Revisiting pachyonychia congenita: a case cohort study in 815 patients

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Introduction

- Pachyonychia congenita (PC) is a group of autosomal dominant disorders caused by mutations in one of 5 keratin genes (*KRT6A*, *KRT6B*, *KRT6C*, *KRT16*, or *KRT17*) encoding keratins 6a, 6b, 6c, 16 and 17.
- The most common clinical features of PC (Figure 1) are thickened toenails, palmoplantar keratoderma, epidermal inclusion cysts (mostly steatocystomas and vellus hair cysts), mucosal leukokeratoses, hoarse voice and natal teeth.
- The establishment of an international registry containing both clinical and molecular data led to the development of a disease classification based on the mutant gene and associated features.
- Here we harness the same resource to clarify the prevalence of PC-associated clinical features, delineate phenotype-genotype correlations and identify prognostic features for disease severity.

Figure 1. Clinical phenotype in genetically-confirmed PC patients (a) Fingernail involvement with subungual hyperkeratosis, fingernail elevation and premature termination of nail plate; (b) Diffuse yellowish hyperkeratotic plantar plaques; (c) Focal palmar keratoderma; (d) Oral leukokeratosis over the tongue; (e) Steatocystoma multiplex lesions.

Material and methods

- 815 individuals with confirmed keratin mutations registered in the International Pachyonychia Congenita Research Registry (IPCRR) were surveyed for clinical findings associated with PC.
- Data were analyzed using various statistical methods including Student T-test, Chi-Square and ANOVA tests for differences in means/proportions. Spearman correlation and logistic regression were used for phenotype-genotype correlations.

Results

Patients characteristics	
	Median; range
Patients' age at evaluation (years)	30; 0-87
	Number of patients (%)
Male: female	388 (48%):427 (52%)
Mutated gene	
<i>KRT6A</i>	332 (41%)
<i>KRT16</i>	251 (31%)
<i>KRT17</i>	134 (16%)
<i>KRT6B</i>	74 (9%)
<i>KRT6C</i>	24 (3%)
Mutation type	
Spontaneous:Inherited	249 (31%):566 (69%)

Table 1: Epidemiologic and molecular characteristics of the cohort

Phenotypic features of PC

- Toenail and fingernail dystrophy were evident in 96% and 75% of cases, respectively, while all 20 nails were involved in 50% of cases. More than 50% of cases demonstrated nails involvement during the first year of life.
- Plantar and palmar keratoderma were reported in 94% and 70% of cases, respectively, and in 60% of cases plantar keratoderma was evident by 4 years of age.
- Oral leukokeratosis, natal teeth and hoarseness were reported in 54%, 14% and 24% of cases, respectively, with the former being evident by 1 year of age in 60%. Cysts were evident in 54% of cases.
- Ear wax, ear pain and impaired sweating were reported in 28%, 14% and 50% of cases, respectively. 26% reported emotional impairments with depression/mood changes being most common. Hearing loss, eye anomalies and hair abnormalities were relatively rare in our cohort and accordingly are probably not directly related to the disease.

Results – cont.

Effect of PC-associated clinical manifestations on quality of life

Plantar keratoderma is the clinical feature associated with the most significant effect on daily function (Table 2). More than 65% of patients with plantar involvement indicate the persistent effect of this finding which is associated with significant pain in more than 60% of patients. Other PC-associated clinical features were not associated with a significant effect on quality of life or pain.

Impact on QoL	Plantar keratoderma	Palmar keratoderma	Fingernail dystrophy	Toenail dystrophy	Oral leukokeratosis	Cysts
No impact	55/628 (8.7%)	268/514 (52.1%)	168/539 (31.1%)	187/668 (28%)	182/287 (63.4%)	146/386 (37.8%)
Sometimes a problem	148/628 (23.6%)	175/514 (34%)	269/539 (49.9%)	320/668 (47.9%)	88/287 (30.7%)	180/386 (46.6%)
Always a problem, able to function	391/628 (62.3%)	66/514 (12.9%)	95/539 (17.6%)	150/668 (22.7%)	17/287 (5.9%)	52/386 (13.5%)
Impossible to function	34/628 (5.4%)	5/514 (1%)	7/539 (1.3%)	9/668 (1.4%)	0/287 (0%)	8/386 (2.1%)
Associated pain						
Not painful	42/739 (5.7%)	260/515 (50.5%)	NA	NA	197/269 (73.2%)	155/384 (40.4%)
Sometimes painful	201/739 (27.2%)	202/515 (39.2%)	NA	NA	69/269 (25.7%)	149/384 (38.8%)
Very painful no need for medications	314/739 (42.5%)	25/515 (4.9%)	NA	NA	2/269 (0.7%)	45/384 (11.7%)
Often requires medications	182/739 (24.6%)	28/515 (5.4%)	NA	NA	1/269 (0.4%)	35/384 (9.1%)

Table 2: Major PC clinical features impact on quality of life and pain. QoL - quality of life

Phenotype-genotype correlations

- KRT6A* mutations are associated with youngest age or highest number of fingernails/toenails involvement, oral leukokeratosis and hoarseness while *KRT17* mutations are most commonly associated with cysts and natal teeth (Table 3).
- Plantar keratoderma was common among all PC patients regardless of the causative mutation; however palmar keratoderma was most common with *KRT16* mutations (Table 3).
- Lack of fingernail involvement was most commonly associated with mutations in *KRT16* and *KRT6B* (57% and 19%, respectively).

Mutated gene	Toenail dystrophy	Fingernail dystrophy	Keratoderma	Mucosal/teeth involvement	Cysts
<i>KRT6A</i>	98% Age of onset (y): 1.2 Mean#: 9.6	98% Age of onset (y): 1.1 Mean#: 9.3	Plantar: 93% Palmar: 66%	Leukokeratosis 88.3% Natal teeth 3.3% Hoarseness 38.9%	60.2%
<i>KRT6B</i>	99% Age of onset (y): 2.8 Mean#: 7	46% Age of onset (y): 3.5 Mean#: 2.4	Plantar: 99% Palmar: 50%	Leukokeratosis 24.3% Natal teeth 0% Hoarseness 18.9%	67.6%
<i>KRT6C</i>	62% Age of onset (y): 3.2 Mean#: 1.6	0% Age of onset (y): NA Mean#: 0	Plantar: 100% Palmar: 41%	Leukokeratosis 21.7% Natal teeth 4.2% Hoarseness 18.2%	17.4%
<i>KRT16</i>	96% Age of onset (y): 2.9 Mean#: 6.7	57% Age of onset (y): 3 Mean#: 4.1	Plantar: 99% Palmar: 86%	Leukokeratosis 35.6% Natal teeth 0% Hoarseness 8.1%	25.6%
<i>KRT17</i>	95% Age of onset (y): 1.4 Mean#: 8.6	85% Age of onset (y): 1.4 Mean#: 6.9	Plantar: 83% Palmar: 62%	Leukokeratosis 26.3% Natal teeth 77.3% Hoarseness 22%	91.8%

Table 3: Phenotype-genotype correlation

Predictors of clinical outcomes

- Using logistic regression models, increased number of affected toenails and earlier age of toenails involvement predicted fingernail dystrophy while increased number of affected fingernails correlated with toenails involvement ($p < 0.0001$).
- Earlier onset of toenails involvement correlated with plantar keratoderma ($p < 0.01$) while fingernail dystrophy age of onset and walking aids use predicted palmar keratoderma ($p < 0.05$).
- Oral leukokeratosis correlated with earlier toenail involvement ($p < 0.0001$), walking aids, nursing difficulties and hoarseness ($p < 0.05$).
- Natal teeth and oral leukokeratosis were inversely correlated whereas natal teeth and cysts significantly predicted each other's development.

Conclusions

- Here, we establish phenotype-genotype correlations in the largest cohort of PC patients described to date and reveal novel and clinically useful predictors of disease course and manifestations.

References

- Eliaison et al, J Am Acad Dermatol, 2012; 67: 680-686.
- Wilson et al, J Invest Dermatol, 2010; 130, 425-429
- Smith et al, Hum Mol Genet, 1998; 7: 1143-1148.
- McLean et al, Nat Gnet, 1995; 9:273-278
- Bowden et al, Nat Genet, 1995; 10: 363-365.
- Paller et al, Arch Dermatol, 1991; 127: 701-703.