Research letter

Genotype-phenotype correlations of neurovascular structures on the feet in patients with pachyonychia congenita: A cross-sectional study

To the Editor: Pachyonychia congenita (PC) is a rare skin disorder caused by an autosomal dominant mutation in 1 of 5 keratin genes. In the diagnostic triad of PC, plantar pain has the most significant impact on the quality of life.[1,2] A potential contributor to this pain is the development of putative neurovascular structures (NVSs), previously referred to as "capillary thromboses," a feature identified through a patient-focused drug development meeting with the Food and Drug Administration.[3] NVSs in patients with plantar keratoderma are characterized by 1-2—mm blood-red or dark-red spots, occurring alone or in clusters, with associated extreme pain, suggesting the presence of an adjacent nerve. NVSs may also bleed while paring calluses and can fluctuate in size. NVSs are bigger than the capillary thromboses seen in verrucae and do not have a verrucous surface. Understanding the prevalence of NVSs, their association with PC genotype, and their impact on the quality of life will be important in improving the future management of PC.

Individuals enrolled in the International PC Research Registry,[4] a global registry of genetically confirmed PC patients, were administered an online survey developed by physicians in the Pachyonychia Congenita Project in September 2019 (Supplementary Appendix 1, available via Mendeley at https://data.mendeley.com/datasets/bkkpcbfb62/1) after they received education about NVSs' typical appearance aided by photographs (Fig 1). The study gained ethical approval from the Western Institutional Review Board (#1057496; protocol #20040468). Differences between groups were analyzed using the χ^2 test for frequency data and the Kruskall-Wallis test for ordinal scales. Logistic regression analyses were also performed. Statistical analyses were conducted using R (v.3.5.1) and SPSS 24.0 (IBM Corp).

There were 281 responses (response rate, 37.2%). NVSs were present in 62.3% (mean age, 47.4 ± 16.5 years; 62.3% were women) of the patients, and majority reported that NVSs increased their plantar pain (64.6%). The NVS prevalence varied by PC genotype (PC-K6a, 57.7%; PC-K6b, 77.8%; PC-K6c, 50.0%; PC-K16, 73.1%; and PC-K17, 36.1%; $P < .0005$, χ^2 test). The regression analysis showing genotype predictors of NVS is shown in Table I. Extra pain and difficulty trimming calluses were the most common ways in which NVSs impacted daily life (62.3%) (Supplementary Table I, available via Mendeley at https://data.mendeley.com/datasets/bkkpcbfb62/1).

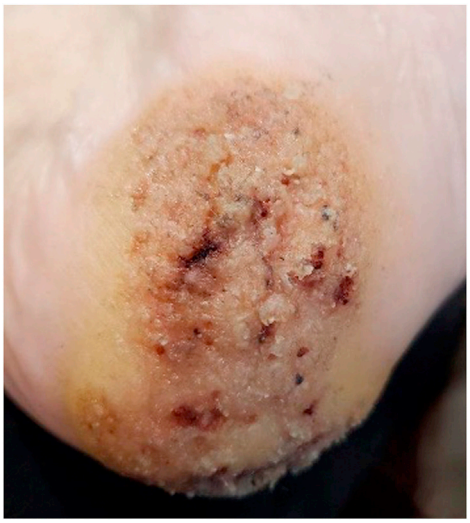

Fig 1. Neurovascular structures in a callus in a patient with pachyonychia congenita.

The patients were significantly more likely to have difficulty wearing socks if they had PC-K6a ($P < .01$) and shoes if they had PC-K17 ($P < .001$). PC-K6a and PC-K17 have been reported to be more severely affected by neuropathic pain than the other PC genotypes, with increased sensitivity in the patients' feet, as detected using quantitative sensory testing, severe pain on walking, and the poorest quality of life.[5] Our findings highlighted that the consideration of footwear may be particularly important in patients with these genotypes.

There is currently no approved effective treatment for PC, which is generally managed symptomatically by paring calluses. Rapamycin was recently identified as a viable treatment option because it led to the resolution of "cutaneous thromboses" in an off-label study.[3]

The limitations include reliance on patient self-reporting and the fact that the questions were limited only to those with NVSs. Mutation analyses were limited to PC-K6a and PC-K16 because of the limited sample size (Supplementary Appendix 2; Supplementary Tables II and III). A potential bias may have been introduced by the incomplete response rate. However, the respondents' genotypes

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Table I. Genetic predictors of the presence of neurovascular structures*

PC genotype	β	SE	Unadjusted OR (95% CI)	*P* value	β	SE	Adjusted OR (95% CI)‡	*P* value
K16†	1.00	0.22	2.71 (1.78-4.26)	.000006	−0.22	0.39	0.81 (0.37-1.73)	.578
K6a	−0.69	0.30	0.50 (0.28-0.91)	.02	−0.53	0.32	0.59 (0.31-1.09)	.09
K6b	0.25	0.51	1.29 (0.49-3.81)	.62	0.30	0.56	1.35 (0.48-4.46)	.59
K6c	−1.00	0.62	0.37 (0.11-1.27)	.11	−1.24	0.67	0.29 (0.07-1.08)	.06
K17	−1.57	0.41	0.21 (0.09-0.46)	.0001	−1.48	0.43	0.23 (0.095-0.52)	.0006

OR, Odds ratio; β, regression coefficient.
*$P < .05$ was considered statistically significant. The full list of mutations within each pachyonychia congenita genotype is presented in Supplementary Table V.
†Intercept - the reference group (β_0).
‡Age/sex adjusted.

were proportional to the International PC Research Registry[4] (Supplementary Table IV). Our study is the first and largest on NVS genotype-phenotype correlations and provides further information on the understanding of PC and the development of mutation-specific treatments.

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Conflicts of interest

Professor O'Toole has received funding for the university from Palvella Therapeutics (consultancy), Timber Pharma (consultancy), and Kamari Pharma (research grant and consultancy). Dr Hansen has received support from Palvella as a principal investigator for a clinical study in pachyonychia. Drs Tan, Steele and Thomas and Ms Schwartz have no conflicts of interest to declare.

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