Clinical and Pathological Features of Pachyonychia Congenita

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Pachyonychia congenita (PC) is a rare genodermatosis affecting the nails, skin, oral mucosae, larynx, hair, and teeth. Pathogenic mutations in keratins K6a or K16 are associated with the PC-1 phenotype whereas K6b and K17 mutations are associated with the PC-2 phenotype. Analysis of clinical, pathological, and genetic data from the literature and two research registries reveal that >97% of PC cases exhibit fingernail and toenail thickening, and painful plantar keratoderma. Prospective evaluation of 57 PC patients from 41 families revealed variable clinical findings: hyperhidrosis (79%), oral leukokeratosis (75%), follicular keratosis (65%), palmar keratoderma (60%), cutaneous cysts (35%), hoarseness or laryngeal involvement (16%), coarse or twisted hair (26%), early primary tooth loss (14%), and presence of natal or prenatal teeth (2%). Stratification of these data by keratin mutation confirmed the increased incidence of cyst formation and natal teeth among PC-2 patients, although cysts were more commonly seen in PC-1 than previously reported (25%–33%). Previously unreported clinical features of PC include development of painful oral and nipple lesions during breastfeeding, copious production of waxy material in ears, and inability to walk without an ambulatory aid (50%). Possible pathogenic mechanisms are discussed with respect to the clinicopathologic and genetic correlations observed.

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Pachyonychia congenita (PC) is a rare, autosomal dominant keratin disorder that typically affects the nails and palmoplantar skin, and often the oral mucosa, tongue, larynx, teeth, and hair. Because of its rarity, the condition has been difficult to characterize or investigate, and no controlled prospective clinical trials have been published using this patient population. Our understanding of the clinical and pathological features of the disorder has been based upon case reports, a few case series, and some excellent reviews that have attempted to unify the case report literature (Kumer, 1935; Moldenhauer and Ernst, 1968; Schonfeld, 1980; Franzot *et al*, 1981; Stieglitz and Centerwall, 1983; Sivasundram *et al*, 1985; Feinstein *et al*, 1988; Su *et al*, 1990; Paller *et al*, 1991; Dahl *et al*, 1995). A comprehensive bibliography of PC, complete with translations of non-English articles, is available at http://www.pachyonychia.org. Unfortunately, many publications include photographs of dramatic or unusual manifestations of the condition and there is little discussion about the spectrum of clinical or pathological phenotypes that may be observed. This bias makes it extremely difficult for the average practitioner, who may only see one or two cases in an entire career, to be assured that they have made the correct diagnosis, especially in an individual without classic symptomatology.

History and classification of PC. The term *pachyonychia congenita* (Greek: thick nails from birth) was coined by Jadassohn and Lewandowski in 1906 and this case report is frequently quoted as the original description of the condition (Jadassohn and Lewandowski, 1906). But based on the descriptions and photographs of cases reported by Müller in 1904 and Wilson in 1905, it is likely that they were also describing PC (Müller, 1904; Wilson, 1905). Jan Bondeson has performed a comprehensive review of the medical history of PC (Bondeson, 1993). This paper provides compelling evidence that St George Ash described an Irish case of PC as early as 1685, and that the first reported case of PC-tarda was by the philosopher John Locke in 1695 (Ash, 1685; Locke, 1695). A doctoral dissertation in 1716 by Carl Musaeus on "monstrous nails" was apparently the first to postulate that the constellation of symptoms seen in PC represented a systemic disease called "morbus corneus" (Musaeus, 1716). The form of PC with widespread pilosebaceous cysts was first described in the recent literature by Jackson and Lawler (1951).

Abbreviations: H&E, hematoxylin and eosin; HIM, helix initiation motif; HTM, helix termination motif; IPCRR, International Pachyonychia Congenita Research Registry; NRIRD, National Registry for Ichthyosis and Related Disorders; PC, pachyonychia congenita

Prior to the discovery of the genetic basis of PC, several clinical classification schemes were proposed (Kumer, 1935; Schonfeld, 1980; Sivasundram *et al*, 1985; Feinstein *et al*, 1988; Dahl *et al*, 1995). A review of the modern literature by Feinstein *et al* (1988) summarized the majority of PC reports in the worldwide literature and discussed each of the major classification schemes proposed up to 1985. Based on these 168 cases of PC reported in the literature, Feinstein *et al* (1988) proposed a classification of PC into four overlapping subtypes which are frequently used in case reports. The literature was again reviewed in 1995 (Dahl *et al*, 1995), and simplified criteria were proposed in which the diagnosis of PC could be made when the characteristic nail changes (major criteria) occurred in association with at least one minor criterion (autosomal dominant inheritance, palmoplantar keratoderma, leukokeratosis oris, follicular keratosis, bullae on palms or soles, or laryngeal leukokeratosis). Unfortunately, classification of PC by purely clinical criteria was hindered by significant variability of the phenotype, even within affected members of the same family, a common feature of most or all keratin disorders (Irvine and McLean, 1999).

Clinical genetics of PC. A major advance in the capacity to classify PC came in 1995 when the genes encoding keratins K16 and K17 were identified as harboring the first genetic mutations underlying PC (McLean *et al*, 1995), following genetic linkage data showing a probable keratin defect (Munro *et al*, 1994). These findings were followed by identification of mutations in keratins K6a and K6b (the polymerization partners of K16 and K17) in additional PC families (Bowden *et al*, 1995; Smith *et al*, 1998). To date, over 82 mutations in these four keratins have been identified in independently ascertained families (Fig 1 and Smith *et al*, this issue). Nearly all the reported mutations occur at either the start or the end of the central keratin rod domain. These regions are known as the helix boundary motifs of the keratin polypeptide, or, individually, the helix initiation motif (in the 1A domain) and the helix termination motif (in the 2B domain). As discussed elsewhere in this issue (Smith *et al*, McLean *et al*), these regions are critically important for end-to-end association of protein subunits in the assembly of keratin filaments and, furthermore, represent mutation hotspots in all keratin genes so far associated with human disease phenotypes.

In the genetic studies described above, the phenotypic classification of PC families into two major subtypes emerged, termed as PC-1 (or the Jadassohn–Lewandowski type) and PC-2 (or the Jackson–Lawler type) based on early clinical descriptions (Jadassohn and Lewandowski, 1906; Jackson and Lawler, 1951). The most prominent clinical feature of both PC subtypes is hypertrophic nail dystrophy. Specifically, the nail changes in PC consist of three abnormal findings: hyperkeratosis of the nail bed; thickening of the nail plate; and distortion or curvature of the nail plate. Importantly, both PC types also show variable degrees of a focal palmoplantar keratoderma with accentuation in weight-bearing or traumatized areas. Both PC-1 and PC-2 patients sometimes develop follicular keratoses of the elbows, knees, and hips. The clinical discrimination between PC-1 and PC-2 usually depends on more prominent oral leukokeratosis in PC-1, or, conversely, in findings of steatocystomas/pilosebaceous cysts, vellus hair cysts, hair abnormalities (alopecia, *pili torti* (twisted hair)), and natal teeth in PC-2. The occurrence of natal teeth appears to be diagnostic of PC-2, but, unfortunately, this feature is not fully penetrant, i.e., not all PC-2 patients present with natal teeth. The PC-1 clinical phenotype is associated with mutations in K6a and K16 whereas the PC-2 phenotype is associated with mutations in K6b and K17. The major phenotypic differences between the two types are clearly correlated with known differences in the expression ranges of these two pairs of keratins (Lane, 1993). A delayed onset, or tarda subtype of both PC-1 and PC-2 has also been described and keratin mutations associated with PC-tarda have been found outside the helix boundary motif regions of the K16 and K17 proteins (Connors *et al*, 2001; Xiao *et al*, 2004). It is tempting to speculate that the tarda phenotype occurs because these mutations are not so disruptive to keratin assembly (see McLean *et al*, this issue), but additional cases will be necessary to confirm this hypothesis. Despite the incomplete information available regarding the mechanistic details, practitioners can now confirm clinical suspicion of PC by mutation testing.

As genetic testing of PC patients is becoming more common, the complexity of the relationship between the keratin mutation status and the clinical phenotype also becomes more obvious (Munro, 2001). Mutations within the same functional domain of the keratins produce variable clinical manifestations, and even patients with the same mutation sometimes display different levels of severity and different clinical spectra. For example, the same mutation in K17 gives rise to the full PC-2 phenotype in some families and to steatocystoma multiplex without nail changes in others (Smith *et al*, 1997; Covello *et al*, 1998). Similarly, mutations in the helix initiation motif of K16 can produce a full-blown PC-1 presentation (Smith *et al*, 1999a, b; 2000) or just focal non-epidermolytic palmoplantar keratoderma in other cases (Shamsher *et al*, 1995). The variability of phenotype and incomplete penetrance seen in PC strongly suggests that genetic and/or environmental modifier effects are modulating the genotype–phenotype relationship. Comprehensive investigation of these genotype–phenotype–environment interactions in PC may ultimately provide clinically relevant clues to the pathogenesis and optimal treatment of the disease. Thus, the goals of this paper are to provide the medical community with a comprehensive review of the clinical and pathological spectrum seen in PC, report new prospective data on a cohort of 57 PC participants, correlate the clinical findings of PC patients with their genetic mutation status, and provide clinicians with a user-friendly summary of genetic test results seen in PC.

Results

Literature review and analysis of PC cases Three sources of cases were evaluated: cases in the literature, cases from the International Pachyonychia Congenita Research Registry (IPCRR), and cases from the National Registry for Ichthyosis and Related Disorders (NRIRD). A comprehensive literature review revealed a total of 198 articles containing 457 independent cases of PC from 214 different