,4–6 thus prompting adoption of a new classification system (PC-6a, PC-16, etc.) based on the mutated gene.7 The variability of clinical phenotypes in PC is further highlighted by reports of unique mutations within the same gene leading to different clinical symptoms.8,9
In this study, we sought to describe the clinical characteristics of 89 patients with keratin 6a mutations and 68 patients with keratin 16 mutations that were grouped into the PC-1 subtype. We hypothesized that patients with mutations in KRT6A vs. mutations in KRT16 may differ clinically, thus illustrating the necessity of a genotype-based nomenclature.7

Materials and methods

In 2004, the Pachyonychia Congenita Project established the IPCRR, an international registry for patients with PC. The registry was approved by the Western Institutional Review Board (IRB) (#20040468) and subjects gave written informed consent; details are online (http://www.pachyonychia.org). All patients in this study underwent genetic testing, as previously described.1,7 Sequencing of genes was performed on genomic DNA from blood or saliva samples at the University of Dundee and confirmed using an independent buccal DNA sample (GeneDx, Gaithersburg, MD, U.S.A.). Each patient received a standardized survey with questions on the presence/absence and severity of PC clinical features (Table 1); survey responses were confirmed by consultation with a dermatologist. Patients also answered questions regarding age of onset of each PC symptom. For questions on persistence of each symptom, answer choices were: ‘never affected’, ‘seldom (usually clear of symptoms)’, ‘sometimes (clear up completely at times)’ and ‘always (never completely go away)’. Pain was graded using a 4-point Likert scale with answer choices of ‘not painful’, ‘somewhat painful’, ‘very painful, but do not use medication’ and ‘often require medication for pain’. Severity of nail disease was assessed using the absolute number of affected fingernails or toenails (Table 1). Impact of disease on quality of life was assessed by asking how much each symptom affected daily life: ‘no impact’, ‘sometimes creates a problem’, ‘always

Table 1 Demographics of and symptoms reported by patients with pachyonychia congenita who have mutations in KRT6A vs. KRT16 in subjects ≥ 12 years of age

<table>
<thead>
<tr>
<th>Demographic characteristics</th>
<th>KRT6A (n = 89)</th>
<th>KRT16 (n = 68)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years) at the time of questionnaire (range)</td>
<td>37 (12–79)</td>
<td>44 (12–81)</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>40</td>
<td>59</td>
<td>NS</td>
</tr>
<tr>
<td>Positive family history (%)</td>
<td>51</td>
<td>59</td>
<td>NS</td>
</tr>
<tr>
<td>Number of families represented</td>
<td>64</td>
<td>40</td>
<td>NS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical findings and symptoms, % (n) or mean (range)</th>
<th>KRT6A (n = 89)</th>
<th>KRT16 (n = 68)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plantar symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent keratoderaa</td>
<td>99 (88)</td>
<td>100 (68)</td>
<td>NS</td>
</tr>
<tr>
<td>Plantar painb</td>
<td>74 (66)</td>
<td>87 (59)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean age (years) onset plantar keratoderma (range)</td>
<td>3-7 (0–15)</td>
<td>3-9 (0–30)</td>
<td>NS</td>
</tr>
<tr>
<td>Thickened toenailsc</td>
<td>99 (88)</td>
<td>71 (48)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Palmar symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent keratoderaa</td>
<td>53 (47)</td>
<td>82 (56)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Palmar painb</td>
<td>6 (5)</td>
<td>13 (9)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean age onset palmar keratoderma (range)</td>
<td>6-6 (0–20)</td>
<td>7-2 (0–30)</td>
<td>NS</td>
</tr>
<tr>
<td>Thickened fingernailsc</td>
<td>91 (81)</td>
<td>59 (40)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Presence of oral leucokeratosis</td>
<td>94 (84)</td>
<td>56 (38)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mean age (years) onset oral leucokeratosisd (range)</td>
<td>3-5 (0–50)</td>
<td>11-8 (0–79)</td>
<td>0.04</td>
</tr>
<tr>
<td>Persistent hoarseness of voice</td>
<td>40 (36)</td>
<td>7 (5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Presence of cysete</td>
<td>53 (47)</td>
<td>13 (9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Presence of follicular hyperkeratosis</td>
<td>78 (69)</td>
<td>15 (10)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*aComparing patients reporting persistence of keratoderma as ‘always’ or ‘sometimes’ with those answering ‘seldom’ or ‘never’. bComparing those reporting ‘very painful but no medication needed’ or ‘often require medication for pain’ with those answering ‘some pain’ and ‘no pain’. cComparing numbers of patients with > 8 nails affected. dResponses for age of onset of oral leucokeratosis was limited with only 60 KRT6A patients and 26 KRT16 patients responding. ePresence of pilosebaceous cysts or steatocystomas. NS = P-values > 0.05. All P-values were calculated using χ² test or two-tailed t-test where appropriate. All percentages are rounded to the nearest whole number.

In this study, we sought to describe the clinical characteristics of 89 patients with keratin 6a mutations and 68 patients with keratin 16 mutations that were grouped into the PC-1 subtype. We hypothesized that patients with mutations in KRT6A vs. mutations in KRT16 may differ clinically, thus illustrating the necessity of a genotype-based nomenclature.7
a problem, but able to function’ or ‘makes it impossible to function’.

Differences in proportions were analysed with χ² tests and continuous variables with two-tailed t-tests. Statistical significance was defined as P < 0.05. SAS version 9.2 (SAS Institute Inc., Cary, NC, U.S.A.) was used for all statistical analyses.

Results

This analysis was restricted to patients who were 12 years of age or older in order to obtain more accurate data regarding pain, as adolescents are better able to communicate their experiences than younger children.10 Out of 271 genetically confirmed patients with PC in the IPCRR, 89 with KRT6A mutations and 68 with KRT16 mutations were aged 12 years or older at the time of survey (Table 1). The majority of KRT6A mutations were single base pair changes (69%), although 28% were deletions and 3% were insertions. The vast majority of KRT16 mutations were single base pair changes (89%) with 4% being deletions and 9% insertions.

Patients with mutations in KRT6A (PC-K6a) and KRT16 (PC-K16) were similar in reporting persistent plantar keratoderma and plantar pain (Table 1, K16) were similar in reporting persistent plantar keratoderma changes (89%) with 4% being deletions and 9% insertions.

Comparing plantar keratoderma and nail involvement in patients with pachyonychia congenita who have KRT6A (a–d) and KRT16 (e–h) mutations.

Fig 1. Comparing plantar keratoderma and nail involvement in patients with pachyonychia congenita who have KRT6A (a–d) and KRT16 (e–h) mutations.

Patients with mutations in KRT6A (PC-K6a) and KRT16 (PC-K16) were similar in reporting persistent plantar keratoderma and plantar pain (Table 1, Fig. 1). In terms of palmar symptoms, patients with PC-K6a and those with PC-K16 reported similar palmar pain and age of onset of palmar keratoderma, although patients with PC-K16 more commonly reported palmar keratoderma (P < 0.001). Quality of life was similarly affected in patients with KRT6A and KRT16 mutations, with 93% and 89% reporting a severe impact on quality of life, respectively. Thus, these two groups cannot be distinguished based on keratoderma, pain or quality of life (Table 1, Fig. 1).

However, patients with PC-K6a and patients with PC-K16 can be distinguished based on the extent of nail involvement: those with PC-K6a have more extensive nail involvement [8–10 thickened toenails (P < 0.001) and fingernails (P < 0.001)], which starts at a much younger age (0–4 vs. 7–4 years, P < 0.001 and 0–4 vs. 6–6 years, P < 0.001, respectively) than their PC-K16 counterparts (Fig. 1). Furthermore, oral leukokeratosis was reported in 94% of patients with PC-K6a and in 56% of patients with PC-K16 (Fig. 2), while persistent hoarseness of voice was reported more commonly in PC-6a vs. PC-K16 (40% vs. 7% respectively, P < 0.001) (Fig. 2). Patients with oral leukokeratosis also more frequently reported hoarseness of voice [odds ratio (OR) 7.75; 95% confidence interval (CI) 2–34; P = 0.007]. Cysts and follicular hyperkeratosis were also more likely to be present in patients with PC-K6a than in patients with PC-K16 (P < 0.001 and P < 0.001, respectively) (Fig. 2).

Discussion

These data illustrate that patients with KRT6A and KRT16 mutations have significantly different manifestations of their disease, and thus should be classified separately by genotype (PC-K6a and PC-16, respectively). Patients with KRT16 mutations have considerably more palmoplantar keratoderma and pain than those with KRT6A mutations. Patients with PC-K6a experience more extensive, early onset nail disease, and more substantial disease outside of the palms and soles, as they report higher prevalence of oral leukokeratosis, hoarseness of voice, cysts, and follicular hyperkeratosis than their PC-K16 counterparts. Nearly half of PC-K6a respondents report cysts even though they are classically considered to be features of PC-2.

Patients with PC who had oral leukokeratosis were more likely to report hoarseness of voice (P < 0.001), suggesting that leukokeratosis may extend to the larynx to cause hoarseness. Three patients with PC with laryngeal involvement have been reported, with some patients requiring tracheostomies for life-threatening respiratory insufficiency.11–13

The main limitation of this study is that the results may be subject to selection bias, as the IPCRR only includes patients who found the online registry or were referred to it by their physician; it is not a population-based sample. Strengths of this study include a validated questionnaire8 and genotype analysis, which determined that all patients did indeed have PC with identified mutations, thus allowing these results to be the largest study comparing PC-K6a subjects with PC-K16.
These data support the proposed reclassification of PC based on genotype (i.e. PC-K6a and PC-K16) rather than the historic designation of PC-1 (Jadassohn–Lewandowsky). This information may aid clinicians in prognosticating the distinct disease involvement in these different patients.

What’s already known about this topic?
- Historically, pachyonychia congenita has been classified into two groups based on the mutated keratin, type 1 (Jadassohn–Lewandowsky subtype, KRT6A and KRT16 mutations) and type 2 (Jackson–Lawler subtype, KRT6B and KRT17 mutations).

What does this study add?
- This study illustrates that despite being previously classified into one subtype, patients with KRT6A and KRT16 mutations exhibit significantly different phenotypes. It supports the reclassification of pachyonychia congenita into a genotype-based nomenclature scheme.

References
3 Jackson ADM, Lawler SD. Pachyonychia congenita; a report of six cases in one family, with a note on linkage data. Am Eugen 1951; 16:142–6.