



# 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.

## ORIGINAL ARTICLE

# A review of the clinical phenotype of 254 patients with genetically confirmed pachyonychia congenita

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**Background:** Pachyonychia congenita (PC) is a group of autosomal dominant keratinizing disorders caused by a mutation in one of 4 keratin genes. Previous classification schemes have relied on data from case series and case reports. Most patients in these reports were not genetically tested for PC.

**Objective:** We sought to clarify the prevalence of clinical features associated with PC.

**Methods:** We surveyed 254 individuals with confirmed keratin mutations regarding their experience with clinical findings associated with PC. Statistical comparison of the groups by keratin mutation was performed using logistic regression analysis.

**Results:** Although the onset of clinical symptoms varied considerably among our patients, a diagnostic triad of toenail thickening, plantar keratoderma, and plantar pain was reported by 97% of patients with PC by age 10 years. Plantar pain had the most profound impact on quality of life. Other clinical findings reported by our patients included fingernail dystrophy, oral leukokeratosis, palmar keratoderma, follicular hyperkeratosis, hyperhidrosis, cysts, hoarseness, and natal teeth. We observed a higher likelihood of oral leukokeratosis in individuals harboring *KRT6A* mutations, and a strong association of natal teeth and cysts in carriers of a *KRT17* mutation. Most keratin subgroups expressed a mixed constellation of findings historically reported as PC-1 and PC-2.

**Limitations:** Data were obtained through questionnaires, not by direct examination. Patients were self- or physician-referred.

**Conclusions:** We propose a new classification for PC based on the specific keratin gene affected to help clinicians improve their diagnostic and prognostic accuracy, correct spurious associations, and improve therapeutic development. (J Am Acad Dermatol 10.1016/j.jaad.2011.12.009.)

**Key words:** genodermatosis; hyperkeratosis; keratin; keratinizing disorder; keratoderma; pachyonychia congenita.

Pachyonychia congenita (PC) is a group of autosomal dominant disorders caused by a mutation in one of 4 keratin genes: *KRT6A*, *KRT6B*, *KRT16*, or *KRT17*.<sup>1-5</sup> There are an estimated 5000 to 10,000 cases worldwide.<sup>6</sup> The variable clinical findings affect a number of ectodermal structures, including nails, skin, teeth, and oral mucosa.<sup>2</sup> Although Muller<sup>7</sup> and Wilson and Cantar<sup>8</sup> are credited with describing PC in 1904, Jadassohn and

#### Abbreviations used:

IPCRR:	International Pachyonychia Congenita Research Registry
OR:	odds ratio
PC:	pachyonychia congenita

Lewandowski,<sup>9</sup> whose names constitute the eponym for PC type 1, published the first case series of two siblings in 1906. Kumer and Loos<sup>10</sup> proposed a

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clinical classification scheme for PC variants based on their report of a 5-generation family with 23 affected family members. Classification criteria were developed and refined over subsequent years by authors who painstakingly reviewed and summarized the available literature.<sup>11-19</sup> Two clinical subtypes ultimately emerged, the Jadassohn-Lewandowski PC type 1 and the Jackson-Lawler PC type 2.

In 1994, Munro et al<sup>20</sup> studied a large Jackson-Lawler pedigree and linked the first PC gene to chromosome 17q12-q21. In 1995, McLean et al<sup>3</sup> identified the first causative mutations in keratin genes *KRT16* and *KRT17*. Additional mutations were subsequently identified in *KRT6a* and *KRT6b*—genes encoding the type II keratins that form heteropolymers with type I keratins K16 and K17.<sup>4,5</sup> The identification of these mutations and the advent of clinical genetic testing allowed the classification of PC based on clinical and genetic criteria.

Erroneous reports of PC manifestations in patients who did not have PC have been clarified by investigators through genetic testing.<sup>21</sup> Large, well-characterized and mutation-confirmed pedigrees offer the opportunity to draw valid conclusions regarding genotype-phenotype relationships.<sup>22</sup> However, even these pedigrees are prone to bias because of shared modifier genes and environments that might influence the clinical presentation. This report summarizes data collected from 254 patients with mutation-verified PC (derived from 147 families) and, to our knowledge, represents the largest and most comprehensive genotype-phenotype study of PC to date.

## METHODS

In 2004, the International Pachyonychia Congenita Research Registry (IPCRR) was established by the nonprofit organization Pachyonychia Congenita Project to collect clinical and genetic data on patients with PC worldwide. The registry was approved by the Western Institutional Review Board (study #20040468). All patients gave written informed consent and the study was conducted according to the Declaration of Helsinki Principles. Participant enrollment began in May 2004.

Participants in the registry were solicited through an Internet World Wide Web site designed to educate patients and physicians about PC ([www.pachyonychia.org](http://www.pachyonychia.org)). Referral to the registry was permitted through patients, family, physicians, and family expansion. To be included in the registry, each patient completed a detailed questionnaire

and provided information regarding whether and to what extent they were affected by the clinical features of PC. Patients were also asked about the age of onset and the impact each feature had on their quality of life. The completed questionnaire, along with photographs of visible skin and nail changes, was submitted to the IPCRR. A telephone consultation was then arranged with a dermatologist on the Pachyonychia Congenita Project medical

advisory board to: (1) clarify any confusing or missing information from the questionnaire; (2) confirm that the clinical features were consistent with PC; and (3) provide genetic counseling before mutation testing. Genetic testing was provided without charge and was performed in Dr Frances Smith's laboratory, University of Dundee, College of Life Sciences, Division of Molecular Medicine, Dundee, Scotland. Before being released to patients, the results were confirmed by independent testing of a buccal DNA sample by GeneDx (Gaithersburg, Maryland), a US Clinical Laboratory Improvement Amendments—certified laboratory. All participant data included in the analysis were from patients with a confirmed PC keratin mutation.

## Statistical methods

We performed logistic regression analysis to compare how different PC keratin mutations influence the probability of developing a specific clinical finding. For outcomes such as age of onset and quality of life, ordinal logistic regression was used. Because there were more *KRT6A* carriers than other mutation carriers we used the frequency of a trait in the *KRT6A* group as a reference when calculating odds ratios (OR) for the same trait to occur in the other keratin groups. To increase the power of analysis, all family members having a PC phenotype were included in the test, with intrafamilial correlation adjusted. Software was used to perform the comparisons (STATA v9.2, StataCorp, College Station, TX).

## CAPSULE SUMMARY

- Pachyonychia congenita (PC), a rare genodermatosis caused by mutations in keratin genes, is currently classified as PC-1 and PC-2 based on clinical features.
- We report the prevalence of clinical findings in 254 patients with genetically confirmed PC.
- We propose a new classification system based on the specific keratin mutation (eg, PC-6a, PC-6b, PC-16, PC-17).

## RESULTS

### An international case series of patients with mutation-verified PC

At the time the data were collected, 254 individuals had completed the necessary steps for inclusion in the IPCRR (Table I). Additional demographics (eg, country of residence) can be found at [www.pachyonychia.org](http://www.pachyonychia.org). In addition to the 254 patients harboring keratin mutations in one of the 4 “classic” PC genes (*KRT6A*, *KRT6B*, *KRT16*, and *KRT17*) 34 other individuals were found to have no detectable mutation, or mutations in other genes including connexin-30, *KRT6C*,<sup>23</sup> and desmoglein-1. In this article we will focus on the results of those with mutations in the 4 classic PC keratin genes.

We present the most commonly reported clinical findings according to mutation status in Table II.

### Major phenotypic features of PC

Three clinical features that were reported in more than 90% of patients across all mutation subtypes were thickened toenails, plantar keratoderma, and plantar pain (Table II).

**Thickened toenails.** Thickened toenails (Fig 1) were the most frequently reported clinical finding in the IPCRR with 249 of 254 (98%) patients reporting this phenotype (Table II). The average number of toenails affected was 8.8 (range 0-10, mode = 10). We performed logistic regression analysis to compare the relative likelihood of having all 10 toenails affected between the different PC keratin mutation carriers. Using the prevalence of 10 affected nails in participants with mutations in *KRT6B*, *KRT16*, and *KRT17* as the reference, we found that *KRT6A* mutation carriers were 11.1 times as likely ( $P < .001$ ) to have all 10 toenails affected. The average age of onset of toenail dystrophy across all keratin mutation types was 2.8 years with a median of 0.08 years (1 month). *KRT6A* mutation carriers had the earliest average onset at 0.35 years (about 4 months). The average age of onset for patients with a *KRT6B*, *KRT16*, and *KRT17* mutations was 9.5, 6.8, and 0.9 years, respectively.

**Plantar keratoderma.** Plantar keratoderma (Fig 2) was the next most commonly reported finding, present in 241 of 254 (95%) patients (Table II). The registry includes individuals of ages younger than 1 year to older than 86 years (Table I). Of the 13 individuals who were not reported as having plantar keratoderma, 9 were younger than 1 year, and the oldest was 3 years of age (data not shown). Plantar keratoderma can variably manifest as calluses, blistering, fissures, thickened skin, and open sores. Most patients experienced more than one of these

**Table I.** International Pachyonychia Congenita Research Registry demographics

	No. of individuals
Mode of inheritance	
Familial	157
Spontaneous	97
Gender	
Male	121
Female	133
Location of residence	
United States	125
Outside United States	129
Age, y	
Median	33
Range	<1-86

manifestations of keratoderma, with calluses being the most commonly reported (210/223, 94%) (data not shown).

To better understand the persistence of the plantar lesions, patients were asked to approximate how long the lesions lasted: 228 of 254 (95%) indicated that their feet were always affected and that the lesions never completely resolved. Among 241 patients who reported the age of onset of their plantar keratoderma, the average age was 4.2 years with a range of 0 (birth) to 30 years, and a median and mode of 3 and 2 years, respectively. Of patients, 20% were affected by 1 year of age and 66% were affected by 4 years of age (data not shown).

We found that the *KRT16* mutation carriers developed plantar keratoderma at a similar age to *KRT6A* carriers whereas *KRT6B* and *KRT17* carriers were significantly more likely to report later onset.

**Plantar pain.** Plantar pain was reported by 225 of 254 (89%) surveyed patients. The prevalence of pain was high across keratin subgroups (Table II). The age of the patient was found to have a dramatic effect on the reporting of plantar pain: only 3 patients older than 10 years did not report plantar pain (data not shown). Plantar pain was the most important feature of PC affecting quality of life (see below).

### Other common clinical findings in PC

**Fingernail involvement.** As shown in Fig 3, thickened fingernails were reported in 220 of 254 (87%) patients (Table II). The prevalence was lower in the other mutation carriers, with 9 of 20 (45%) *KRT6B* and 56 of 76 (74%) *KRT16* mutation carriers reporting at least one affected nail (Table II). Interestingly, when the number of fingernails affected was evaluated based on mutation type, patients with *KRT6B* mutations appeared to have far

**Table II.** Prevalence of selected clinical features in pachyonychia congenita

Phenotype	Keratin gene affected				
	Total N = 254	<i>KRT6A</i> N = 115	<i>KRT16</i> N = 76	<i>KRT6B</i> N = 20	<i>KRT17</i> N = 43
Thick toenails	249/254 (98%)	115/115 (100%)	71/76 (93%)	20/20 (100%)	43/43 (100%)
Plantar keratoderma	241/254 (95%)	105/115 (91%)	76/76 (100%)	20/20 (100%)	40/43 (93%)
Plantar pain	225/254 (89%)	101/115 (88%)	72/76 (95%)	20/20 (100%)	32/43 (74%)
Thick fingernails	220/254 (87%)	115/115 (100%)	56/76 (74%)	9/20 (45%)	40/43 (93%)
Oral leukokeratosis	177/254 (70%)	111/115 (97%)	45/76 (59%)	7/20 (35%)	14/43 (33%)
Palmar keratoderma	149/254 (59%)	60/115 (52%)	63/76 (83%)	6/20 (30%)	20/43 (30%)
Follicular hyperkeratosis	140/254 (55%)	88/115 (77%)	10/76 (13%)	7/20 (35%)	35/43 (81%)
Hyperhidrosis	124/254 (49%)	60/115 (52%)	33/76 (43%)	10/20 (50%)	21/43 (49%)
Cysts	104/254 (41%)	47/115 (41%)	8/76 (11%)	11/20 (55%)	38/43 (88%)
Hoarseness	71/254 (28%)	49/115 (45%)	15/76 (20%)	7/20 (35%)	10/43 (23%)
Natal teeth	39/254 (15%)	3/115 (3%)	0/76 (0%)	0/20 (0%)	36/43 (84%)

**Fig 1.** Clinical phenotype in genetically confirmed pachyonychia congenita. Toenail involvement usually demonstrates significant subungual hyperkeratosis and sometimes presents with premature termination of nail.

fewer nails affected on average compared with those with other keratin gene mutations. Comparison of the OR to develop fingernail involvement later than *KRT6A* mutation carriers revealed a statistically significantly elevated OR for *KRT6B* and *KRT16* but not for *KRT17* carriers.

**Mucosal involvement.** Oral leukokeratosis was reported in 177 of 254 individuals (70%) with the breakdown by mutation noted in Table II. Of the 177 individuals with self-identified oral leukokeratosis, 125 reported an average age of onset of 5.1 years with a median and mode of 0 years. Onset at birth was reported by 67 of 125 (54%), whereas 84 of 115 (73%) reported onset affected by 1 year of age and 119 of 125 (95%) by age 20 years (data not shown). *KRT6A* and *KRT17* carriers had a significantly increased OR of earlier onset of oral leukokeratosis compared with *KRT6B* and *KRT16* carriers.

**Cysts.** Pilosebaceous cysts and steatocysts have been reported in conjunction with PC types 1 and 2. Overall, 104 of 254 (41%) patients reported cysts of any type (Table II). *KRT17* mutation carriers had a

much higher likelihood of reporting cysts (OR of 23.2 [ $P = .003$ ]) compared with *KRT6A* mutation carriers.

**Natal teeth.** The phenomenon of erupted teeth present at birth known as “natal teeth” has been reported in patients with PC. Of the 39 patients who reported the presence of teeth at birth, 36 were *KRT17* mutation carriers. No *KRT16* or *KRT6B* mutation carriers reported natal teeth and only 3 of 115 (3%) *KRT6A* carriers were affected (Table II).

### PC reduces the quality of life

In Table III the severity and frequency of common PC symptoms are detailed.

Of the 240 patients who reported plantar pain, 214 indicated its frequency. A total of 138 (64%) indicated that their quality of life was affected at least weekly by plantar pain. In all, 41 (20%) of respondents were affected “every month or two”; 26 (12%) reported being affected “seldom” (defined as “once a year or less”); and 9 (4%) indicated that they were never affected. Describing the pain, 99 of 240 (41%) reported it was “very painful, but do not use





**Fig 2.** Clinical phenotype in genetically confirmed pachyonychia congenita. Plantar hyperkeratosis often follows pressure distribution, but can involve entirety of plantar surface. Environmental factors play significant role in development and persistence of plantar keratoderma.



**Fig 3.** Clinical phenotype in genetically confirmed pachyonychia congenita. Fingernail findings include dramatic elevation of fingernails because of subungual debris or premature termination of nail plate.

medication”; 62 of 240 (26%) answered that they “often require medication for the pain”; and 79 of 240 (33%) reported that plantar pain was “somewhat to not painful.”

## DISCUSSION

This cohort includes patients with the 4 most common PC keratin mutations in sufficient numbers to draw conclusions regarding the prevalence and penetrance of the most common PC clinical findings. To our knowledge, it includes the most diverse collection of patients of any cohort thus far evaluated and reduces the impact of genetic background or founder bias among the clinical features reported for different mutations.

Because of difficulties inherent in the study of a rare genodermatosis there are several limitations with our data. The patients were ascertained either by self- or physician-referral, not from a population-based assessment. Because most self-referrals were from individuals who became aware of PC through the Internet, our cohort probably represents a more affluent, better-educated population with access to health care. Because of the geographically dispersed nature of the cohort, our data were mostly gathered through telephone interviews and evaluation of photographs, rather than by direct examination, which makes the objective quantification of clinical severity more difficult. The quality-of-life measures and reporting of pain, although key to

**Table III.** Impact of specific features of pachyonychia congenita on quality of life

Impact on quality of life	Plantar keratoderma	Thickened toenails	Cysts	Thickened fingernails	Oral leukokeratosis
No impact	19/216 (9%)	71/221 (32%)	63/154 (41%)	67/199 (34%)	40/64 (63%)
Sometimes a problem	56/216 (26%)	113/221 (51%)	65/154 (42%)	109/199 (55%)	23/64 (35%)
Always a problem, but able to function	133/216 (62%)	36/221 (16%)	23/154 (15%)	22/199 (11%)	1/64 (2%)
Unable to function	8/216 (4%)	1/221 (0.5%)	3/154 (2%)	1/199 (0.5%)	0/64 (0%)

understanding the most important issues that affect patients with PC, were not performed using a validated metric.

The most common clinical findings in our PC cohort were toenail thickening, plantar keratoderma, and plantar pain. Only one patient, who was younger than 1 year, lacked all 3 findings. The impact of age on their prevalence is significant as children seldom develop plantar keratoderma or plantar pain before they start to walk. If children 3 years of age and younger were excluded from the analysis, 216 of 230 (94%) individuals would meet all 3 criteria and 227 of 230 (99%) of our participants would have met two criteria. For the clinician, these findings suggest that the presence of toenail dystrophy with plantar keratoderma and plantar pain in children older than 3 years is a much more sensitive means of clinically diagnosing PC than 20-nail dystrophy, which is often thought to be requisite to the diagnosis.

Additional diagnostic findings associated with PC included fingernail dystrophy, follicular hyperkeratosis, leukokeratosis, cysts, and natal teeth. Less common findings included ear pain, hoarseness, and hyperhidrosis. In the literature there are reports of corneal findings, deafness, skeletal abnormalities, and mental retardation associated with PC. We found no support for these findings among our cohort. A more detailed discussion of features spuriously associated with PC will be reported elsewhere.

Although a detailed discussion of the clinical findings linked to a specific mutation is beyond the scope of this article, we found that the *KRT16* mutations, p.Asn125Ser and p.Arg127Cys, were strongly associated with lack of fingernail involvement whereas *KRT16* mutation carriers with the p.Leu132Pro mutation frequently presented with 10-fingernail dystrophy. Our group has recently published a large study reviewing new and previously known mutations in patients with PC.<sup>24</sup> As more data are gathered we hope to be able to provide phenotypic prognosis based on the specific mutation identified.

Plantar pain has the most profound effect on quality of life for most patients with PC as it can limit mobility and social interaction along with the ability

to find and maintain work. The pain reported by patients with PC is often out of proportion to the extent or duration of callus, suggesting that the mechanism is not merely the result of pressure from callus formation. Clinicians will better meet the needs of patients with PC by inquiring about the extent of pain and helping them manage their calluses to facilitate pain reduction.

Historically, PC has been subdivided into two major phenotypic variants, PC-1 (Jadassohn-Lewandowski) and PC-2 (Jackson-Lawler). The PC-1/PC-2 classification was designed to improve the ability to predict phenotypic prognosis without genetic testing. The PC-1/PC-2 classification assumes that because certain keratin proteins predictably dimerize that a mutation in either protein gene will result in a similar clinical phenotype. Hence, a mutation in either of the PC-1 keratin proteins (K6a/K16) should cause similar features, whereas a mutation in K6b/K17 (PC-2 proteins) will present with a different, predictable phenotype.

Instead, our data demonstrated that clinical phenotypes overlapped substantially across genotypic categories and could not be used to predict genotype reliably. Specifically, we found a significant overlap of oral leukokeratosis, cysts, and natal teeth that purportedly distinguish PC-1 and PC-2. Overall, our data demonstrate that the PC-1/PC-2 nomenclature does not accurately reflect the molecular pathogenesis of PC and does not represent a rational or clinically useful classification at this time.

We recommend the elimination of the terms "PC-1" and "PC-2" and propose their replacement with notation of the specific keratin defect. In this classification scheme a diagnosis of PC-6a, PC-6b, PC-16, and PC-17 would correspond to mutations in the *KRT6A*, *KRT6B*, *KRT16*, and *KRT17* genes, respectively. A designation of PC-U (unknown) may be applied when the classic clinical findings of PC are found in the absence of a known PC keratin gene mutation. Classification based on keratin mutation subtype will allow clinicians to provide more accurate prognoses for patients with PC. We recommend genetic testing for individuals with the triad of toenail dystrophy, plantar keratoderma, and plantar

pain as they have a high likelihood of carrying a PC mutation. Genetic testing is provided free of charge to all patients who enroll in the PC registry through the nonprofit patient advocacy group, Pachyonychia Congenita Project ([www.pachyonychia.org](http://www.pachyonychia.org)).

We look forward to the development of specific genetic techniques to minimize or eliminate the clinical expression of this rare keratin disorder.<sup>25-27</sup>

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