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Case report

Identification of a novel substitution mutation (R103C) in the rod domain of the keratin 17 gene associated with pachyonychia congenita type 2

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Introduction

Pachyonychia congenita (PC) is a rare group of genodermatoses, inherited by autosomal dominant mutations in epithelial specific keratin genes: KRT6A, KRT6B, KRT6C, KRT16, and KRT17.[1–3] Keratins are major structural proteins in epithelial cell cytoarchitecture where, as heterodimers of keratin I and II, they act as resilient scaffolds that withstand mechanical and non-mechanical stresses. The keratin protein is composed of central alpha-helical rod domain flanked by a head and a tail domain at the N- and C- termini, respectively. The helical rod domain is divided by linker sequences into 1A, 1B, 2A, and 2B subdomains. Most of the identified keratin genetic defects in PC comprise of missense mutations or small in-frame insertion or deletion mutations, altering the amino acid sequence in the helical boundary motif.[4,5] The defective keratin protein is able to form heterodimers with the wild-type protein and result in fragility and weakening of the keratin cytoskeleton.[1,6,7] In this report, we describe the case of a child with clinical findings of PC, and subsequent gene sequencing analysis that identified a novel mutation in the α-helical rod domain of the KRT17 gene. We also discuss the clinical implication of this mutation on the pathogenesis and progression of PC.

Case report

Here, we present a 3-1/2-year-old boy who presented to our pediatric dermatology clinic at 14 months of age with severe nail dystrophy involving all his toenails (Fig. 1). The child was born with multiple natal teeth (had already erupted at birth and were present above the gum line) and has had multiple cysts on alveolar crests. He was born to nonconsanguineous parents and has two older healthy siblings.

The child initially presented to dental medicine at 5 days of age with 15 supernumerary teeth, and the natal teeth were removed. At 20 days of age, multiple small gingival cysts and hypertrophic dystrophy of all toenails were noted. The clinical picture was consistent with a diagnosis of pachyonychia congenita type 2.

In a commercial laboratory, GeneDx Inc. (Gaithersburg, MD, USA), which provides genetic testing for genetic skin diseases including keratin disorders, the patient's genomic DNA was PCR-amplified for the two mutation hotspot regions coding for the helix initiation and termination motif in KRT6B (exons 1 and 7) and KRT17 (exons 1 and 6) using proprietary methods.[8] Bidirectional sequence was obtained by capillary sequencing, analyzed, compared to the published gene sequence,[3,4] and

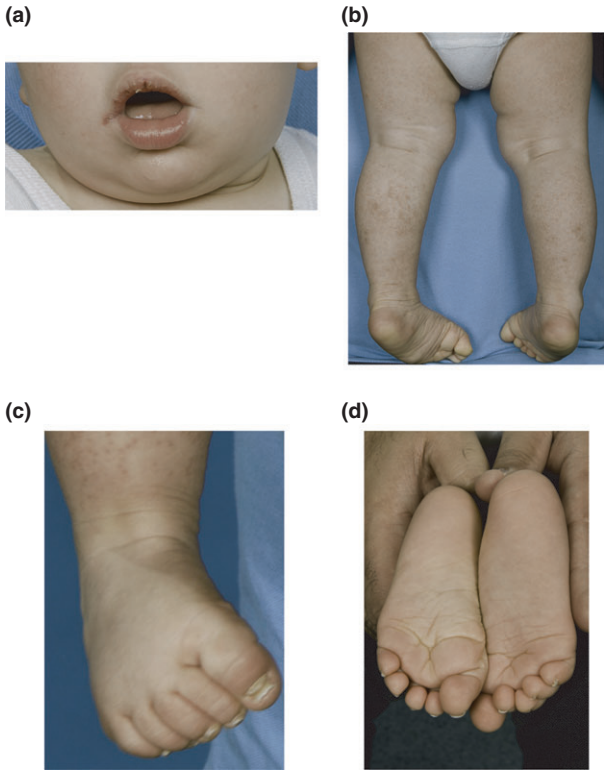

Figure 1 Clinical phenotype in a child with pachyonychia congenita 2, confirmed by genetics testing to have a substitution mutation in the KRT17 gene, demonstrating the following clinical manifestations (a) diffuse ulcerations with irregular margins, involving the upper lip and cobblestoning of the gingiva (not observed in the photo) (b) keratosis pilaris of the thighs and legs (c) subungual hyperkeratosis and dystrophy of the toenails, and (d) absence of plantar hyperkeratosis. It should be noted that the child is still young and may not have developed plantar hyperkeratosis yet, and this will be monitored as he becomes more active/older

sequence variants were confirmed by capillary sequencing. The genetic sequencing analysis of the KRT6B gene revealed no disease-associated mutations in the hotspot regions on exons 1 and 7. However, a novel mutation variant (R103C) within the KRT17 gene was identified.

At 14 months of age, the child presented to our clinic for management of his nail dystrophy. Upon examination, he was noted to have keratosis pilaris on legs, arms, and trunk, toenail dystrophy of all ten toenails, and cobblestoning of the gingiva. His hair growth was normal, and there was no palmoplantar keratoderma (Fig. 1).

Discussion

Pachyonychia congenita (PC) is a rare autosomal dominant keratin disorder. The main clinical features reported in the majority of patients with this condition include nail dystrophy, plantar keratoderma, and plantar pain. Other common features of PC include leukokeratosis of the oral mucosa, follicular hyperkeratosis, and the formation of cysts.

Historically, PC has been classified into two major subtypes, PC-1 (Jadassohn-Lewandowski syndrome) and PC-2 (Jackson-Lawler syndrome) based on clinical characteristics.[9,10] Mutations in KRT6A and KRT16 are associated with PC-1, and mutations in KRT6B and KRT17 are associated with PC-2. PC-1 is the most common type, characterized by pachyonychia, symmetric hyperkeratosis of the palms and soles, follicular hyperkeratosis, and oral leukokeratosis. PC-2 has the features of PC-1 with the additional findings of steatocystoma multiplex, vellus hair cysts, and natal teeth.[6] In comparison to PC-1, PC-2 demonstrates milder palmoplantar keratoderma and a lower frequency of oral leukokeratosis.

A large analysis of genetically confirmed PC cases enrolled in the International PC Research Registry (IPCRR) shows a significant phenotypic overlap between cases previously classified as PC-1 and PC-2.[11,12] Recently, a new classification was proposed that divides PC into four subtypes based on the keratin gene mutations. The subtypes are classified as PC-K6a, PC-K6b, PC-K6c, PC-K16, and PC-K17 for mutations in KRT6A, KRT6B, KRT6C, KRT16, and KRT17 genes, respectively.[3,11] Given the recent proposed classifications and the overlapping symptoms between the different subtypes of PC, and with other genodermatoses, genetic testing is required for confirmation of the diagnosis.

KRT17 gene is located on the long arm of chromosome 17 at locus q21.2. At least 20 pathogenic variants of KRT17 have been described.[3,13,14] Figure 2 outlines mutations documented in the 1A domain of the KRT17 gene. In fact, most pathogenic variants of KRT17 are a result of missense mutations, and the remaining mutations are deletions within the 1A helical domain.[15,16] These mutations are located in the initiation helix domain of the gene, disrupting the formation of intermediate filament network. However, mutations were also reported in the 1B, 2A, and 2B domains of the KRT17 gene.[4,8,17]

This case of PC-K17 was found to have a novel missense mutation, not previously reported in the literature, resulting in transition of arginine to cysteine at codon 103 (R103C). The identification of this mutation, which is located within a mutational hotspot region present in most keratin disorders, contributes to our current understanding of the KRT17 gene mutations that are involved in Pachyonychia congenita (Fig. 2). *In silico* analysis predicts this variant is probably damaging to the protein structure and function. This mutation likely impacts secondary protein structure as arginine and cysteine differ in size, polarity, charge, and other properties and hence likely are damaging to protein structure and function. Indeed, mutations in the rod domain are known to distort alpha-helix structure and lead to instability of the heteropolymeric intermediate filaments and to disease progression.[18,19]

Mutation-specific genetic testing of the child's parents will allow us to determine if the mutation was inherited or arose *de novo* as well as will provide detailed genetic counselling and

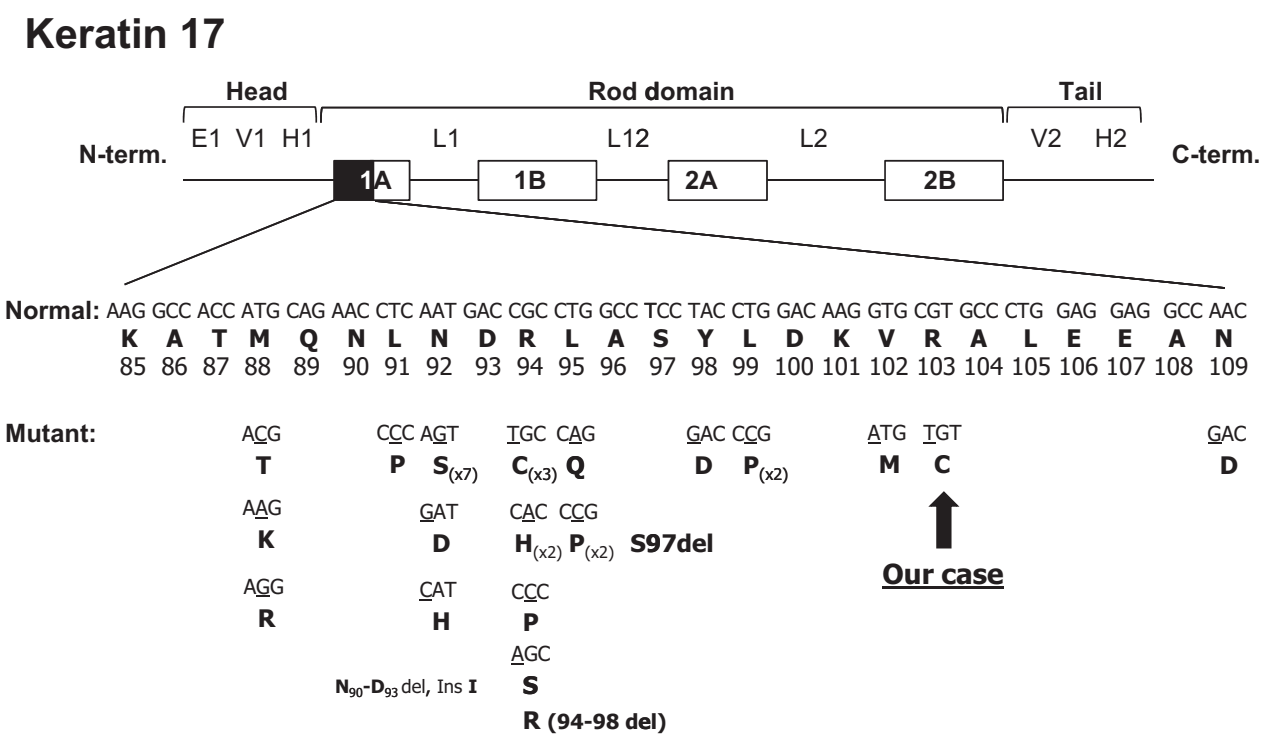

Figure 2 Summary of reported mutations in the 1A domain of the KRT17 gene in Pachyonychia congenita. Keratin has several domains depicted in the schematics, which are linked by linker domains. Amino acid residues were depicted using standard abbreviations: A, Ala; C, Cys; D, Asp; H, His; K, Lys; L, Leu; M, Met; N, Asn; Q, Gln; R, Arg; S, Ser; T, Thr; V, Val; Y, Tyr. Numbers in brackets (×2 or ×7, etc.) indicate the mutations have been reported more than once. Adapted from several sources[3,14,15]

future molecular prenatal diagnosis. Furthermore, gene mutations are involved in the pathogenesis of such inherited disorder and identifying them, such as R103C reported here, can help confirm clinical diagnosis of this skin disorder and may help in the development of novel therapeutics.

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