

# Can skin disease cause neuropathic pain? A study in pachyonychia congenita

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## Summary

**Introduction.** Pachyonychia congenita (PC) is a rare skin disorder caused by an autosomal dominant mutation in one of five genes encoding keratin (K6a, K6b, K6c, K16 or K17; each defining one PC subtype). Pain is a prominent symptom, but its severity and type are poorly characterized.

**Methods.** In total, 35 genotyped US patients with PC consented to clinical assessment including the quality of life (QoL) questionnaire EQ-5D-3L, the Brief Pain Inventory (BPI) and painDETECT. Abbreviated quantitative sensory testing (QST) was also performed, and included mechanical detection threshold (MDT), mechanical pain threshold (MPT), wind-up pain ratio (WUR) and vibration detection threshold (VDT).

**Results.** Significant pain in patients with PC was confirmed, as indicated by mean BPI severity and interference of  $4.2 \pm 1.7$  and  $4.4 \pm 2.2$ , respectively, as well as QoL impairment, as indicated by mean EQ-5D index of  $0.69 \pm 0.18$ . PD identified neuropathic pain in 62% of patients, the remainder being nociceptive. The pain-DETECT score was most significantly related to EQ-5D index ( $R^2 = 0.26$ ,  $P = 0.02$ ). The K17 and K6a subtypes exhibited significantly worse QoL (0.584 and 0.613 respectively) than the K16 and K6b subtypes ( $P = 0.02$ ). In QST analysis, abnormal pressure pain (assessed as MPT) was frequently observed, with more than half of patients with PC affected (54%), and 57% of patients with K17 also exhibiting abnormality in minimum touch threshold (assessed as MDT,  $P < 0.05$ ). Very few patients were receiving analgesic therapy appropriate for neuropathic pain.

**Conclusion.** Significant neuropathic pain was observed in PC, which warrants appropriate treatment. The health states observed in this sample are at a level that the average US citizen would forfeit one-third of their remaining lifespan to avoid.

## Introduction

Pachyonychia congenita (PC) is a rare skin disorder caused by an autosomal dominant mutation in one of at least five keratin genes, *KRT6A* (encodes K6a protein), *KRT6B* (K6b), *KRT6C* (K6c), *KRT16* (K16) and

*KRT17* (K17).<sup>1–3</sup> These mutations classify PC clinical subtypes as PC-K6a, PC-K6b, PC-K6c, PC-K16 and PC-K17, respectively.<sup>4</sup> There are currently 619 genetically confirmed cases of PC worldwide.<sup>5</sup> PC prevalence in western developed nations is 0.9 cases per million,<sup>6</sup> and extrapolation suggests a worldwide PC population of 6500, consistent with previous estimates.<sup>7</sup>

The clinical phenotype of PC is a triad of nail dystrophy, plantar keratoderma (Fig. 1) and plantar pain.<sup>4,8</sup> PC keratoderma is exquisitely painful, especially on weight-bearing areas. Other common clinical manifestations include: cysts, follicular hyperkeratosis, oral leucokeratosis and palmar keratoderma.

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**Figure 1** (a–d) Callus state of plantar keratoderma in pachyonychia congenita evident in a selection of research subjects with different keratin subtypes: (a) K16, (b) K17, (c) K6a and (d) K6b.

Keratins are key structural proteins that impart structural strength and integrity to epithelial cells and tissues. Defective processing of the keratin cytoskeleton can cause fragility in epithelial cells and tissues in which the defective keratin is expressed.<sup>9</sup> PC keratins are predominantly expressed in keratinocytes of the nail, palmoplantar skin and oral mucosa.

Physical pain is either nociceptive or neuropathic. Nociceptive pain arises from actual or threatened tissue damage, and involves the activation of nociceptors, whereas neuropathic pain (NeP) arises from damage or disease to the somatosensory nervous system.<sup>10</sup> Patients with NeP may experience abnormal sensations such as burning, tingling or numbness, in addition to persistent or paroxysmal pain independent of painful stimuli. The treatment of NeP is often unresponsive to typical agents used for nociceptive pain.<sup>11</sup>

Pain is an over-riding symptom of PC, but there has been little research into its nature. In this study, we investigated pain in PC, including its characteristics, severity and effect on quality of life (QoL). Validated patient-reported outcome questionnaires (PROs) and clinical assessment measured the prevalence of neuropathic pain and QoL within PC subtypes. A better understanding of the nature of pain in PC and the associated burden of illness should enable more appropriate management.

## Methods

This observational study had full ethics approval from the institutional review board [WIRB Study number IPCRR (registry): 20040468, WIRB Study number for the pain study: 20111060, Western IRB, Olympia, WA, USA], and all recruited subjects provided informed written consent.

### Selection criteria and participants

Study subjects had to meet all of the following inclusion criteria: (i) age 18–90 years inclusive, (ii) prior diagnosis of PC with confirmed genotype and (iii) ability to understand and comply with the study as judged by the investigator (BH). Patients were ineligible if they met any of the following exclusion criteria: (i) lack of consent capacity, (ii) secondary skin infections of the feet, (iii) diabetes-related or other distal sensory neuropathy, (iv) NeP conditions caused by any other injury, (v) any unstable disease incompatible with the study objectives or (vi) any psychiatric disorder confounding reliable information-gathering.

In total, 35 adult patients (17 men, 18 women; mean  $\pm$  SD age  $45.8 \pm 16.0$ , range 18–84 years) with genetically confirmed PC registered in the International PC Research Registry (IPCRR)<sup>12</sup> and attending a patient support meeting focusing on pain in PC were invited to participate in the study. The study comprised three different components: (i) self-assessment questionnaires [the Brief Pain Inventory ((BPI),<sup>13</sup> a neuropathic pain symptom inventory (painDETECT)<sup>14</sup> and a generic QoL instrument (EQ-5D-3L)<sup>15</sup>]; (ii) standardized quantitative sensory testing (QST);<sup>16</sup> and (iii) clinical evaluation by an experienced pain physician. The clinical assessments were conducted within a fully air-conditioned hotel, in Philadelphia (USA) during August 2010. Patients continued all their regular medications including analgesics during the study period (Table 1).

### Questionnaires

**Brief Pain Inventory.** The short-form BPI (BPI-SF)<sup>13</sup> is a validated questionnaire frequently used for measuring pain, and is suitable for either patient self-reporting or interviewer administration.<sup>17</sup> BPI-SF records the severity of pain and its effect on daily functioning. Each BPI question is scored from 0 to 10, from which two indices, pain severity (ranging from 'no pain' to 'worst imaginable pain') and pain interference with daily life (from 'does not interfere' to 'completely interferes'), are derived.

**Table 1** Subject characteristics by PC subtype.\*

Parameter	PC (keratin) subtype				Overall	P
	K6a	K6b	K16	K17		
n	11	3	14	7	35	
Sex (M/F), %	55/46	67/33	64/36	14/86	51/49	0.16†
Age, years	45 (8)	44 (23)	52 (19)	41 (17)	47 (16)	0.44‡
BMI, kg/m <sup>2</sup>	25.6 ± 6.2	23.5 ± 2.4	27.2 ± 4.9	27.8 ± 5.2	26.5 ± 5.2	0.60‡
BPI severity	4.7 ± 1.5	3.4 ± 0.6	4 ± 1.8	4.2 ± 1.9	4.2 ± 1.7	0.60‡
BPI interference	5.3 ± 2.4	3.1 ± 1.8	3.5 ± 1.7	5.1 ± 2.5	4.4 ± 2.2	0.13‡
EQ-5D index	0.61 ± 0.20	0.87 ± 0.12	0.76 ± 0.11	0.58 ± 0.21	0.70 ± 0.18	0.02‡
EQ-5D VAS	75.4 ± 15.3	94 ± 3.6	79.4 ± 11.8	64.8 ± 25.3	77 ± 17	0.08‡
painDETECT score	19.1 ± 6.5	10.7 ± 10.3	12.2 ± 6.4	17.3 ± 7.3	15 ± 7	0.07‡
painDETECT class, %						
Nociceptive	27	67	50	14	37	0.02†
Mixed	9	0	36	71	31	
Neuropathic	64	33	14	14	31	
Clinical examination, %						
Nociceptive	9	67	57	43	40	0.33†
Mixed	18	0	21	14	17	
Neuropathic	73	33	21	43	43	
QST, %						
MDT abnormal	9	0	14	57	20	0.05†
MPT abnormal	55	0	64	57	54	0.25†
WUR abnormal	27	33	29	29	29	0.10†
VDT abnormal	9	0	7	29	11	0.44†
QST abnormality, %						
None	18	67	14	14	20	0.18†
1	55	33	36	14	37	
2+	27	0	50	71	43	
Painkiller used, %						
Opiate	0	0	7	43	11	0.03†
Anticonvulsant	0	0	0	14	3	0.25†
Antidepressant	18	0	7	14	11	0.76†
NSAID	55	0	71	71	57	0.12†
Aspirin/paracetamol	18	0	7	0	8	0.52†
Topical analgesia	18	0	7	0	8	0.52†
Other analgesia	9	0	7	0	5	0.82†

BPI, Brief Pain Inventory; MDT, mechanical detection threshold; MPT; mechanical pain threshold; NSAID, nonsteroidal anti-inflammatory drug; PC, pachyonychia congenita; QST, quantitative sensory testing; VAS, visual analogue score; VDT, vibration detection threshold; WUR; wind-up pain ratio. \*Data are mean ± SD unless otherwise specified; † $\chi^2$  test for proportions; ‡ANOVA.

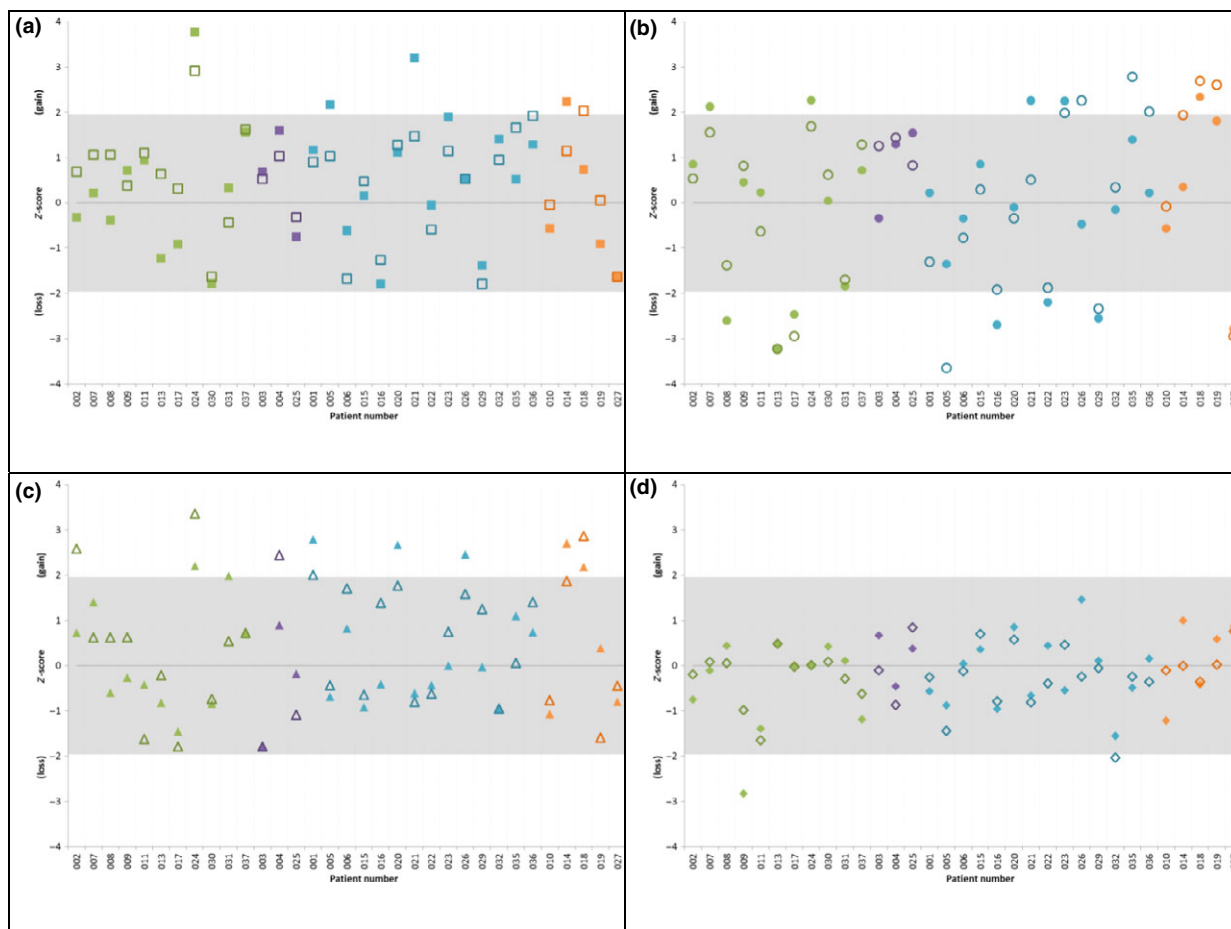
*painDETECT*<sup>TM</sup>. The painDETECT questionnaire is a validated patient-reported outcome (PRO) instrument with high sensitivity and specificity for predicting NeP.<sup>14</sup> Four sections assess the intensity, localization, pattern and quality of pain. Summary scores ≤ 12 indicate that NeP is unlikely, scores of 13–18 suggest pain of uncertain/mixed aetiology and scores ≥ 19 denote prominent NeP.<sup>18</sup>

*EQ-5D*. EQ-5D-3L assesses health-related (HR)QoL<sup>15</sup> and consists of a five-item questionnaire (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and a visual analogue scale (VAS). Each question has three levels of response ('no problem', 'some problems' or 'severe problems'). Individual

patient responses to the EQ-5D index questionnaire were converted to a single summary societal preference measure of health utility using the US tariff.<sup>19</sup> The EQ-5D VAS is a linear score, with 100 representing 'best imaginable health state' and 0 representing 'worst imaginable health state'.

#### Quantitative sensory testing

QST is a noninvasive method for testing the integrity of sensation in neurological disorders.<sup>16</sup> We used a four-stage paradigm to measure both loss of sensation and hypersensitivity in the lower limbs. Time constraints limited these tests to those expected to have the greatest sensitivity in this population, namely:



**Figure 2** Individual patient quantitative sensory testing (QST) parameter scores by pachyonychia congenita (PC) subtype. (a) Mechanical detection threshold (MDT) (green, K6a; purple, K6b; blue, K16; orange K17). (b) Mechanical pain threshold (MPT) (solid, right foot; clear, left foot). (c) wind-up ratio (WUR). Z-scores represent individual score standardized for population reference values specific to sex, age and anatomical site. Scores within  $\pm 1.96$  SD of the age-/sex-/site-specific population mean are considered to be ‘normal’ (grey shading), while scores  $> 1.96$  SD represent hypersensitivity to evoked stimuli and scores  $< 1.96$  SD represent loss of function. (d) Vibration detection threshold (VDT).

(i) mechanical (touch) detection threshold (MDT); (ii) pressure-evoked pain (mechanical pain threshold; MPT); (iii) repeated tapping of the skin using a non-painful filament (wind-up pain ratio; WUR); and (iv) vibration detection threshold (VDT). Thermal testing of patients with PC was considered inappropriate because of the dense plantar hyperkeratosis. Operators were fully competent in the application of QST, and patients received practice and training prior to data collection.

The QST protocol was similar to that developed by Rolke *et al.*,<sup>16</sup> except that only the feet (the primary site for PC pain) were assessed, in line with recommended practice for bilateral NeP conditions. QST scores were converted to z-scores using published

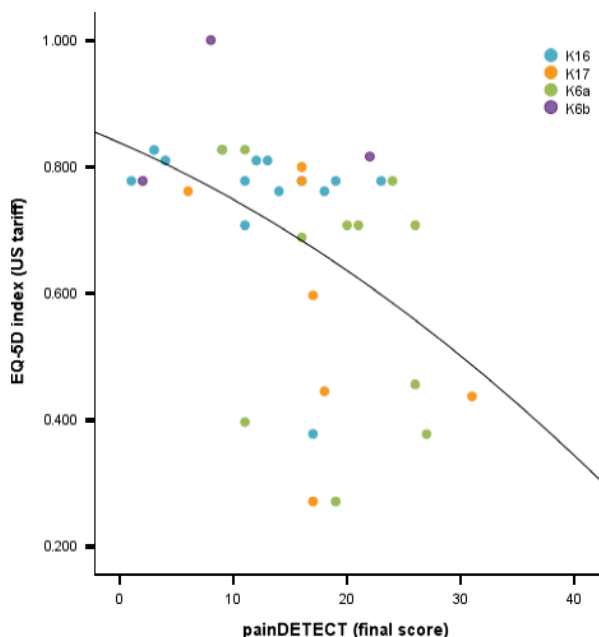
population mean reference values specific to sex, age group and anatomical site.<sup>16</sup>

### Clinical examination

A clinical examination taking 30 min was carried out by an experienced consultant specializing in the management of chronic pain (BH).

### Statistical analysis

Statistical comparisons between PC subtypes were made by ANOVA for continuous variables and the  $\chi^2$  test for categorical variables. Correlations between continuous variables were made with curve estimation



**Figure 3** Relationship between painDETECT score and quality of life (QoL) as represented by EQ-5D index (US tariff). painDETECT: final score  $\leq 12$  indicates that neuropathic pain is unlikely, scores of 13–18 indicate pain of uncertain/mixed aetiology and scores  $\geq 19$  indicate a significant neuropathic component to the patient’s pain. EQ-5D index: US-specific societal preference for health states. A score of 1 indicates ‘perfect health’, i.e. no impairments; a score of 0 indicates a state of health equivalent to death i.e. the ‘average’ US citizen would trade all their remaining lifespan to avoid such health states. Best fit trend line represent cubic function ( $R^2 = 0.26$ ,  $P = 0.02$ ).

regression. All analyses were conducted using IBM SPSS Statistics (v20; IBM Inc., Armonk, NY,USA).

## Results

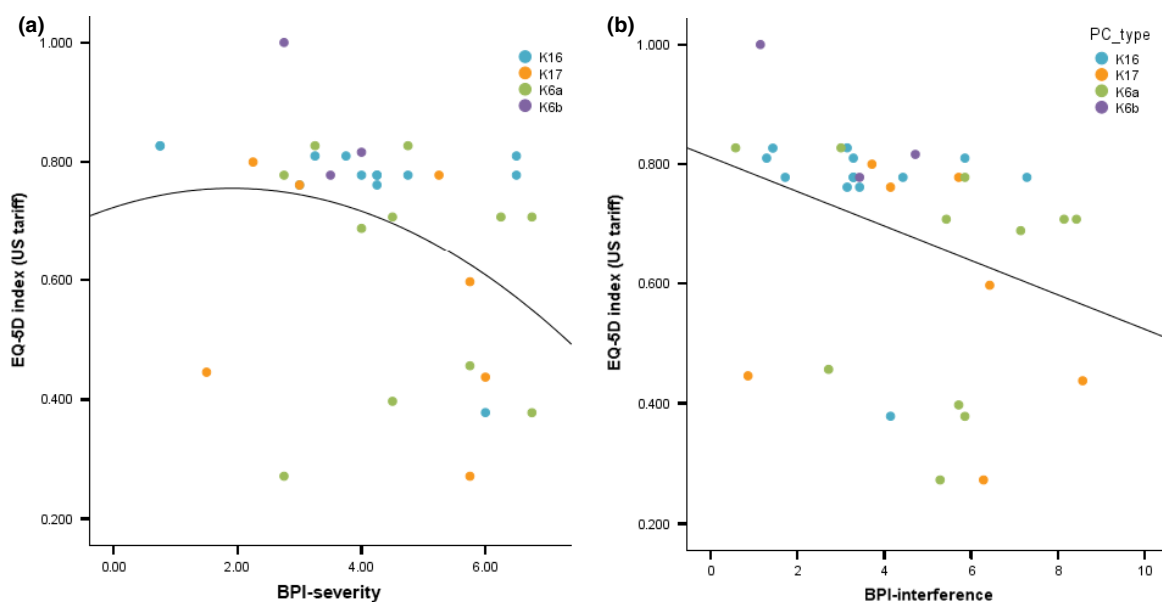
### Subjects

Subject numbers in each gene classification were: K6A  $n = 11$ , K6B  $n = 3$ , K16  $n = 14$  and K17  $n = 7$ , and mean body mass index (BMI) was  $26.5 \pm 5.2 \text{ kg/m}^2$ . Comorbidity was generally low in this cohort of relatively young active adults. There were no statistically significant demographic differences between PC subtypes (Table 1).

### Pain characteristics

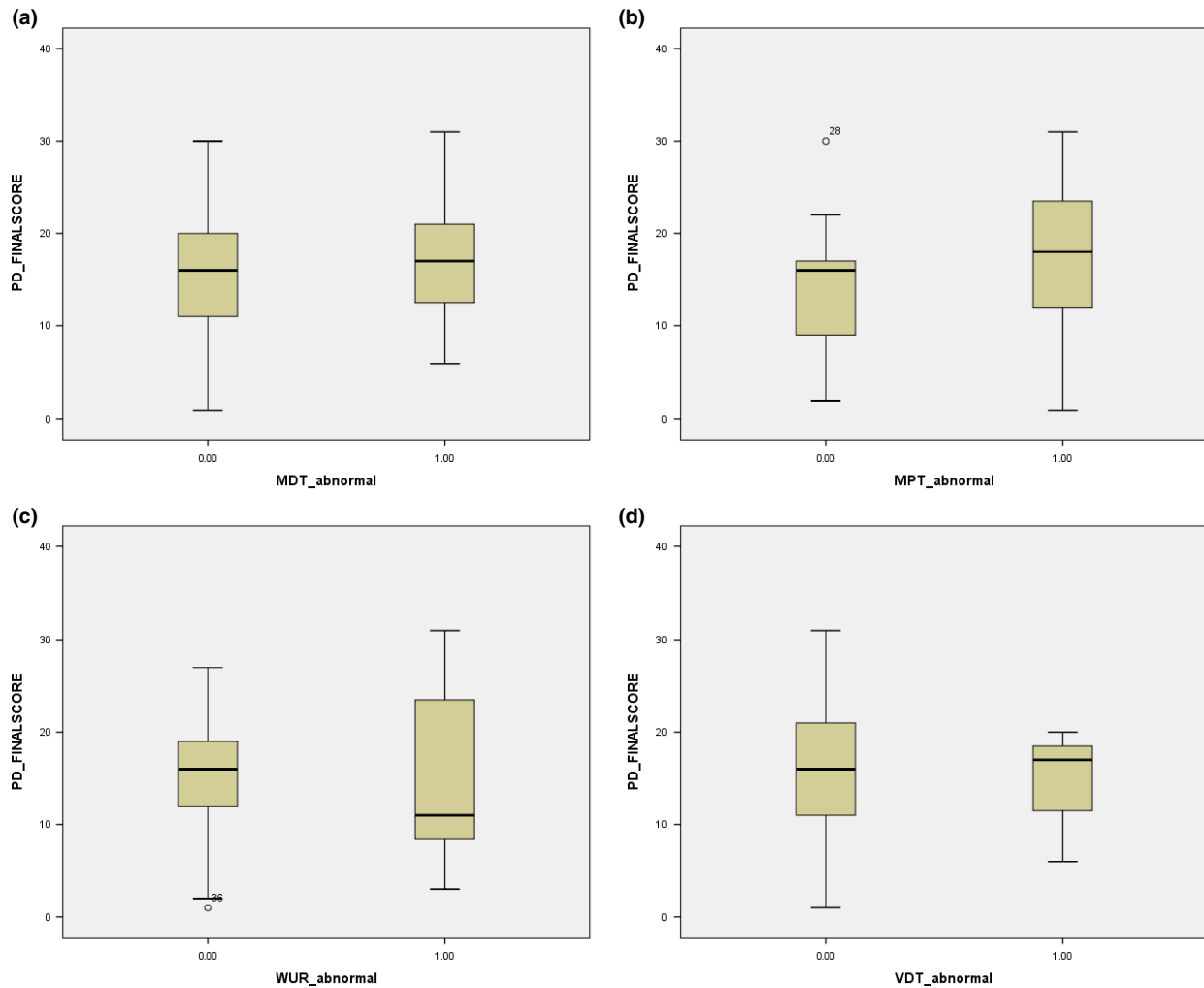
BPI pain severity and pain interference were similar across subtypes, with overall means of  $4.2 \pm 1.7$  and  $4.4 \pm 2.2$ , respectively.

A trend for higher painDETECT scores was observed in the K6a and K17 subtypes (mean scores of  $19.1 \pm 6.5$  and  $17.3 \pm 7.3$  respectively) compared with K6b or K16 subtypes (mean scores of  $10.7 \pm 10.3$  and  $12.2 \pm 6.4$ , respectively;  $P = 0.07$ ). This was reflected in a higher proportion of NeP cases in the K6a group (64%) ( $P = 0.02$ ). QoL appeared to be lowest in the K17 group, with mean EQ-5D index and VAS scores of  $0.58 \pm 0.21$  ( $P = 0.05$ ) and  $64.8 \pm 25.3$  ( $P < 0.08$ ), respectively.



**Figure 4** Association of EQ-5D index (US tariff) with Brief Pain Inventory (BPI) indices: (a) BPI Severity (quadratic function  $R^2 = 0.19$ ,  $P = 0.121$ ) and (b) BPI Interference (linear function  $R^2 = 0.12$ ,  $P < 0.05$ ).





**Figure 5** Association between quantitative sensory testing (QST) item abnormality and painDETECT score. (a) mechanical detection threshold ( $t$ -test  $P = 0.54$ ); (b) mechanical pain threshold ( $t$ -test  $P = 0.23$ ); (c) wind-up ratio ( $t$ -test  $P = 0.98$ ); (d) vibration detection threshold ( $t$ -test  $P = 0.85$ ). For each parameter, '1.00' denotes presence of an abnormal score, i.e. patient has at least one  $z$ -score either  $> 1.96$  SD or  $> -1.96$  SD the age-/sex-/site-standardized population mean. '0.00' denotes no abnormal score recorded.

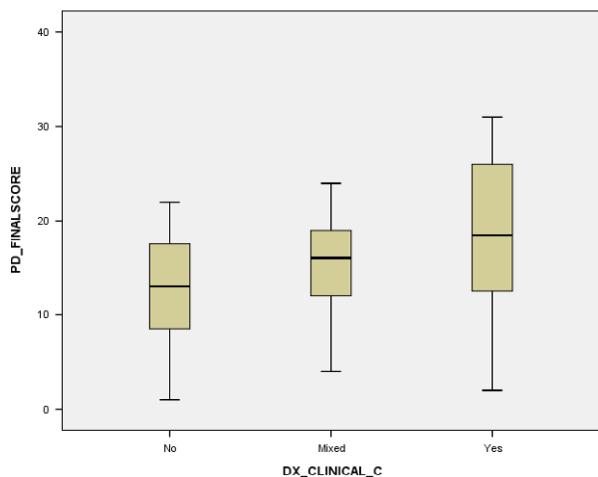
QST indicated that most patients with PC experienced abnormal detection of pressure-invoked pain; 55% of K6a, 64% of K16, and 57% of K17 patients showed altered MPT function, whereas this was not the case for the K6b subtype. In addition, 57% of K17 patients exhibited abnormal detection threshold for touch (assessed by MDT) ( $P < 0.05$ ). Variation in QST parameters is illustrated in Fig. 2.

The predominant (by 57%) type of pain relief used by these patients was nonsteroidal anti-inflammatory drugs (NSAIDs), although opiates were used by nearly half of K17 patients (43%) ( $P = 0.03$ ). Few

patients took medications considered helpful for neuropathic pain (antidepressant 11%, anticonvulsant 3%).

### Correlations

There was a significant cubic correlation ( $P = 0.02$ ) between painDETECT score and EQ-5D index (Fig. 3), but not BPI severity ( $P = 0.121$ ). A weak negative linear relationship between EQ-5D index and BPI pain interference (Fig. 4) was also observed. QST abnormality was not discriminated by painDETECT score



**Figure 6** painDETECT scores (PD\_FINALSCORE) by clinical assessment classification (ANOVA  $P < 0.08$ ). Diagnostic clinical classification (DX\_CLINICAL\_C): 'No', no clinical evidence of neuropathic pain; 'Mixed', mixed nociceptive and neuropathic pain; 'Yes', predominantly neuropathic pain.

(Fig. 5), although a nonsignificant trend ( $P < 0.08$ ) was seen for variation in painDETECT scores across clinical investigator assignment of nociceptive pain, mixed pain and NeP (Fig. 6).

## Discussion

The nature of pain in PC (NeP or nociceptive pain) and a quantitative assessment of its effect on QoL has not been reported previously. As NeP is poorly recognized,<sup>20</sup> understanding the varied aetiology of pain in PC will improve research to guide pain management. All groups in this study reported moderate to severe pain as assessed by the BPI. Pain interfered with daily life in all PC subgroups of PC and there was weak evidence to suggest that the K17 and K6a groups may have been more severely affected, although this difference was not statistically significant ( $P = 0.13$ ).

One-third of patients had predominately NeP while another third had a mixture of NeP and nociceptive pain, suggesting a five-fold greater prevalence of NeP in patient with PC than in the general population.<sup>21,22</sup> Despite this, only a minority of patients with PC were receiving medications considered to be helpful in alleviating NeP.

The mean EQ-5D index observed in this study (0.67) is equivalent to that of patients with cardiac illness.<sup>23</sup> Our analysis showed the poorest QoL in the

K17 and K6a patients, which were the groups with the highest prevalence of NeP.

Patients with PC often experience severe pain on walking. The majority of patients in our study had increased sensitivity in the feet on QST testing, suggesting that some of this discomfort is neuropathic in origin. This was particularly evident in the K6a and K17 patients.

Time constraints and limited patient availability necessitated a reduced profile of QST testing. This might be a potential weakness of our study; nevertheless, others have shown that NeP can be detected prior to and following knee surgery using a similarly reduced profile of QST tests.<sup>24,25</sup>

The triad for diagnosing NeP includes clinical examination. In this study, the diagnosis of NeP by clinical examination correlated with the painDETECT questionnaire, indicating that this instrument might prove useful for clinicians less experienced in diagnosing NeP in this and other skin diseases.<sup>11</sup>

## Conclusion

We have shown that NeP is an appreciable problem in patients with PC. Recognizing NeP is important, as it is known to be associated with significant impairment of QoL and requires appropriate medication.<sup>26</sup> The painDETECT questionnaire combined with clinical assessment will aid diagnosis of NeP in skin disease and improve patient care.

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### What's already known about this topic?

- PC is a rare skin disorder caused by an autosomal dominant mutation in keratin-encoding genes.
- Pain is a significant symptom, and negatively affects QoL.

### What does this study add?

- Pain is a primary symptom of PC, and a significant proportion of this pain is neuropathic in nature.
- The effect of PC on QoL in adults has been quantified.
- Understanding the aetiology of pain in PC will enable more appropriate treatment.

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