Pachyonychia congenita (PC) is a rare, autosomal dominant inherited disorder of keratinization that is characterized by a triad of focal palmoplantar keratoderma, plantar pain, and hypertrophic nail dystrophy. It can be debilitating, causing significantly impaired mobility. PC is diagnosed clinically alongside identification of a heterozygous pathogenic mutation in one of five keratin genes: \textit{KRT6A}, \textit{KRT6B}, \textit{KRT6C}, \textit{KRT16}, or \textit{KRT17}. Each keratin gene mutation is associated with a distinct clinical phenotype, with variable age of onset and additional features, which has allowed classification by genotype. Additional features include pilosebaceous cysts, follicular hyperkeratosis, natal teeth, oral leukokeratosis, hidradenitis suppurativa, itching, and neurovascular structures. Although classed as rare, the prevalence of PC is likely to be underestimated. There is no cure or specific treatment for PC at present. Current treatments are limited to conservative measures to reduce plantar friction and trauma, mechanical debridement, topical treatments, and treatments for associated features or complications, most commonly infection. However, through active research in collaboration with PC Project, a patient-advocacy group, and the International PC Research Registry, a global registry of PC patients, there are now many new potential therapeutic options on the horizon. This review summarizes the clinical features associated with PC and highlights the current and future treatment of its manifestations. (DOI: 10.2302/kjm.2023-0012-IR)

\textbf{Keywords:} pachyonychia congenita, palmoplantar keratoderma, genodermatosis, jadassohn–lewandowsky syndrome, jackson–lawler syndrome

\textbf{Introduction}

Inherited monogenic palmoplantar keratodermas (PPK) are a heterogeneous group of conditions characterized by thickening of the palmoplantar epidermis. Accompanied by chronic plantar pain and hypertrophic nail dystrophy, pachyonychia congenita (PC) is a rare, inherited cause of PPK that is attributed to autosomal dominant missense mutations in one of five keratin genes (\textit{KRT6A}, \textit{KRT6B}, \textit{KRT6C}, \textit{KRT16}, and \textit{KRT17}).\textsuperscript{1-5} Keratin proteins form the intermediate filament cytoskeleton of all epithelial cells and are required to maintain epidermal integrity and regulate growth and maturation. They are divided into two types: the smaller acidic type I (e.g., K16, K17) and the larger basic type II (e.g., K6a, K6b, K6c).\textsuperscript{6} Keratins form a heterodimer between one type I keratin and one type II keratin; for example, KRT16-6 and KRT17-6 heterodimers are expressed in response to wounding.\textsuperscript{7} PC is estimated to affect between 1000 and 10,000 individuals worldwide, although the actual prevalence is likely to be higher, with equal sex distribution and no reported ethnic or racial differences.\textsuperscript{8} PC imposes significant psychological and financial burdens on patients.\textsuperscript{9} Although plantar pain is the most debilitating feature of the disease, issues regarding physical appearance, the requirement of a sedentary occupation, and the expenses...
incurred for mobility aids, manicuring devices, and/or podiatric appointments can impact the patient. There is a growing need for a treatment that can reduce pain and the impact on daily life. Currently, this is being addressed by active research in collaboration with PC Project, a patient-advocacy group, and the International PC Research Registry (IPCRR), a global registry of PC patients. This review summarizes the clinical features and management options for PC, including therapeutic options on the horizon.

**Classification**

PC was first defined by Jadassohn and Lewandowski in 1906, although case reports predate this. Historically, PC was categorized into two distinct subtypes [PC type 1 (Jadassohn–Lewandowski) and PC type 2 (Jackson–Lawler)] according to the clinical features. However, the introduction of genetic testing has resulted in genotype–phenotype correlations and diagnoses of PC based upon molecular classification. The current accepted classification of PC is based on the mutation of a keratin gene to create five subtypes: PC-K6a (prevalence 39.7%), PC-K6b (9.0%), PC-K6c (3.3%), PC-K16 (32.6%), and PC-K17 (15.5%).

Approximately 70% of patients have a family history of PC, while the remaining 30% are associated with de novo pathogenic variants. The diagnosis is established with the triad of PPK, plantar pain, and dystrophic nails in the context of a positive family history and is confirmed via identification of a heterozygous pathogenic mutation in one of the five keratin genes (*KRT6A, KRT6B, KRT6C, KRT16, KRT17*).

Patients usually present by the age of 10 years. Nail dystrophy usually appears by 1 year of age, and plantar keratoderma appears by the age of 4 years in 60% of patients. However, the age of onset, extent of these features, and the presence of other features vary by subtype. Specific clinical features predicting certain subtypes include widespread nail dystrophy predicting PC-K6a or PC-K17, cysts predicting PC-K17, and natal teeth predicting PC-K17. Typical genotype–phenotype correlations are summarized in Table 1.

### Palmoplantar keratoderma

Keratin genes implicated in PC are normally expressed in epithelial appendages and are robustly induced in response to injury or environmental stress. Focal PPK usually presents in the first years of life once a child begins walking. The extent of PPK varies (Fig. 1a,b) and is unrelated to the severity of pain experienced. Calluses typically develop on pressure points on plantar and/or palmar surfaces, with marked hyperkeratosis and epidermal thickening. Neurovascular structures, appearing as blood-red or dark-red spots (1–2 mm), may develop within the callus and are associated with extreme pain, suggesting association with a nearby peripheral sensory nerve. Hyperhidrosis may accompany PPK, and many patients report intermittent itching, most frequently affecting the callus site.

### Table 1. Clinical features of pachyonychia congenita subtypes PC-K6a, K6b, K6c, K16, and K17

<table>
<thead>
<tr>
<th>Subtype</th>
<th>PC-K6a (n=412)</th>
<th>PC-K6b (n=93)</th>
<th>PC-K6c (n=34)</th>
<th>PC-K16 (n=338)</th>
<th>PC-K17 (n=161)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene</td>
<td>KRT6A</td>
<td>KRT6B</td>
<td>KRT6C</td>
<td>KRT16</td>
<td>KRT17</td>
</tr>
<tr>
<td>Proportion*</td>
<td>39.7%</td>
<td>9.0%</td>
<td>3.3%</td>
<td>32.6%</td>
<td>15.5%</td>
</tr>
<tr>
<td>Clinical features</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plantar keratoderma</td>
<td>86% (352)</td>
<td>97% (90)</td>
<td>100% (34)</td>
<td>98% (332)</td>
<td>80% (128)</td>
</tr>
<tr>
<td>Palmar keratoderma</td>
<td>67% (277)</td>
<td>48% (45)</td>
<td>35% (12)</td>
<td>71% (241)</td>
<td>51% (82)</td>
</tr>
<tr>
<td>Plantar pain</td>
<td>95% (391)</td>
<td>100% (93)</td>
<td>91% (31)</td>
<td>96% (319)</td>
<td>84% (108)</td>
</tr>
<tr>
<td>Dystrophic toenails</td>
<td>98% (404)</td>
<td>97% (90)</td>
<td>62% (21)</td>
<td>97% (327)</td>
<td>95% (153)</td>
</tr>
<tr>
<td>Dystrophic fingernails</td>
<td>97% (399)</td>
<td>43% (40)</td>
<td>6% (2)</td>
<td>57% (191)</td>
<td>84% (135)</td>
</tr>
<tr>
<td>Oral leukokeratosis</td>
<td>86% (356)</td>
<td>24% (22)</td>
<td>26% (9)</td>
<td>33% (112)</td>
<td>25% (40)</td>
</tr>
<tr>
<td>Natal or prenatal teeth</td>
<td>5% (20)</td>
<td>0% (0)</td>
<td>9% (3)</td>
<td>1% (3)</td>
<td>76% (122)</td>
</tr>
<tr>
<td>Follicular hyperkeratosis</td>
<td>48% (197)</td>
<td>39% (36)</td>
<td>0% (0)</td>
<td>10% (35)</td>
<td>63% (101)</td>
</tr>
<tr>
<td>Cysts</td>
<td>58% (237)</td>
<td>65% (60)</td>
<td>24% (8)</td>
<td>23% (78)</td>
<td>93% (149)</td>
</tr>
<tr>
<td>First-bite syndrome</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Steatocystomas</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Adapted from GeneReviews/IPCRR: a total of 1038 patients enrolled in the IPCRR as of January 2021.

* Proportion of PC attributed to pathogenic variants in this gene/proportion of each subtype.
Plantar pain

Plantar pain is the most debilitating feature of PC. Severe pain may require permanent or intermittent use of mobility aids (crutches, canes, or wheelchairs) or patients may need to lean on furniture or people for support. Some patients report the need to crawl at times because of pain. Hypotheses for the etiology of this pain include the development of subepidermal blisters, nociceptive pain secondary to tissue damage, and neuropathic pain secondary to damaged peripheral sensory nerves. Severity of pain varies between subtypes and patients, but all experience chronic, severe pain. Patients frequently report that the severity of plantar pain is worse in warmer and more humid weather than in cooler weather. Although the mechanisms behind this are not fully understood, possible reasons may include increased inflammation, overexpression of TRPV3, or increased sweating.

Nail dystrophy

Hypertrophic nail dystrophy is one of the first recognized features of PC. It is typically noticed in the first months of life. It can affect toenails and fingernails, and may include all nails of the fingers and toes or individual nails only. Nail dystrophy presents as nails that grow to full length and have an upward slant caused by prominent distal hyperkeratosis or nails that have a sloping region of hyperkeratosis and exposed distal fingertip. Leukokeratosis can present in infancy and persist into adulthood. Pilosebaceous cysts are observed in all PC subtypes but are the most common in PC-K17.

Leukokeratosis

Leukokeratosis of the mucous membranes presents as thickened white patches on the tongue and cheek and is most seen in PC-K6a. It can be misdiagnosed as Candida albicans infection in infants and may impact sucking during feeding. In severe cases, leukokeratosis can involve the laryngeal surfaces, which presents as hoarseness. Large laryngeal lesions can, in rare cases, cause life-threatening respiratory tract obstruction in infants and may be precipitated by upper respiratory tract infection.
Natal/pre-natal teeth

Natal or pre-natal teeth are occasionally seen in PC, predominantly in PC-K17; however, subsequent primary and secondary dentition is normal. In addition, PC-K6a, PC-K6b, and PC-K6c patients are thought to have a higher risk of tooth decay. Infants with PC may experience first-bite syndrome, an extreme pain near the jaw or ears lasting 15–25 s at the beginning of eating or swallowing. It is most often seen in children with PC-K6a aged 4–12 years for whom it can cause difficulties with eating. It typically resolves spontaneously.

Other cutaneous manifestations

Follicular hyperkeratosis occurs in some PC patients, most commonly on the elbows, knees, and trunk. It is worst in childhood and adolescence and improves in adulthood. Pilosebaceous cysts (Fig. 1f) including velvus hair cysts and steatocystomas are common and seen in almost all PC-K17 patients. Steatocystoma multiplex (SM) is a genodermatosis that is also caused by mutations in KRT17 and is characterized by widespread steatocystomas with pubertal onset and subtle nail involvement, but with mild or no associated PPK. The same heterozygous pathogenic KRT17 variant within one family can present with PC in some family members and SM in others, displaying phenotypic heterogeneity for the same genetic variant. Hidradenitis suppurativa has also been reported in association with PC: a recent survey to the IPCRR found 25.9% of respondents reported HS-associated features and 43% had PC-K17. KRT17 is highly expressed in the sebaceous glands and hair follicles and mutations could account for inflamed cysts in flexural areas such as the axilla.

Differential diagnoses

Diagnosis can be made based on the presence of typical clinical symptoms and signs, but genetic testing is required for definitive diagnosis and may be required for access to clinical trials and personalized medicine. The main differentials for PC based on the classical presentation of PPK and dystrophic nails are summarized in Table 2.

Clouston syndrome is a rare autosomal dominant disorder caused by mutations in GJB6 encoding gap junction protein connexin-30. It is a common alternative diagnosis in PC Project. It is characterized by hypotrichosis, nail thickening, and dyschromia and is occasionally associated with PPK. It should be considered when a patient presents with hair abnormalities and without plantar pain. Painful PPK is a key feature of Olmsted syndrome, which is an autosomal dominantly inherited condition caused by pathogenic variants in TRPV3. Unlike PC, Olmsted syndrome can also present with periorificial keratotic plaques, mutilating PPK, alopecia, and constricting digital bands that can cause digital autoamputation, but milder cases of Olmsted syndrome can resemble PC. Punctate PPK type 1 may also present as a painful and focal PPK because of coalescing lesions. Mutations in DSG1 can cause PPK with marked phenotypic variation including painful, focal plantar keratoderma and striate palmar keratoderma but usually lacks nail changes. Diffuse epidermolytic PPK, which presents with PPK in early life, can be painful and is associated with hyperhidrosis, but the distribution is diffuse, not focal. In children showing blistering over PPK, PC can be confused with epidermolysis bullosa simplex (EBS); however, EBS does not share the characteristic nail changes observed in PC. Dyskeratosis congenita has features that overlap with PC including nail dystrophy, hyperhidrosis, and oral leukoplakia; however, it also has distinctive features that include reticulate flexural hyperpigmentation and bone marrow failure.

Hypertrophic nail dystrophy in PC may be mistaken for onychomycosis or possible co-infection with dermatophytes. Nail infections should be considered when there is a change in nail appearance or if single nails are involved. Typically, dermatophytic infection does not affect all nails except in the cases of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy and systemic mucocutaneous candidiasis where infection may involve all nails. Scrapings should be taken to rule out infection as the cause of the condition or whether it co-exists with dystrophic nails. Other syndromes that cause dystrophic nails, without PPK or other features of PC, include nail psoriasis, twenty-nail dystrophy, yellow nail syndrome, familial onychogryphosis, and non-syndromic congenital nail disorder 10. Scrapings should be taken to rule out infection as the cause of the condition or whether it co-exists with dystrophic nails. Other syndromes that cause dystrophic nails, without PPK or other features of PC, include nail psoriasis, twenty-nail dystrophy, yellow nail syndrome, familial onychogryphosis, and non-syndromic congenital nail disorder 10. Similarly, oral leukokeratosis in the absence of dystrophic nails or PPK should be investigated for possible Candida albicans infection.

Management

There is no cure or targeted treatment for PC at present. Current therapeutic options are limited. Treatment of the manifestations of PC are based on patient preference and consist of lifestyle adjustments, mechanical techniques, and symptomatic relief (Fig. 2). As a condition with significant impact on quality of life, an empathetic approach and support are vital. Support is available via the PC Project website with links to patient information and support groups.

Keratoderma

Keratoderma can be managed mechanically by regularly filing, grinding, cutting, or clipping calluses. Patients often choose to do this themselves with razor
blades, scalpels, clippers, paring knives, emery boards, pumice stones, and specialist foot files or they may visit a podiatrist if possible. There is a balance whereby paring callus improves appearance and plantar pain, but, paradoxically, over-trimming can worsen plantar pain. The frequency and method of paring calluses is down to patient preference, and patients report varying benefit. Topical emollients including those containing keratolytics (such as urea 40%, salicylic acid 10%-20%, or lactic acid) can have some benefit. Retinoids (oral vitamin A derivatives), including acitretin and isotretinoin, can cause thinning of hyperkeratosis, but many patients report increased skin blistering and plantar pain, leading to discontinuation. Acitretin is highly teratogenic with a 3-year washout period, so may not be appropriate for women of childbearing age.

**Pain**

Lifestyle adjustments focus on reducing friction and trauma by wearing comfortable footwear and orthotics, limiting activities that require standing, and using walking aids such as walking sticks, crutches, four-wheeled walkers, and/or wheelchairs. Weight loss and/or maintenance of healthy body weight can reduce pressure and friction at callus sites; however, most exercise programs designed toward weight loss are challenging because of pain during exercise. Symptomatic relief of pain by using simple analgesia or neuropathic agents such as amitriptyline, gabapentin, or pregabalin is used by some patients. Consultation with a pain specialist may be helpful in severe cases.

**Nails**

Dystrophic nails in PC can become infected or traumatized, leading to pain. Many patients control nail dystrophy through filing or clipping nails. Diagnosis via swabs or scrapings and treatment of bacterial and fungal nail infections with systemic antibiotic or antifungal therapy is often required. Periodic soaking in dilute bleach may reduce infection frequency but has not been proven effective.
in clinical trials. For particularly problematic nails, patients may choose to have them surgically removed, although there remains the possibility that the nails may regrow.

**Leukokeratosis**

Oral leukokeratosis can be managed with frequent gentle brushing with a toothbrush and maintaining good dental hygiene. Most cases will resolve without intervention and there are reports of improvement with oral antibiotics, suggesting a bacterial element. Leukokeratosis with laryngeal involvement has been reported most in children with PC-K6a which can present as hoarseness and breathing difficulty and should prompt review by an ear–nose–throat surgeon. Regular monitoring and early investigation, diagnosis, and intervention can prevent life-threatening complications of respiratory distress. Paradoxically, surgical interventions to the larynx can worsen the condition. Children and infants should also be closely monitored for eating/feeding difficulties. In the event of feeding difficulties, the use of thickened formula, feeding with a syringe, or use of a bottle with a larger hole may be beneficial.

**Other symptoms**

Incision and drainage or excision can be used to treat pilosebaceous cysts, including SM. The use of keratolytic emollients (lactic acid, salicylic acid, urea) or alpha-hydroxy acid creams has been trialed for follicular hyperkeratosis with varying success. To address plantar hyperhidrosis, the use of wicking socks or silver socks may be helpful.

**Genetic counselling**

Patients should be referred to clinical genetics or genetic counsellors for support and guidance, particularly for family planning. In vitro fertilization, pre-implantation genetic diagnosis (PGD), and selective embryo transfer may be utilized to prevent PC in the offspring. This is a controversial, time-consuming, and expensive option that has many ethical implications. PGD in PC requires a genetic diagnosis and is generally pursued by patients with severe debilitating features. Decision making should be guided with specialist input from genetics teams.

**Future management options**

There is a clinically unmet need for effective treatments for PC, which historically has been underserved by clinical trials because of its status as a rare disease. Following increased understanding of the pathogenesis and genetic basis of PC, many new treatments are in the various stages of clinical evaluation with collaborative input from PC Project and the IPCRR.

The mTOR inhibitor sirolimus (rapamycin) selectively reduces KRT6A expression in human keratinocyte cell lines. Oral sirolimus significantly reduced neurovascular structures and keratoderma and improved quality of life in three patients in an off-label study, but its systemic side effects were intolerable. In a case report of two PC-K6a patients, topical sirolimus was reported to reduce plantar pain. A pharmaceutical-sponsored phase IIIb study is currently investigating the efficacy and safety of...
topical sirolimus (see https://clinicaltrials.gov/ct2/show/NCT05180708).

Statins downregulate KRT6A expression via Stat1, and case reports have reported reduced hyperkeratosis and plantar pain, particularly in children. However, these results have not been confirmed in a placebo-controlled randomized controlled trial.\(^{52,53}\) Risks and benefits need to be balanced.\(^{54}\)

Plantar injections with botulinum toxin type A have showed reduced keratoderma and plantar pain in PC-K6a and PC-K16, thought to be initiated through inhibition of sweating, and subsequent reduced epidermal damage, blistering, and pain.\(^{55–57}\) However, it requires repeated and painful administrations requiring local anesthetic nerve block and reports are limited to small numbers.\(^{55}\)

Short interfering RNA approaches have been used successfully in hematology and have been used in PC via intraleisional injection to selectively inhibit KRT6A to reduce plantar callus in a single patient in a split-body study. However, injection site pain limits this approach.\(^{58,59}\)

PC-affected skin has overactivity of TRPV3 and epidermal growth factor receptor (EGFR).\(^{47}\) Oral EGFR inhibitors erlotinib and lapatinib have reduced hyperkeratosis and plantar pain in two recent case series.\(^{57,60}\) A topical selective TRPV3 antagonist is also in the early stages of clinical trials (see https://clinicaltrials.gov/ct2/show/NCT05435638).

**Conclusion**

PC should be considered as a possible diagnosis in patients presenting with early onset focal keratoderma and plantar pain. Given that infection, particularly fungal, can commonly complicate PC, we recommend investigation via swabs and scrapings/nail clippings and treatment as appropriate. PC Project can provide links to patient information and support groups and can facilitate genetic testing, which allows subtyping, genetic counselling, and entry to clinical trials. Despite its profound impact on quality of life, current management has variable success and is limited to lifestyle adjustments, mechanical debridement, and active treatments. Advances in understanding of the pathophysiology and improved accessibility to genetic testing will continue to guide the development of new pathway-specific therapeutics.

**Conflicts of Interest**

RMC: Position funded by Palvella Therapeutics to work on a clinical trial unrelated to this work. All funding goes to the university. MdB: Position funded by Chang Zuckerberg Initiative and Leo Foundation and is unrelated to this work. EOT: Research funding: Kamari Pharma, Unilever. Consultancy: Azitra, Palvella Therapeutics, and Kamari Pharma. Speaker: Almirall. All unrelated to this work, and all funding goes to the university.

**References**


Dr McCarthy is an Internal Medicine Trainee in London. She graduated with honours and was awarded the prestigious Dean’s Award from the University of Southampton in 2020. Following this she completed the Academic Foundation Programme and subsequently was sub-investigator on the VAPAUS study phase three trial for pachyonychia congenita at the Blizard Institute, Queen Mary University of London. She is interested in rare, inherited skin diseases and the development of new therapeutics.