RESEARCH LETTER

Prevalence and Patient Characteristics of Pachyonychia Congenita

Pachyonychia congenita (PC) is a rare genetic skin disease characterized by a triad of palmoplantar keratoderma, plantar pain, and hypertrophic nail dystrophy.[1,2] PC is an autosomal dominant disorder caused by pathogenic variants in *KRT6A*, *KRT6B*, *KRT6C*, *KRT16*, and *KRT17* genes.[3,4] Nationwide population-based studies on the epidemiological features of PC, including prevalence, are lacking.

Supplemental content

Methods | In this cross-sectional study, we identified a nationwide registry-based PC cohort in Denmark from January 1, 1995, to August 25, 2021. We searched the Danish National Patient Registry for patients registered with the diagnosis code Q84.5D for PC in the Danish version of the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*. Medical records were obtained for diagnosis validation and characterization. Patients with genetically confirmed PC were included. Those with clinically suspected PC but no genetic confirmation were included as possible cases. Patients with no medical records available were excluded. We estimated the positive predictive value (PPV) of the Q84.5D diagnosis code, PC prevalence, and distribution of patient characteristics. The Danish Data Protection Agency and Central Denmark Region approved this study. Central Denmark Region waived informed consent requirement and granted access to medical records data in accordance with the Danish Health Care Act. Written informed consent was obtained for clinical photographs (**Figure**). We followed the STROBE reporting guideline. Details are provided in the eMethods in Supplement 1.

Results | We identified 22 patients registered with PC (12 females [54.5%], 10 males [45.5%]; median [IQR] age, 29 [3-39] years), of whom 21 (95.5%) had available medical records. Twelve patients had genetically confirmed PC (PPV, 57.1%; 95% CI, 36.5%-75.5%) and 2 had possible PC, resulting in a cohort of 14 cases (PPV, 66.7%; 95% CI, 45.4%-82.8%). Coding validity was higher in dermatological (13 of 16 registered cases; PPV, 81.3%; 95% CI, 57.9%-93.4%) than nondermatological (1 of 5 registered cases; PPV, 20.0%; 95% CI, 3.6%-62.4%) departments.

We estimated a point prevalence of 2.1 per 1 000 000 (95% CI, 1.2-3.6 per 1 000 000) for genetically confirmed PC and 2.4 per 1 000 000 (95% CI, 1.4-4.0 per 1 000 000) including possible cases. Birth prevalence of genetically confirmed PC was 3.0 per 1 000 000 (95% CI, 1.2-7.7 per 1 000 000) live births from 1995 to 2015. Patient characteristics are shown in the **Table**. Genetically confirmed cases had a median (IQR) age at diagnosis of 29.8 (2.7-34.3) years, and 7 were female (58.3%). Main features included palmoplantar keratoderma (12 [100%]), nail dystrophy (9 [75.0%]), and steatocystoma multiplex (3 [25.0%]). Pathogenic variants identified were *KRT6A*, *KRT16*, and *KRT17*.

Discussion | We estimated a point prevalence of genetically confirmed PC of 2.1 per 1 000 000 Danish residents and a birth prevalence of 3.0 per 1 000 000 live births. Occurrence of PC has been poorly investigated.[5] One prevalence estimate of 0.9 cases per 1 000 000 people seemed to stem from the International Pachyonychia Congenita Research Registry (IPCRR), dividing the number of patients registered in Western countries by their combined population size.[6] IPCRR represents a major effort in PC research; as of January 2024, IPCRR included 2702 patients with PC from 53 countries (7 from Denmark) and 1186 with genetic confirmation.[5] Missing cases in IPCRR may, however, precede underestimation of true prevalence. Unclear population denominators may further add to this bias.

Study strengths include a nationwide cohort representation and a high validation rate (95.5%). Most identified patients had genetic confirmation (12 of 14 [85.7%]). Still, validity could have been enhanced if all patients had genetic testing. Study limitations include the low numbers underlying the estimates, resulting in wide CIs and the possibility of undiagnosed patients

Figure. Clinical Characteristics of Pachyonychia Congenita in a Patient With a *KRT6A* Variant

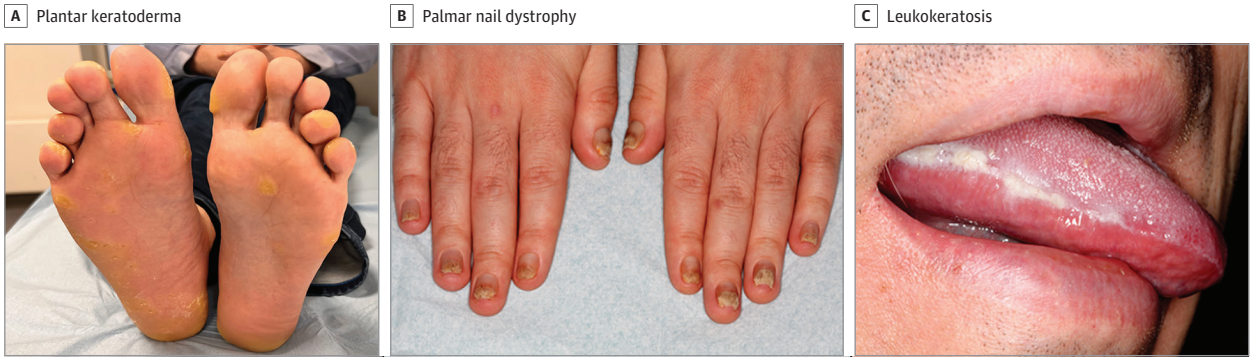

Table. Clinical and Genetic Characteristics of 14 Patients With Genetically Confirmed or Possible Pachyonychia Congenita

Characteristics	Cases, No. (%)	
	Genetically confirmed (n = 12)	Genetically confirmed and possible (n = 14)
Age at diagnosis, median (IQR), y	29.8 (2.7-34.3)	30.6 (3.2-39.5)
Sex		
Male	5 (41.7)	6 (42.9)
Female	7 (58.3)	8 (57.1)
Clinical characteristics		
Palmoplantar keratoderma	12 (100)	14 (100)
Nail dystrophy, including pachyonychia	9 (75.0)	10 (71.4)
Steatocystoma multiplex	3 (25.0)	4 (28.6)
Fragile hair	2 (16.7)	3 (21.4)
Natal teeth	2 (16.7)	2 (14.3)
Palmoplantar hyperhidrosis	1 (8.3)	1 (7.1)
Leukoplakia	1 (8.3)	1 (7.1)
Genetics		
KRT6A	6 (50.0)	6 (43.0)
KRT16	1 (8.3)	1 (7.0)
KRT17	3 (25.0)	3 (22.0)
Tested but result unavailable	2 (16.7)	2 (14.0)
Not tested	NA	2 (14.0)

Abbreviation: NA, not applicable.

or inappropriately registered patients. Thus, true PC prevalence is likely to be higher.

We identified a nationwide registry-based cohort of PC. We used this cohort to provide, to our knowledge, the first population-based prevalence estimates for this disease, which are higher than previously reported.

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Author Contributions: Dr Herlin had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Herlin, Schmidt, Sommerlund.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Andersen, Herlin.
Critical review of the manuscript for important intellectual content: Herlin, Schmidt, Sommerlund.
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1. Mccarthy RL, De Brito M, O'toole E. Pachyonychia congenita: clinical features and future treatments. *Keio J Med*. 2023. doi:10.2302/kjm.2023-0012-IR

2. Eliason MJ, Leachman SA, Feng BJ, Schwartz ME, Hansen CD. A review of the clinical phenotype of 254 patients with genetically confirmed pachyonychia congenita. *J Am Acad Dermatol*. 2012;67(4):680-686. doi:10.1016/j.jaad.2011.12.009

3. Smith FJD, Hansen CD, Hull PR, et al. Pachyonychia congenita. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. *GeneReviews*. University of Washington; 2024.

4. McLean WH, Hansen CD, Eliason MJ, Smith FJ. The phenotypic and molecular genetic features of pachyonychia congenita. *J Invest Dermatol*. 2011; 131(5):1015-1017. doi:10.1038/jid.2011.59

5. Pachyonychia Congenita Project. PC data: pachyonychia congenita genes & mutations. Accessed April 2, 2024. https://www.pachyonychia.org/pc-data/

6. Wallis T, Poole CD, Hoggart B. Can skin disease cause neuropathic pain? a study in pachyonychia congenita. *Clin Exp Dermatol*. 2016;41(1):26-33. doi:10.1111/ced.12723