



Pachyonychia Congenita Project

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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.

Nail that Mutation—Keratin 17 Defect in Late-Onset Pachyonychia

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Pachyonychia congenita (PC) is one of a number of epithelial fragility disorders that has been linked to mutations in keratin genes over the last decade (Smith, 2003). Keratins belong to the intermediate filament family of proteins that provide a structural cytoskeleton within all epithelial cells. When compromised by keratin mutations, epithelial cells become fragile and less resilient to mild physical trauma. Clinically, this presents as a variety of phenotypes depending on the keratin affected, ranging from blistering in epidermolysis bullosa simplex (EBS) to hypertrophic nail dystrophy in PC. Nineteen keratin genes have now been identified in human epithelial fragility disorders and some keratin mutations are now emerging as predisposing factors in more common multifactorial diseases (Smith, 2003). Four keratin genes are known to be responsible for the main types of PC and variants thereof, allowing diagnosis at the molecular level to confirm the clinical diagnosis. This allows genetic counseling with knowledge of the precise genetic lesion, with the option of prenatal testing in severe cases. Molecular diagnosis is also very useful to determine the type of PC in cases of young children where some of the phenotypic characteristics do not develop until later in life.

PC encompasses a variety of inherited ectodermal dysplasias whose main clinical characteristic is hypertrophic nail dystrophy. Typically, thickening of the nails begins within the first few months of life, as illustrated in Fig 1. It is the constellation of other ectodermal structures affected which allows classification of PC into two main types: PC-1 (Jadassohn-Lewandowsky type, OMIM 167200); and PC-2 (Jackson-Lawler type, OMIM 167210). In PC-1, hypertrophic nail dystrophy is accompanied by focal palmoplantar keratoderma, which is often quite severe and debilitating, and oral leukokeratosis. The presence of multiple pilosebaceous cysts in PC-2 is the predominant feature distinguishing it from PC-1. However, these cysts are not normally present until puberty when the sebaceous glands become active, thus making the diagnosis of PC-1 versus PC-2 difficult in young children. Also, in PC-2 there may be other ectodermal defects including: oral leukokeratosis (less common than in PC-1), mild focal palmoplantar keratoderma; *pili torti*; and natal teeth. The causative keratin genes are specifically expressed in the nail bed, palmoplantar epidermis, epidermal appendages and other epithelia affected in each type of PC. Mutations in keratins K6a and K16 result in PC-1 (Bowden *et al*, 1995; McLean *et al*, 1995); whereas genetic defects in K6b and K17 lead to PC-2 (McLean *et al*, 1995; Smith *et al*, 1998). The expression patterns of these proteins and associated phenotypes are summarized in Table 1.

In this issue, Xiao *et al* describe an unusual PC-2 case where the proband did not show any phenotype until 12 years of age when she developed thickened toenails. Later, at about 20 years of age her fingernails also became thickened. Pilosebaceous cysts developed at puberty, as is usual in PC-2. Other family members showed similar late-onset nail abnormalities. This type of PC could be classified as pachyonychia congenita tarda, a previously described variant of PC (Paller *et al*, 1991; Hannaford and Stapleton, 2000). In these individuals hypertrophic nail changes do not develop until the second or third decade of life. Xiao and colleagues found K17 mutation N109D in this kindred, the first genetic defect in a case of late-onset PC-2. The mutation differs from those reported previously in K17 as it is located in the second half of the 1A domain. With the exception of one mutation in K6b, all reported PC-2 mutations occur within the helix initiation motif at the start of the 1A domain of K17 (www.interfil.org). However, as more PC families are analyzed, it is likely that mutations will be found throughout the K17 molecule. The majority of keratin mutations in epithelial fragility disorders are in the highly conserved boundary domains at either end of the α -helical rod domain (Fig 2). By *in vitro* experiments, these regions have been demonstrated to be important in keratin filament assembly, and mutations in these regions shown to be highly disruptive to the integrity of keratin filament networks. From studies in the keratin disorder EBS, where



Figure 1
A baby with PC-1 at about 1 yr of age, showing early onset of the marked hypertrophic nail dystrophy that is characteristic of the disorder. This infant carries a mutation in the K6a gene. (Photograph kindly provided by Dr Frances Lawlor and Professor John McGrath, St John's Institute of Dermatology, London).

Table 1

Keratin	Main expression pattern	Helix initiation motif	Helix termination motif	Other regions
K6a	As for K16, below	PC-1	PC-1	?
K16	Nail bed, palmoplantar epidermis (widespread), oral mucosa, wound healing	PC-1, FNEPPK	FNEPPK	PC-1 tarda
K6b	As for K17, below	?	PC-2	?
K17	Nail bed, palmoplantar epidermis (restricted), epidermal appendages, sebaceous gland, other epithelia	PC-2, SM	?	PC-2 tarda

Type I Keratin

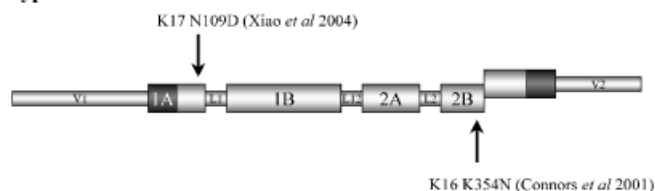


Figure 2

Schematic diagram showing the basic protein structure of a type I keratin. The α -helical rod domain is divided into four domains, the 1A, 1B, 2A and 2B connected by flexible linkers L1, L12 and L2. Non-helical variable domains V1 and V2 flank the rod domain. At either end of the rod domain are the highly conserved helix initiation and helix termination motifs, respectively (*shaded*). The approximate positions of mutations reported in late-onset PC are shown by arrows.

a large number of mutations have been identified in K5 and K14, a good correlation can be drawn between the position of the mutation and the clinical phenotype. In general, mutations in the helix boundary motifs result in a more severe phenotype than those in either the non-helical domains or in internal regions of the α helical rod domain (Fig 2).

Here the authors (Xiao *et al*, p 892) speculate that the later onset of PC-2 in this kindred could be explained by the position of the mutation. The mutation, in the second half of the 1A domain of K17, is in one of the less critical domains which might delay the onset of the clinical phenotype. There is one other report of a mutation in late-onset PC, in this case the phenotype resembled PC-1 and was due to a mutation in K16 (Connors *et al*, 2001). The mutation was again found in a functionally less important region of the keratin molecule, the central portion of the 2B domain, where mutations in the analogous region of K5 and K14 result in the milder forms of EBS. Thus, a trend is emerging where the types of mutations associated with milder, site-restricted forms of EBS appear to give rise to late-onset phenotypes in PC.

As more mutations are identified in PC kindreds including those with unusual variants of PC as described by Xiao *et al*, better genotype/phenotype correlations may be possible. However, from the studies published so far it appears that any genotype/phenotype association for PC could be more complicated than in EBS. Steatocystoma multiplex (SM; OMIM 184500) is another variant of PC-2 caused by mutations in K17. Patients present clinically with widespread pilosebaceous cysts as seen in PC-2, but there is little or no nail involvement. From the genotype/phenotype pattern seen in EBS, one might have predicted that mutations causing SM would be within the rod domain or variable regions and not in the helix boundary motifs. However, the only mutations reported in SM to date are in the helix initiation motif of K17, with some mutations actually occurring at the same codon as

those that produce PC-2 (www.interfil.org). In another unusual case of PC-2, sebaceous cysts developed at a very early age (Feng *et al*, 2003) and here the mutation in K17 was found in the same codon (N92) that can also result PC-2 and SM. Clearly, there must be other factors in combination with the mutation that determine the differing phenotypes in these cases. These could be environmental/lifestyle factors, polymorphisms in other keratins, or in the case of early-onset pilosebaceous cysts, hormonal variability could well be involved. Another level of complexity is the fact that some patients with clinical features resembling PC have recently been shown to carry connexin mutations analogous to those seen in Clouston syndrome (van Steensel *et al*, 2003). Thus, there are still a number of unanswered questions in this area of genodermatology.

In conclusion, another molecular piece of the pachyonychia puzzle has been "nailed". This and similar studies help dermatologists and geneticists make informed diagnoses and allow better prognostic predictions and genetic testing for patients. Ultimately, a fuller understanding of the pathogenetic mechanisms underlying these inherited disorders may help biologists develop novel therapeutic approaches to treat these incurable diseases.

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