



Pachyonychia Congenita Project

15 March 2005

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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.

Steatocystoma multiplex, oligodontia and partial persistent primary dentition associated with a novel keratin 17 mutation

DOI: 10.1111/j.1365-2133.2009.09383.x

Steatocystoma multiplex (SM) is a rare condition presenting at puberty with multiple skin-coloured nodules. Mutations in the keratin 17 gene (*KRT17*) have been identified in patients with pachyonychia congenita type 2 (PC-2),¹ as well as in some patients with SM,^{2,3} and it is likely that in these patients the conditions are phenotypic variants of the same disorder. We report siblings with a novel *KRT17* mutation presenting with a SM phenotype, partial congenital absence of secondary dentition and persistence of primary dentition, which has not previously been reported.

Case

A 17-year-old man presented with multiple papules of the axillae, groins, neck and upper chest since puberty (Fig. 1a,b). He had partial noneruption of secondary dentition with persistence of six deciduous teeth, but no history of prenatal or natal teeth. He did not have any nail, oral or hair features of PC. He had minimal thickening of palmar skin over pressure points, but no palmoplantar keratoderma (PPK). He had normal scalp hair, but sparse facial and axillary hair, as did his mother. Seven of his secondary teeth were confirmed to be congenitally absent on dental X-ray at age 12 years (Fig. 2).

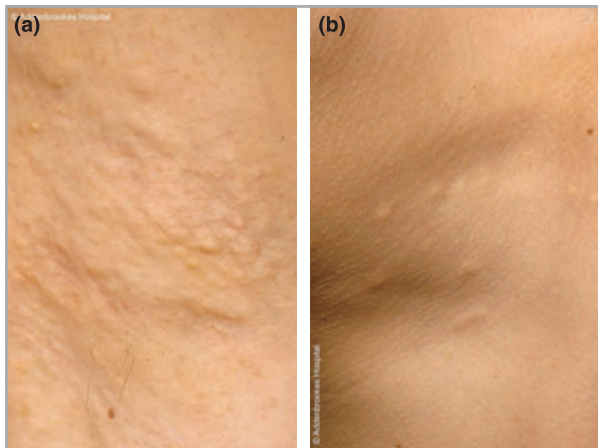


Fig 1. Skin-coloured nodules were present symmetrically in the axillae (a), and on the upper chest and neck (b).

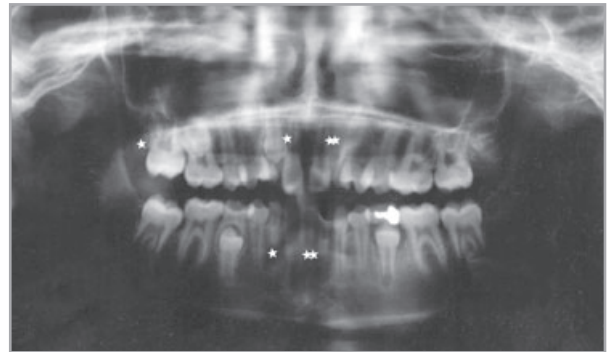


Fig 2. Orthopantomogram at the age of 12 years shows congenital absence of six secondary teeth as marked (12, 22, 23, 31, 41, 43), and the upper right third molar. Orthopantomogram courtesy of S. Graham, Regent Road Orthodontic Clinic, Lowestoft, U.K.

He also had syndactyly of his hands and feet. His 19-year-old sister was similarly affected with nodules over the chest, axillae, neck and groins, and partial noneruptive secondary dentition. They gave a history stating that their father has small teeth and facial cysts. The brother's skin lesions were demonstrated on an axillary skin biopsy to be steatocystomas and

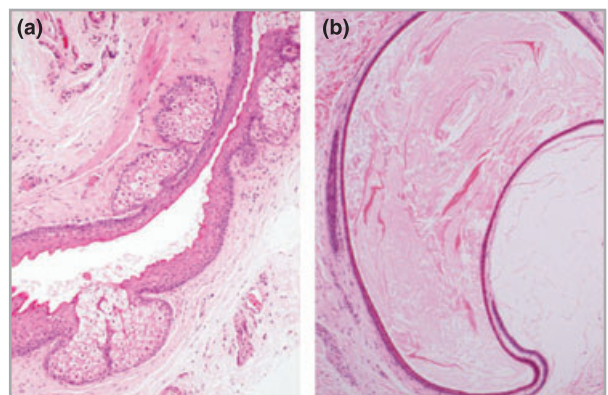


Fig 3. A steatocystoma with sebaceous gland lobules in the cyst wall (a) and vellus hair cysts (b) were present on histology. Haematoxylin and eosin staining; original magnification $\times 4$.

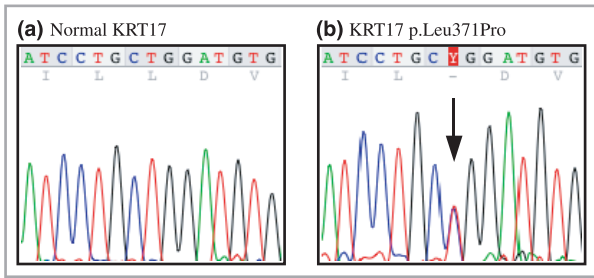


Fig 4. *KRT17* exon 6 mutational analysis. (a) Normal *KRT17* sequence in exon 6, showing codons 269–273. (b) The equivalent region shown in (a) from the proband showing missense mutation c.1112T>C leading to amino acid substitution p.Leu371Pro.

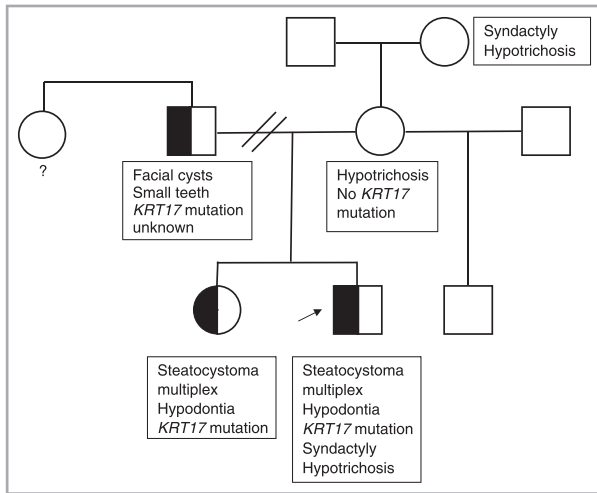


Fig 5. Family tree demonstrating cosegregation of hypodontia and steatocystoma multiplex with the novel *KRT17* mutation in both siblings. Proband indicated by arrow.

vellus hair cysts (Fig. 3a,b), and microscopic examination of scalp hair did not show pili torti. DNA analysis identified a novel heterozygous missense mutation in *KRT17* (c.1112T>C leading to amino acid substitution p.Leu371Pro) in both siblings (Fig. 4). Their clinically unaffected mother did not carry the mutation; their father was unavailable for testing (Fig. 5). The mutation was excluded from 100 normal control samples, and is not listed in the current Single Nucleotide Polymorphism database. Both the hypotrichia and syndactyly are probably unrelated to the identified keratin mutation, as they were present in the otherwise unaffected maternal side of the family.

Discussion

SM is a rare condition in which mid-dermal cysts develop mainly on the torso and proximal extremities from adolescence. Clinically these manifest as skin-coloured papules, which histologically arise in the sebaceous duct.⁴ Although these cysts are usually described as steatocystomas, we propose

that ‘steatocysts’ is a more appropriate term, as these are benign lesions. Some patients may also have a mild PPK and variable nail changes.² Two types of SM are recognized (OMIM 184510; OMIM 184500), based on the presence or absence of natal teeth. *KRT17* mutations have been identified in some patients with SM, as well as in patients with PC-2.

PC is also a rare keratin genodermatosis with a wide phenotypic variation. It is divided into two main types (PC-1, Jadassohn–Lewandowsky form and PC-2, Jackson–Lawler form), both with hypertrophic nail dystrophy and painful PPK as the most frequent clinical features. In addition, patients with PC-2 may develop cutaneous cysts, including pilosebaceous cysts (steatocystomas and vellus hair cysts), milia, flexural abscesses and genital cystomatosis. Cysts usually present around puberty, and may be due to infundibular or ductal occlusion by hyperkeratosis. Although both steatocystomas and vellus hair cysts occur in these patients, co-occurrence of both in a patient with PC has seldom been reported.⁵ Patients with PC-2 may also have natal teeth, hair anomalies including pili torti, and a milder PPK. Dental anomalies are well recognized, with natal or neonatal teeth present in between 2% and 50% of patients.⁶ However, it is one of the less common clinical features, and not fully penetrant even within families. Other dental anomalies that have been described include early development of teeth, early primary tooth loss,⁵ Hutchinson-like teeth⁷ and friable adult teeth.⁸ To our knowledge, congenital absence of secondary dentition with persistent partial primary dentition has not previously been described.

Although extremely unlikely, we cannot rule out that this phenotype may have been caused by cosegregation of unlinked disorders. The pattern of oligodontia expressed in this family is unlike that seen in selective tooth agenesis due to mutations in the *PAX9* or *MSX1* genes (OMIM 604625, OMIM 106600), which predominantly cause loss of molar and premolar teeth.⁹

Previously a specific *KRT17* mutation has been found in both SM and PC-2.³ *KRT17* is expressed in the sebaceous gland, nail bed, hair shaft and epidermal appendages. Mutations in *KRT6B* have also been reported in PC-2 but not in SM. All previously described *KRT17* mutations in SM¹ have been situated in the *KRT17* helix initiation motif within the 1A domain, as have most of those in PC-2. Our patients display a mutation not previously described, *KRT17* p.Leu371Pro, which lies in the 2B domain just upstream of the helix termination motif of the keratin 17 protein, outside the usual mutation hotspot for keratin genes. Proline substitution mutations are particularly disruptive to α -helical structures compared with other amino acid substitutions.¹⁰

It is probable that at least some cases of SM, such as the family we have described, are a milder phenotypic variant of PC-2, and that other factors alter phenotypic expression. This report extends the range of dental anomalies recognized in PC-2, and we propose that this association of SM and hypodontia with a new mutation in *KRT17* represents a previously unrecognized variant of PC-2. As in most keratin disorders, there is wide variability of expression of PC even within

families. Recognition and genetic counselling of families affected by this autosomal dominant ectodermal dysplasia is important.

Acknowledgments

F.J.D.S was supported by a fellowship grant from PC Project (<http://www.pachyonychia.org>). W.H.I.M. and E.B.L. were supported by funding from the Dystrophic Epidermolysis Bullosa Research Association, the U.K. Medical Research Council (G0700314) and the British Skin Foundation.

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Accepted for publication: 13 April 2009

Key words: hypodontia, keratin 17, pachyonychia congenita, steatocystoma multiplex

Conflicts of interest: none declared.

This case was presented as an oral presentation at the 2008 Annual Meeting of the British Association of Dermatologists.