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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.
Pachyonychia congenita (PC) is a group of hereditary disorders characterized by hypertrophic nail dystrophy and associated ectodermal features. Two principal PC syndromes are readily distinguished. In PC-1 (Jadassohn–Lewandowsky syndrome, MIM 167200), pachyonychia is associated with focal palmoplantar keratoderma (PPK), follicular keratoses and oral leukokeratosis. In PC-2 (Murray–Jackson–Lawler syndrome, MIM 167210) PC is associated with natal teeth and multiple pilosebaceous cysts, and also focal PPK, follicular keratoses, bushy eyebrows and (in children) unruly hair. Histology and ultrastructure of oral and cutaneous lesions of PC suggest a keratin disorder, and many pedigrees are now known to be due to mutations in genes encoding one of the paired keratins of specialized epidermis, K6a/K16 (PC-1) and K6b/K17 (PC-2). The specific sites and appendages affected in PC-1 and PC-2 correspond to those in which the relevant keratin pairs are normally expressed. The correlation between clinical syndrome and the pair of genes involved has thus far been highly consistent, and has lent no support to the more complex classifications of the disorder which have been formulated from time to time.

However, as more pedigrees of PC are studied, rarer genetic variants may begin to emerge. One candidate variant is late onset PC or 'PC tarda'. PC usually begins in infancy, but onset as late as the 4th or 5th decade has been reported, in two cases with familial occurrence. In this issue of the journal, Connors et al. report a patient with late onset pachyonychia congenita (PC) due to a novel mutation in the mid-region of the 2B helical domain of keratin 16. All previously reported mutations which cause PC have affected one of the highly conserved peptide sequences at either end of the helical rod domain common to all keratin molecules. Mutations in these motifs are predicted to be highly disruptive to intermediate filament assembly, and underlie the majority of genetic diseases due to keratin mutation. In other keratin disorders such as epidermolysis bullosa simplex, the site of mutation is a strong determinant of the severity of the phenotype. On this basis, Connors et al. speculate that the site of the mutation may explain the delayed onset of PC in their patient. However, even mutations in the most critical sites do not always result in significant nail dystrophy. In the case of K16, point or deletion mutations in the helix boundary motifs can cause focal nonepidermolytic PPK (FNEPPK, MIM 600962), in which nail dystrophy is subtle or undetectable. Similarly, boundary peptide mutations in K17 may present as steatocystoma multiplex without pachyonychia (MIM 184500). Such variation might result from specific mutations which have more or less severe effects on tonofilament assembly. However, identical mutations may produce distinct effects in different individuals. For example, mutations predicting substitution of cystine for arginine at position 94 of K17 presented as steatocystoma multiplex or pachyonychia in different families. Thus, phenotype and severity depend on genetic background and environmental factors as well as the underlying mutation.

The 8-year-old child reported by Connors et al. apparently did not have keratoderma or oral lesions (as yet), and although there was extensive hyperkeratosis elsewhere, the presentation was complicated by lichenified atopic dermatitis. However, as noted above, disruptive mutations in helix initiation peptides of K16 and K17, respectively, can cause PPK or cysts in the absence of significant nail dystrophy, and one of 25 cases in a pedigree of typical PC-2 did not develop nail dystrophy until the age of 18 years (Kunkeler and Munro, unpublished data). Hence, it is premature to conclude from a single case that late onset of nail dystrophy is due to the site of the mutation. As Connors et al. recognize, more pedigrees of PC tarda need to be studied.

As with many other genetic disorders, identification
of the underlying keratin gene defects in PC has raised further questions. It is not clear why phenotype and age of onset may vary with the same mutation, and why mutations that are theoretically highly disruptive to filament assembly may in some subjects cause little disease. The fact that PC is almost always due to mutations in the most critical domains may reflect structural redundancy in keratins and associated proteins expressed at these highly stressed sites. Variation in severity may in part be due to polymorphism in ancillary components of the cytoskeleton. However, mutations in variable domains or internal parts of the rod domain of K6a/K16 or K6b/K17 presumably exist as often as they do in other keratins. If such mutations produce clinical disease at all, it is likely to be mild and variable, perhaps isolated nail dystrophy or a reduced threshold for plantar callosities or blistering. Only an awareness of the possibility of subtle familial phenotypes is likely to lead to their detection.

References


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