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 2012;67:680-6.)

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*.[1-5] There are an estimated 5000 to 10,000 cases worldwide.[6] The variable clinical findings affect a number of ectodermal structures, including nails, skin, teeth, and oral mucosa.[2] Although Muller[7] and Wilson and Cantar[8] are credited with describing PC in 1904, Jadassohn and Lewandowski,[9] whose names constitute the eponym for PC type 1, published the first case series of two siblings in 1906. Kumer and Loos[10] proposed a

Abbreviations used:

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

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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.[11-19] Two clinical subtypes ultimately emerged, the Jadassohn-Lewandowski PC type 1 and the Jackson-Lawler PC type 2.

In 1994, Munro et al[20] studied a large Jackson-Lawler pedigree and linked the first PC gene to chromosome 17q12-q21. In 1995, McLean et al[3] 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.[4,5] 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.[21] Large, well-characterized and mutation-confirmed pedigrees offer the opportunity to draw valid conclusions regarding genotype-phenotype relationships.[22] 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.

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).

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). 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).