Prevalence and characterisation of itch in pachyonychia congenita

Running head

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INTRODUCTION

Pachyonychia congenita (PC) is a group of autosomal dominant disorders caused by mutations in one of five keratin genes. Itch is not well-recognised 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).

METHODOLOGY

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 (study # 20040468) and this individual study (study #1047496) were approved by the WCG IRB. A questionnaire was sent to 756 registered participants of the IPCRR on September 20, 2019, with two subsequent reminders. This included a modified 11-item Leuven Itch Scale (LIS)[2] with surface area questions adapted to PC (Appendix S1). The χ^2 test was performed to assess for significant differences in the prevalence of itch in the past month by 1) PC genotype and 2) the location/domain of the keratin mutation (head, central rod, or tail). Itch subscale scores were calculated according to the LIS manual 2.0[2] and data analysis was performed using SPSS 25.

RESULTS

There were 281/756 responses (37.2% response rate). Patient demographics are listed in Table 1. Itch attributed to PC had been experienced by 192/281 participants (68.3%), and in the past month by 144/281 (51.2%) participants.

Itch most frequently affected the feet at callus sites (Figure 1). Itch was described as tickling (31.3%), burning (28.5%), prickling (26.4%), and tingling (6.9%). By subscale, itch frequency had the highest score and itch consequence had the lowest score, although scores were highly variable (Figure 1). Itch frequency was reported as always (6.3%), at least daily (22.9%), at least weekly (47.2%), and at least monthly (22.2%).

Itch in the past month was significantly associated with PC genotype (P=0.001) and keratin domain affected (P=0.002), being most prevalent for *KRT16* mutations (63.5%) and mutations affecting the head domain (100%) (Table 1).

DISCUSSION

In a large cohort of genetically confirmed cases of PC, we report on the prevalence and characteristics of itch in PC for the first time, finding that approximately half of participants had experienced itch in the past month. Itch was not usually a daily symptom and itch consequence scores were generally low, and thus it may be under-reported compared to more overt or troubling features of the disease such as plantar pain.

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 observed in 281 individuals, together with its biological plausibility, suggest that it is a real phenomenon.

We propose two considerations for biological plausibility. Firstly, itch may be neuropathic. A neuropathic element to pain is recognised in PC,[3] including structural changes in peripheral nerve structures on biopsy specimens.[3] A spectrum between neuropathic itch and neuropathic pain is proposed - ranging from “stinging itch” to “itching burn” -[4] and in this study, more than half of patients reported itch sensation as burning or prickling. Secondly, 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 (TSLP), is a relatively recent advance in itch biology.[5] TSLP has been implicated in itch in epidermolysis bullosa simplex (EBS),[6] where mutations affect keratins 5 and 14. Elevated TSLP levels are also observed in *Krt16*$^{-/-}$ mice,[7] and PC-*KRT16* patients had the highest prevalence of itch in our study.

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TWEET

Itch is reported anecdotally in pachyonychia congenita (PC) but is not a well-recognised symptom. We surveyed 281 individuals with genetically-confirmed PC to assess prevalence and discuss potential aetiological mechanisms.

ACKNOWLEDGEMENTS

We thank Philip Moons for kindly providing permission to use the Leuven Itch Scale and its accompanying coding convention in this study. We are grateful to patients in the International PC Research Registry (IPCRR) for their participation and members of the Pachyonychia Congenita Project Medical and Scientific Advisory Board for their guidance and interest in studying itch and PC, and Holly Evans of PC Project for her assistance with data preparation. We also acknowledge PC project who initiated and funded the IPCRR.

FUNDING

The IPCRR is supported by PC Project, a US-based charity.

Conflict of interest statement

LS declares no conflict of interest.

EOT has received funding (research and/or consultancy), which went to the university, from Kamari Pharma and Palvella Therapeutics who are working on treatments for palmoplantar keratoderma.

CDH has received support from Palvella as a PI for a clinical study in Pachyonychia.

JS declares no conflict of interest.

Data Access, Responsibility, and Analysis

LS had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

Ethical approval

Not applicable

Data sharing

Anonymised data of prevalence of itch and itch subscale scores can be provided.

Contributor statement

EOT, JS, and CDH contributed to study conception. Data acquisition was performed by the PC Project administrative staff. LS performed analysis and first draft preparation. All authors were involved in revising the work and final approval. All agree to be accountable for the work.

ABBREVIATIONS

IPCRR = International Pachyonychia Congenita Research Registry

LIS = Leuven Itch Scale

PC = Pachyonychia Congenita

SD = Standard Deviation

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FIGURE LEGEND

Figure 1. (A) Locations of itch in participants with pachyonychia congenita. (B) Itch subscale scores

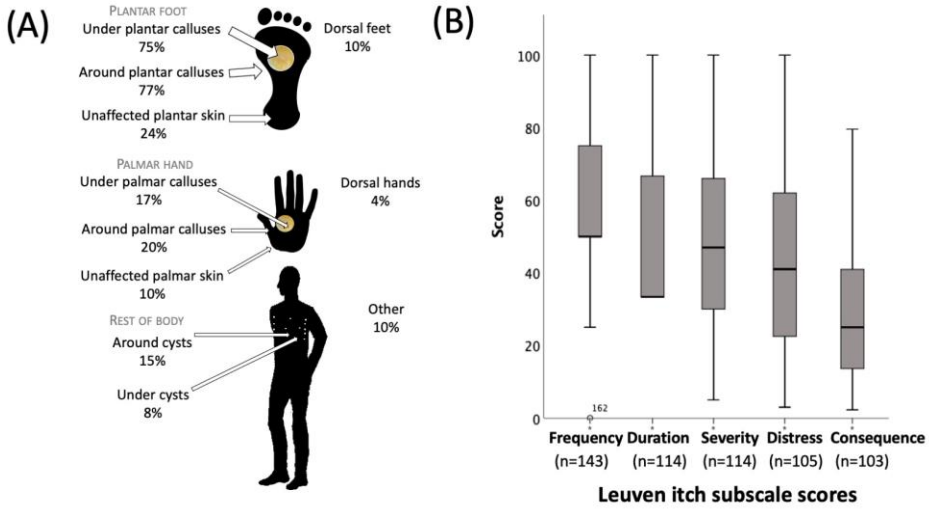

Table 1. Baseline demographics of participants and prevalence of itch by keratin mutation and keratin domain affected.

Baseline demographics	***Responders (n=281)*** *No. (%)*	***Non-responders (n=475)*** *No. %*
Gender		

Male	104 (37%)	235 (49%)
Female	176 (63%)	239 (50%)
Not stated	1 (0%)	1 (0%)
Mutation		
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%)
Rod 1A	*207 (74%)*	*343 (72%)*
Rod 1B	*2 (1%)*	*1 (0%)*
Rod 2A	*0*	*0*
Rod 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))	43 (±20)	38 (±19)

Itch prevalence by keratin mutation and domain affected[a]

Mutation	***Itch in past month*** *No. (%)*	**P-value**[b]
KRT6A	52 (53.6%)	
KRT6B	11 (40.7%)	
KRT6C	2 (16.7%)	0.001
KRT16	66 (63.5%)	
KRT17	12 (33.3%)	
Keratin domain affected[a]	***Itch in past month***	**P-value**[b]
Head	8 (100%)	
Rod		
Rod 1A	113 (54.6%)	0.002
Rod 1B	0 (0%)	
Rod 2B	149 (37.5%)	
Tail	0%	

[a]Keratin domain refers to the location of the mutation in the keratin structure. Keratins are intermediate filament proteins with a long central alpha-helical rod domain (composed of 1A, 1B, 2A, and 2B segments)) flanked by head and tail end domains. Domain affected was

187 determined by matching the location of the mutation to the keratin structure using the Human
188 Intermediate Filament Database (http://www.interfil.org/).
189 [b]The χ^2 test was used to assess for significant differences in the prevalence of itch in the past
190 month between groups of PC genotype and the location/domain of the keratin mutation
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