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Prevalence and Characterization of Itch in Pachyonychia Congenita

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This survey study examines the prevalence and characteristics of itch in pachyonychia congenita.

Pachyonychia congenita (PC) is a group of autosomal dominant disorders that are caused by variants in 1 of 5 keratin genes. Itch is not well recognized as a clinical finding of PC[1] but is anecdotally reported by patients. To assess the prevalence and characteristics of itch in PC, we surveyed participants from the International Pachyonychia Congenita Research Registry (IPCRR).

Methods

The IPCRR is a global registry of individuals with genetically confirmed PC (https://www.pachyonychia.org/patient-registry/).[1] All patients give written informed consent for participation. The IPCRR and this individual study were approved by the WCG institutional review board. A questionnaire was sent to 756 registered participants in IPCRR on September 20, 2019, with 2 subsequent reminders. This included a modified 11-item Leuven Itch Scale[2] with surface area questions adapted to PC (eAppendix in the Supplement). Statistical significance was set at $P < .05$. The χ^2 test was performed to assess for significant differences in the prevalence of itch during the past month by (1) PC genotype and (2) the location/domain of the keratin variant (head, central rod, or tail). Itch subscale scores were calculated according to the Leuven Itch Scale manual 2.0,[2] and data analysis was performed using SPSS, version 25 (IBM).

Results

There were 281 responses (37.2% response rate). Patient demographic characteristics are listed in the Table. Itch attributed to PC was experienced by 192 of 281 participants (68.3%), and during the past month by 144 of 281 participants (51.2%).

Itch most frequently affected the feet at callus sites (Figure). Itch was described as tickling (45 [31.3%]), burning (41 [28.5%]), prickling (38 [26.4%]), and tingling (10 [6.9%]). By subscale, itch frequency had the highest score and itch consequence had the lowest score, although scores were highly variable (Figure). Itch frequency was reported as always (9 [6.3%]), at least daily (33 [22.9%]), at least weekly (68 [47.2%]), and at least monthly (32 [22.2%]). Itch during the past month was significantly associated with PC genotype (*KRT16*, 66 of 104 [63.5%]; *KRT6a*, 52 of 97 [53.6%]; *KRT6b*, 11 of 27 [40.7%]; *KRT17*, 12 of 36 [33.3%]; *KRT6c*, 2 of 12 [16.7%]; $P = .001$) and keratin domain affected (head, 8 of 8 [100%]; 1A, 113 of 207 [54.6%]; 2B, 21 of 56 [37.5%]; 1B, 0; tail, 0; $P = .002$) (Table).

Discussion

In a large cohort of genetically confirmed cases of PC, we examined the prevalence and characteristics of itch in PC for, to our knowledge, the first time, finding that approximately half of participants had experienced itch during the past month. Itch was not usually a daily symptom, and itch consequence scores were generally low; thus, it may be underreported compared with more overt or troubling features of the disease, such as plantar pain. The limitations included an English-language survey, a predominantly North American/European population, and a reliance on patient self-reporting. The incomplete response rate (37.2%) may also result in responder bias from participants with itch being more likely to respond, which may have overestimated itch prevalence. However, the high prevalence of itch that was observed in 281 individuals, together with its biological plausibility, suggest that it is a real phenomenon.

We propose 2 considerations for biological plausibility. First, itch may be neuropathic. A neuropathic element to pain is recognized in PC,[3] including structural changes in peripheral nerve structures on biopsy specimens.[3] A spectrum between neuropathic itch and neuropathic pain is proposed that ranges from stinging itch to itching burn[4]; in this study, more than half of patients reported itch sensation as burning or prickling. Second, itch could arise secondary to keratin abnormalities and inflammation. Itch predominantly affected callus sites, and the recognition that keratinocytes can directly release pruritogens, such as thymic stromal lymphopoietin, is a relatively recent advance in itch biology.[5]Thymic stromal lymphopoietin has been implicated in itch in epidermolysis bullosa simplex,[6] in which variants occur in keratins 5 and 14. Elevated thymic stromal lymphopoietin levels are also observed in *Krt16*$^{-/-}$ mice,[7] and patients with PC-*KRT16* had the highest prevalence of itch in this study.

Notes

Supplement.

eAppendix

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Figures and Tables

Table.

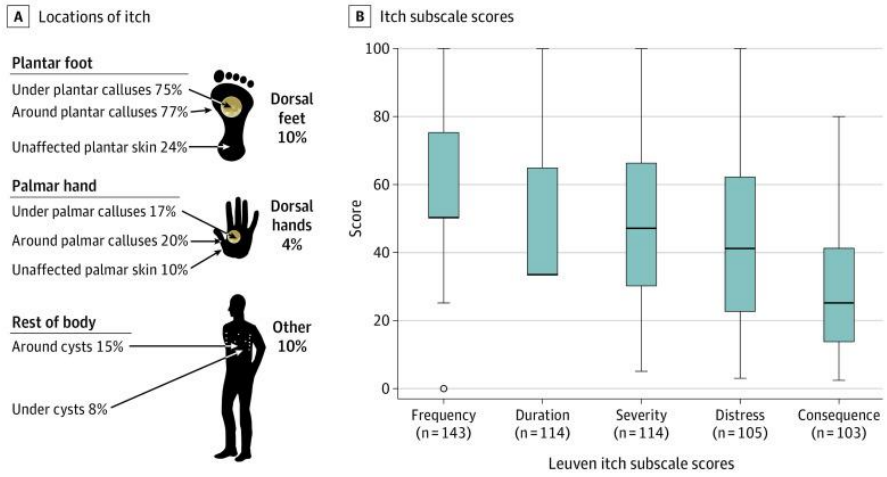
Baseline Demographic Characteristics of Participants and Prevalence of Itch by Keratin Variant and Keratin Domain Affected

Characteristic	No. (%)	
	Responders	Nonresponders
No.	281	475
Sex		
Male	104 (37)	235 (49)
Female	176 (63)	239 (50)
Not stated	1 (0)	1 (0)
Variant		
KRT6A	97 (35)	191 (40)
KRT6B	27 (10)	46 (10)
KRT6C	12 (4)	15 (3)
KRT16	104 (37)	152 (32)
KRT17	36 (13)	71 (15)
Incomplete	5 (2)	0
Keratin domain affected[a]		
Head	8 (3)	16 (3)
Tail	2 (1)	2 (0)
Rod	265 (94)	457 (96)
1A	207 (74)	343 (72)
1B	2 (1)	1 (0)
2A	0	0
2B	56 (20)	113 (24)
Not stated	6 (2)	0
Continent		
North America	158 (56)	257 (54)
Europe	97 (35)	165 (35)
South America	10 (4)	17 (4)
Asia	8 (3)	21 (4)
Australasia	7 (2)	10 (2)
Africa	1 (0)	5 (1)
Age, mean (SD), y	43 (20)	38 (19)

[a] Keratin domain refers to the location of the variant in the keratin structure. Keratins are intermediate filament proteins with a long central α-helical rod domain (composed of 1A, 1B, 2A, and 2B segments) that is flanked by head and tail end domains. The domain affected was determined by matching the location of the variant to the keratin structure using the Human Intermediate Filament Database (http://www.interfil.org/).

[b] The χ^2 test was used to assess for significant differences in the prevalence of itch during the past month between groups of pachyonychia congenita genotype and the location/domain of the keratin variant.

Figure.



Locations of Itch in Participants With Pachyonychia Congenita and Itch Subscale Scores