References

1 Royce PM, Steinmann B, eds. *Connective Tissue and its Heritable Disorders*. New York: Wiley-Liss, 2002.
2 Holbrook KA, Byers PH. Skin is a window on heritable disorders of connective tissue. *Am J Med Genet* 1989; **34**:105–121.
3 Malfait F, Francomano C, Byers P *et al*. The 2017 international classification of the Ehlers-Danlos syndromes. *Am J Med Genet C Semin Med Genet* 2017; **175**:8–26.
4 Blackburn PR, Xu Z, Tumelty KE *et al*. Bi-allelic alterations in AEBP1 lead to defective collagen assembly and connective tissue structure resulting in a variant of Ehlers-Danlos syndrome. *Am J Hum Genet* 2018; **102**:696–705.
5 Cortini F, Vill C, Marinelli B *et al*. Understanding the basis of Ehlers-Danlos syndrome in the era of the next-generation sequencing. *Arch Dermatol Res* 2019; **311**:265–75.
6 Angwin C, Ghali N, Baker D *et al*. Electron microscopy in the diagnosis of Ehlers-Danlos syndromes: correlation with clinical and genetic investigations. *Br J Dermatol* 2020; **182**:698–707.
7 Proske S, Hartschuh W, Enk A. Hausser I. *J Dtsch Dermatol Ges* 2004; **4**:308–18 (in German).
8 Kadler KE. Fell Muir Lecture: collagen fibril formation *in vitro* and *in vivo*. *Int J Exp Pathol* 2017; **98**:4–16.

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Management of symptomatic mucosal involvement in paediatric pachyonychia congenita

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Linked Article: Goldberg *et al*. *Br J Dermatol* 2020; **182**:708–713.

Pachyonychia congenita (PC) is a Mendelian skin disorder with a genetic heterogeneity because of dominant-negative heterozygous mutations in tissue-specific intermediate filament genes. These genes, including *KRT6A*, *KRT6B*, *KRT6C*, *KRT16* and *KRT17*, are highly expressed in the nail bed, palmoplantar skin, pilosebaceous unit, oral mucosa and teeth.[1] A total of 136 distinct mutations have been reported in these five genes, with *KRT6A* and *KRT16* as the most frequently mutated genes in about 40% and 30% of families with PC, respectively (http://www.hgmd.cf.ac.uk).

A triad of subungual hyperkeratosis, plantar keratoderma and plantar pain is present in almost all patients with genetically confirmed PC by the age of 10 years. Other, less frequent manifestations include palmar keratoderma, blistering, pilosebaceous cysts and palmoplantar hyperhidrosis, as well as follicular keratotic papules and cysts, natal teeth, and oral and laryngeal involvement.[2,3] Symptomatic treatment modalities include keratolytics, emollients, retinoids and steroids with limited benefits. Recently, successful treatment with rosuvastatin in a patient with *KRT6A*-associated PC has been reported.[4]

Oral leucokeratosis of the tongue and buccal mucosa is reported in more than half of patients with PC, mostly with mutations in *KRT6A*, with a median age of onset of 3 weeks. Mucosal leucokeratosis is usually misdiagnosed as oropharyngeal candidiasis that has failed to respond to antifungal therapy. Leucokeratosis can interfere with infant breastfeeding, culminating in failure to thrive (FTT). Laryngeal involvement manifests as hoarseness and occasionally as respiratory stridor requiring an emergent tracheotomy. In more than 90% of patients with PC who have oral leucokeratosis, hoarseness is a concurrent presentation.[1–3]

In this issue of *BJD*, Goldberg *et al*. reported a cohort of nine paediatric patients with *KRT6A*-related PC, and with oral leucokeratosis with feeding difficulties and FTT.[5] Additionally, laryngeal involvement was noticed in six patients, which led to the death of a 4-year old patient as a result of acute laryngitis and respiratory arrest. Before participation in the study, the patients experienced frequent unnecessary hospitalizations and medical interventions such as antifungal antibiotic therapy and insertion of feeding tubes that exacerbated their disease. The authors proposed simple and straightforward feeding options that were effective in most patients preventing FTT and obviating the unnecessary medical interventions. In addition, the study suggests that clinicians should consider the diagnosis of PC in patients with candidiasis, especially those who are unresponsive to treatment, with concomitant nail dystrophy and hoarseness.[5]

In sum, this study highlights the importance of symptomatic mucosal involvement, which is prevalent in half of patients with PC. The authors emphasized that the complications described in their paper are manageable with a simple feeding solution, but if left untreated will lead to FTT and further complications.

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References

1 Shah S, Boen M, Kenner-Bell B *et al*. Pachyonychia congenita in pediatric patients: natural history, features, and impact. *JAMA Dermatol* 2014; **150**:146–53.
2 Smith FJD, Hansen CD, Hull PR, Kaspar RL, Irwin McLean WH, Edel O'Toole RSE *et al*. Pachyonychia congenita (2006, updated 2017). In: *GeneReviews* (Adam MP, Ardinger HH, Pagon RA, Wallace SE, eds). Available at: https://www.ncbi.nlm.nih.gov/books/NBK1280/ (last accessed 21 December 2019).

3 International Pachyonychia Congenita Research Registry (IPCRR). *Data Summary (May 9, 2014)*. Available at: http://www.pachyonychia.org (last accessed 21 December 2019).
4 Abdollahimajd F, Rajabi F, Shahidi-Dadras M *et al.* Pachyonychia congenita: a case report of a successful treatment with rosuvastatin in a patient with a *KRT6A* mutation. Br J Dermatol 2019; **181**:584–6.
5 Goldberg I, Mashiah J, Kutz A *et al.* Symptomatic mucosal involvement in pachyonychia congenita: challenges in infants and young children. Br J Dermatol 2020; **182**:708–13.

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Sharing (data) is caring for patients with pachyonychia congenita

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Linked Article: Samuelov *et al.* Br J Dermatol 2020; **182**:738–746.

It has been over a century since the first patients were described with combined features of thickened toenails and thick/painful plantar calluses. We now know this as the ultra-rare condition pachyonychia congenita (PC), an autosomal-dominant condition affecting somewhere around one in one million people globally.

McLean and colleagues first identified pathogenic variants in keratin 16 and 17 as the underlying cause of this condition in 1995.[1] By 2012, Eliason and colleagues had made recommendations around diagnostic criteria in the context of the by-then four well-described molecular causes of PC.[2] In this issue of BJD, Samuelov and colleagues present a series of 815 patients with variations in one of five well-described genes (*KRT6A*, *KRT6B*, *KRT6C*, *KRT16* or *KRT17*), including an in-depth analysis of the genotype–phenotype relationship and a considerable number of new variants, that will enable more complete counselling of patients and families with this condition, as well as planning for future management.[3]

This feat is impressive for multiple reasons with the series analysing data collected from an international collaboration of clinicians, industry, patients and families known as the Pachyonychia Congenita Project, a US-based charity founded in 2003. The data in the current article draws on a Pachyonychia Congenita Project resource in the form of the International Pachyonychia Congenita Research Registry (IPCRR). This output presents a new go-to reference study for the counselling of patients and families with PC. It is a testament to the power of such a collaboration in a condition that might otherwise be considered too infrequent to focus efforts on.

Interestingly, the study describes 112 patients referred to IPCRR in whom the nine gene panel, including the five PC genes (*KRT6A*, *KRT6B*, *KRT6C*, *KRT16* or *KRT17*) and four genes associated with similar but different conditions, were reported. Increasingly patients with undifferentiated symptoms and signs are referred for genetic testing as part of their work-up, and future iterations of the analysis of IPCRR data might add value to a broader group of patients by looking at this cohort of patients.

The study highlights the significant impact of the condition on quality of life, particularly in the form of plantar pain. Recent work has led to the greater elucidation of the underlying pathomechanisms of this condition. Downregulation of the KRT9 gene is thought to play a role in increased expression of the mutant keratin in PC caused by pathogenic variants in KRT16. In the following stages, the Nrf2-linked inflammatory cascade becomes involved. The latter, in particular, presents potential targets for intervention, given the availability of modulators of Nrf2 activity.[4]

A recent update on current research on this archetype of epidermal keratinopathy identified multiple avenues of development, from animal models that reproduce features of the condition, targets for therapeutic intervention (particularly inflammatory pathways), the development of small interfering RNAs, spherical nucleic acids and induced pluripotent stem cells.[5]

Newly diagnosed patients with PC will benefit significantly from this new resource, to assist in counselling and management planning. Five PC genes are now well described, with links to information on similar conditions and a great resource from which to build new insights. Concurrent community-driven efforts are working towards mechanism-based therapies for these individuals.

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References

1 McLean WH, Rugg EL, Lunny DP *et al.* Keratin 16 and keratin 17 mutations cause pachyonychia congenita. *Nat Genet* 1995; **9**:273–8.
2 Eliason MJ, Leachman SA, Feng BJ *et al.* A review of the clinical phenotype of 254 patients with genetically confirmed pachyonychia congenita. J Am Acad Dermatol 2012; **67**:680–6.
3 Samuelov L, Smith FJD, Hansen CD, Sprecher E. Revisiting pachyonychia congenita: a case–cohort study of 815 patients. Br J Dermatol 2020; **182**:738–46.
4 Zieman AG, Coulombe PA. Pathophysiology of pachyonychia congenita-associated palmoplantar keratoderma: new insights into skin epithelial homeostasis and avenues for treatment. Br J Dermatol 2020; **182**:564–73.
5 Funk T, Hansen CD, Paller A, O'Toole EA. Update on pachyonychia congenita research. Br J Dermatol 2020; **182**:788–9.

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