A systematic review of reported cases of pachyonychia congenita tarda

A. Tatiane,1 D. Slape,1,2 R. Lawless1 and J. W. Frew1,2,3

1Department of Dermatology, Liverpool Hospital, Sydney, NSW, Australia; 2University of New South Wales, Sydney, NSW, Australia; and 3Ingham Institute of Applied Medical Research, Liverpool, Sydney, NSW, Australia

doi:10.1111/ced.13980

Summary

Pachyonychia congenita (PC) describes a group of genodermatoses manifesting as thickened nails, palmoplantar keratoderma (PPK) and increased risk of cutaneous infections. PC tarda (PCT) describes late-onset PC, and associated genetic polymorphisms have been identified. There has been discussion that PCT may not be a distinct entity but rather misdiagnosed ectodermal dysplasia (ED) or PPK. Clarification of this is important for appropriate diagnosis, management and patient and genetic counselling. We aimed to conduct a systematic review of all reported cases of PCT in the published literature and collate evidence of genetic polymorphisms and clinical features to compare with known features of PC, ED and PPK. PubMed (1946 to 1 July 2018), Scopus (1955 to 1 July 2018) and Web of Science (1990 to 1 July 2018) databases were searched for case reports of PCT with no search restrictions on date or language. The search strategy included the terms pachyonychia congenita tarda OR pachyonychia congenita AND (late onset OR delayed OR PCT). In total, 13 reports describing 19 individual cases of PCT were identified. Of the three identified genetic polymorphisms, the earliest identified has been shown to be highly probably pathogenic, with the second likely to result in a benign amino acid change, while the third has since been shown to be nonpathogenic. No epigenetic studies have been performed on any reported cases. Previous authors have suggested that a number of cases of PCT may be misdiagnosed ED or PPK. The findings of our review cannot refute this suggestion, and highlight the need for thorough clinical documentation of suspected cases of PCT and thorough genetic screening of kindred to identify causative genetic polymorphisms. Further high-quality datasets and reporting are needed to give further insight into the nature of PCT as a unique entity.

Introduction

Pachyonychia congenita (PC) describes a group of genodermatoses manifesting as painful palmoplantar keratoderma (PPK) and increased risk of cutaneous infections.1 Variable features include thickened nails, natal teeth, cysts, follicular hyperkeratosis and oral leucokeratosis. Classification is based upon identification of the responsible genetic polymorphism. Delayed-onset PC (termed pachyonychia congenita tarda; PCT) has also been described,1 with onset ranging from late childhood to middle age and responsible genetic polymorphisms identified.2–4 It is unclear whether there is overlap between any identified genetic polymorphisms in PC and PCT, which may indicate an as yet unidentified epigenetic mechanism that may be responsible for the delayed onset of symptoms. It is also unclear
whether some cases reported as PCT (particularly those with milder clinical manifestations) may be more appropriately classified as cases of focal nonepidermolytic PPK, which may display delayed onset of symptoms.\textsuperscript{5}

This systematic review aimed to identify all published reports of PCT, and to collate and describe the range of clinical manifestations of the disease. It also aimed to collate the reported genetic polymorphisms in PCT and assess for any overlap with polymorphisms reported in PC.

**Methods**

**Systematic review**

This review was registered with PROSPERO (CRD42018081679) and conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines to identify all published cases of PCT.

**Information sources and search strategy**

PubMed (1946–1 July 2018), Scopus (1955–1 July 2018) and Web of Science (1990–1 July 2018) databases were examined for case reports of PCT with no search restrictions on date or language (Fig. 1). The search strategy included the terms pachyonychia congenita tarda OR pachyonychia congenita AND (late onset OR delayed OR PCT).

Eligibility criteria for this review included published case reports and case series, which (i) included patients with clinically diagnosed PCT, and (ii) included clinical data regarding age of onset and clinical manifestations of disease. No restrictions on patient age, sex, ethnicity, language or presence/absence of sequencing data were applied.

**Data collection process**

Data collection was performed independently by two authors (AT and JF), with any disagreements regarding inclusion of citations being referred to a third author for mediation (DS). Where it was unable to be determined if inclusion criteria were met through title and abstract search (for example, the presence of clinical data), the paper was referred for full text retrieval in order to avoid erroneously excluding published cases. Information was collected using a standardized data collection form (Figure S1). With regards to genetic polymorphism and sequencing data, reported polymorphisms were collated and compared with pre-defined genetic databases (dbSNP, Ensembl, OMIM) for

![Figure 1](https://example.com/f1.png)
assessment of allele frequency and of pathogenicity through SIFT and PolyPhen reports of the same polymorphism(s) in other diseases.

Risk of bias

Potential sources of bias were acknowledged, including publications bias, reporting bias and selective reporting of clinical genetic and family data across reports. Bias was formally assessed (Table S1) using the NIH Quality Assessment Tool for Case Series.6

Results

Study selection

The results of the search strategy are illustrated in Fig. 1. Of the 81 nonduplicate citations screened, 62 were excluded after title and abstract review as not meeting inclusion criteria. The remaining 19 articles were retrieved for full text screening; following this, 6 further articles were excluded as not containing individual demographic or clinical data on manifestations of disease. This left a total of 13 articles1–4,7,–15 containing 19 individual cases of PCT, which were included in this review. From these 19 cases, a total of 3 unique genetic polymorphisms2–4 were identified.

Summary of findings

The summary of demographic and clinical manifestation data is presented in Table 2 and Table S2.

Of the 15 articles and 21 cases, 3 cases reported associated genetic polymorphisms2–4 (Table 1). The first polymorphism, reported by Connors et al.2 in 2001, underwent associated functional studies, which demonstrated impaired protein assembly and is therefore highly probably pathogenic. The second polymorphism, reported by Xiao et al.4 in 2004, has not undergone functional studies, and the third, reported by Guo et al.3 in 2014, has since been shown to be nonpathogenic by an independent research group.13 No epigenetic studies have been performed on any of the reported cases.

Analysis of the identified variants in dbSNP (Table 1) showed an allele frequency of 5% for rs2676074124 in the patient population group, whereas the other polymorphisms (rs593284512 and rs617463553) both had allele frequencies of <1%. SIFT analysis suggested that rs2676074124 was likely to be benign with a low confidence in the deleterious effects of the amino acid change, while rs593284512

<table>
<thead>
<tr>
<th>Reference</th>
<th>Keratin gene</th>
<th>Variant</th>
<th>Exon</th>
<th>Mutation type</th>
<th>Protein domain</th>
<th>Functional studies</th>
<th>Epigenetic studies</th>
<th>dbSNP</th>
<th>OMIM phenotypes</th>
<th>Reported MAF</th>
<th>SIFT</th>
<th>PolyPhen</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Connors et al., 2001</td>
<td>K16</td>
<td>1062A &gt; T</td>
<td>K354N</td>
<td>Missense</td>
<td>2B</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes; rs59328451</td>
<td>6</td>
<td>0.01–0.03: deleterious; (low confidence)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xiao et al., 2004</td>
<td>K17</td>
<td>325A &gt; G</td>
<td>N109D</td>
<td>Missense</td>
<td>1A</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes; rs61746355</td>
<td>1%</td>
<td>0.54: tolerated 0: benign</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guo et al., 2014</td>
<td>K6b</td>
<td>1495G &gt; A</td>
<td>G499S</td>
<td>Missense</td>
<td>V2</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes; rs61746355</td>
<td>1%</td>
<td>0.54: tolerated 0: benign</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>Clinical manifestations</td>
<td>Age of onset (years)</td>
<td>Atypical features</td>
<td>Comments</td>
<td>Alternative diagnoses</td>
<td>Quality of evidence</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------------</td>
<td>---------------------------------------------</td>
<td>----------------------</td>
<td>-------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>------------------------------</td>
<td>-------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mawhinney et al., 1981 (n = 3)</td>
<td>Minimal clinical information</td>
<td>Childhood</td>
<td>Minimal clinical information</td>
<td>Autosomal dominant inheritance in family</td>
<td>PC</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paller et al., 1991 (n = 5)</td>
<td>PPK, hyperhidrosis</td>
<td>Teenage</td>
<td>1 case with no PPK</td>
<td>3 cases familial for PC</td>
<td>PC/PPK</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jaiswal et al., 1994 (n = 5)</td>
<td>Nail dystrophy, mild hyperhidrosis, pincer nails</td>
<td>8</td>
<td>No PPK</td>
<td>Positive family history in niece</td>
<td>PC</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chang et al., 1994 (n = 5)</td>
<td>PPK and leucokeratoses</td>
<td>44</td>
<td>No family history</td>
<td>–</td>
<td>PPK</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mouai-Midoun et al., 1996 (n = 5)</td>
<td>Nail dystrophy and PPK, pincer nail deformity</td>
<td>39</td>
<td>No previous manifestations</td>
<td>Amenorrhoea and anovulation</td>
<td>Acquired endogenous endocrinological cause more likely than PCT</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hannaford et al., 2000 (n = 5)</td>
<td>Nail dystrophy, cysts, leucokeratoses</td>
<td>20</td>
<td>Positive family history in sister</td>
<td>–</td>
<td>PC or steatocystoma multiplex</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Connors et al., 2001 (n = 5)</td>
<td>Nail dystrophy and PPK</td>
<td>6</td>
<td>2 first-degree relatives with ‘severe eczema’</td>
<td>Genetic polymorphism likely to be pathogenic</td>
<td>PC/PPK</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xiao et al., 2004 (n = 5)</td>
<td>Minimal clinical information</td>
<td>Unknown</td>
<td>Minimal clinical information</td>
<td>–</td>
<td>PPK/ED</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccaro et al., 2008 (n = 5)</td>
<td>Nail dystrophy only</td>
<td>40</td>
<td>Isolated late-onset nail involvement</td>
<td>Nail biopsy refused</td>
<td>Endogenous cause of nail dystrophy much more likely than PCT</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bahhady et al., 2008 (n = 5)</td>
<td>Nail dystrophy only</td>
<td>51</td>
<td>No previous manifestations</td>
<td>Known diabetes, hysterection in weeks prior to symptom onset</td>
<td>Acquired endogenous endocrinological cause more likely than PCT</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moger et al., 2013 (n = 5)</td>
<td>Nail dystrophy, PPK and leucokeratoses</td>
<td>10</td>
<td>No family history</td>
<td>Onset in first decade of life</td>
<td>PC/PPK</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guo et al., 2014 (n = 5)</td>
<td>Nail dystrophy only</td>
<td>6</td>
<td>No PPK</td>
<td>K6b mutation, likely to be nonpathogenic</td>
<td>PC</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sravanthi et al., 2016 (n = 5)</td>
<td>Nail dystrophy and PPK</td>
<td>13</td>
<td>No family history</td>
<td>No natal teeth</td>
<td>Clouston syndrome/steatocystoma multiplex</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ED, ectodermal dysplasia; K6b, keratin 6b; PC, pachyonychia congenita; PPK, palmoplantar keratoderma.
was likely to be deleterious and result in a damaging amino acid change, whereas rs61746355 in keratin 6b was reported to not result in a significant amino acid change and reported as benign.

**Discussion**

The evidence from this systematic review brings into question the diagnosis of PCT in many of the reported cases. Previous authors have commented that PCT may represent cases of misdiagnosed PPK or ectodermal dysplasia (ED).Eight of the reported cases had onset of symptoms prior to puberty, which would still fall within the range of normal onset of symptoms in PC (Table 2 and Table S2). Many cases had inadequate length of follow up and moderate risk of reporting bias (Table S3). The initial reports of PCT by Paller et al. define PCT as having onset in the second and third decade of life. Although that report does suggest that any onset after infancy may be considered ‘late onset’, many physicians would consider development of symptoms over the first decade of life as within the normal spectrum of PC. Indeed, genotype-phenotype studies have identified a number of patients with keratin 6c polymorphisms who had absence of nail changes within the first 6 years of life, and only 89.1% of patients with confirmed genetic polymorphisms diagnostic for PC display PPK within the first decade of life. The presence of alopecia in one case is suggestive of an alternative diagnosis such as steatocystoma multiplex (which has been reported with alopecia) or Clouston syndrome. An additional three cases describe endocrinological abnormalities which would make an alternative endogenous cause for the late-onset nail changes much more likely than PCT. One case described PPK without nail changes, more suggestive of PPK than PC, and the presence of multiple dermal cysts with a positive family history raises the possibility of steatocystoma multiplex in another case (Table 2).

Only one case had a genetic polymorphism that was likely to have a deleterious effect on the resultant protein. This highlights the importance of functional studies to confirm the results of genetic studies prior to diagnosis. We acknowledge that a limitation to this study is the possibility that post-publication genetic testing may have been undertaken in individual cases, which may confirm (or refute) an alternative diagnosis. Where contact information was available in the respective case reports, authors were approached for any updated diagnostic information; no new information was forthcoming. Despite this lack of new functional data, enough clinical suspicion remains to bring into question PCT as a distinct clinical entity.

The fact that alternative causes for the clinical findings exist in the cases collated suggests that anchoring bias may exist in the diagnosis of PCT. As ED and PPK are a heterogeneous and complex group of conditions, anchoring bias may lead clinicians to maintain a diagnosis of PCT, despite emerging evidence to the contrary.

**Conclusion**

Based on the data in this systematic review, the suggestion that cases diagnosed as PCT may represent other disorders cannot be refuted. Thorough clinical documentation of suspected cases of PCT (with the use of minimum clinical datasets such as the International Pachyonychia Congenita Research Registry and use of appropriate genetic screening to identify causative genetic polymorphisms is required to firmly establish diagnoses and direct genetic counselling and treatment options.

**Learning points**

- PCT describes late-onset PC with onset from late childhood to middle age.
- It has been questioned whether PCT is a unique entity or misdiagnosis of PPK or ED.
- The findings of our review cannot refute this suggestion, and highlight the need for thorough clinical documentation of suspected cases of PCT and thorough genetic screening of kindred to identify causative genetic polymorphisms.

**References**


CPD questions

Learning Objective
To demonstrate up-to-date knowledge regarding the diagnosis and differential diagnoses of pachyonychia congenita tarda.

Question 1
Pachyonychia congenita tarda was originally defined by symptom onset during which stage of life?
(a) After puberty.
(b) After the first decade of life.
(c) After 26 years of age.
(d) After infancy.
(e) After 5 years of age.

Question 2
The genetic polymorphisms in pachyonychia congenita tarda demonstrate which of the following?
(a) Epigenetic signatures not present in pachyonychia congenita.
(b) Genetic loci not found in pachyonychia congenita.
(c) Questionable functional significance.
(d) Autosomal dominant inheritance.
(e) Complete penetrance.

Question 3
The following conditions all may mimic pachyonychia congenita tarda except for one; which one?
(a) Palmoplantar keratoderma.
(b) Nonepidermolytic ectodermal dysplasia.
(c) Clouston syndrome.
(d) Steatocystoma multiplex.
(e) Epidermolysis bullosa.
Instructions for answering questions

This learning activity is freely available online at http://www.wileyhealthlearning.com/ced

Users are encouraged to

• Read the article in print or online, paying particular attention to the learning points and any author conflict of interest disclosures
• Reflect on the article
• Register or login online at http://www.wileyhealthlearning.com/ced and answer the CPD questions
• Complete the required evaluation component of the activity

Once the test is passed, you will receive a certificate and the learning activity can be added to your RCP CPD diary as a self-certified entry.

This activity will be available for CPD credit for 2 years following its publication date. At that time, it will be reviewed and potentially updated and extended for an additional period.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Risk of bias in included studies.
Table S2. Data collection proforma.
Table S3. Demographic and clinical information of included cases.
Figure S1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Checklist.