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Pain Mechanisms in Hereditary Palmoplantar Keratodermas

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What's already known about this topic?

- Pain is a prominent symptom in hereditary palmoplantar keratodermas (PPKs)
- Pain in patients with PPK can be difficult to treat
- Pain mechanisms in PPKs are poorly understood

What does this study add?

- Defines multiple potential sources of pain in PPK, including both structural lesions (fissures, blisters) and specific cell types
- Highlights the variability of pain among several forms of hereditary PPK
- Provides mechanistic insights into how neuropathic and inflammatory mechanisms might contribute to pain in some forms of PPK

Abstract:
Palmoplantar Keratodermas (PPKs) are a heterogeneous group of skin disorders whose common feature is thickening of the epidermis in the palms of the hands and soles of the feet. Individuals with PPKs report varying degrees of palmoplantar pain that can severely affect quality of life. Due in part to the rarity of these conditions, PPK-associated pain remains poorly understood and inadequately treated. The heterogeneity of pain prevalence and presentations across the many

forms of PPK suggests that there may exist corresponding heterogeneity in the cellular and molecular mechanisms that drive and shape PPK-associated pain. In this review we discuss candidate mechanisms for this pain, including alterations in skin architecture, involvement of multiple cell types, and neuropathic changes to the sensory nervous system. Greater understanding of these mechanisms might provide a rational basis for the development of improved approaches to prevention and treatment of pain in individuals with PPK.

Introduction

Palmoplantar keratodermas (PPKs) are rare skin disorders characterized by profound thickening of the skin, particularly on the palms of the hands and the soles of the feet, due to hyperkeratosis. PPKs can be acquired, through malnutrition, inflammatory disease, paraneoplastic effects, or chemical exposure, but are most commonly inherited[1-4]. Gain- or loss-of-function mutations in at least 25 genes have been implicated in hereditary PPK[5], though the total may be substantially higher (https://panelapp.genomicsengland.co.uk/WebServices/list_panels/). Examples include genes encoding ion channels, secreted proteins, adhesion molecules, and keratins[5]. Pain can be a prominent symptom of PPK, and can significantly impact quality of life. Despite similar histological presentations, some forms of PPK are more consistently associated with pain than others. Yet, the rarity of PPK makes gathering data on pain prevalence difficult, and pain is not always addressed in case reports. This review focuses on candidate mechanisms underlying pain in PPK (summarized in Figure 1) and describes a few PPKs that exemplify the spectrum of pain phenotypes seen in these conditions.

Multiple Candidate Structural and Cellular Contributors to Pain in PPK

Blisters and Fissures One "structural" disruption that might contribute to pain in PPK is subepidermal blistering, which is observed in some, but not all individuals with PPK. These blisters have been attributed to excessive sweating near PPK lesions[6,7]. A second likely structural contributor to PPK-associated pain is fissure formation in the callused skin with attendant wound-related symptoms [3,8]. While these two types of skin disruption undoubtedly contribute to pain in PPK, multiple findings, described in greater detail below, suggest that additional factors likely influence the incidence or severity of pain in PPK.

Keratinocytes A defining pathologic feature of PPK is over-proliferation and abnormal differentiation of epidermal keratinocytes. Although keratinocytes are best recognized as constituents of the epidermal barrier[9], they also play roles in immune and sensory functions. With respect to pain sensation, the outer membranes of keratinocytes and of the sensory neurons that mediate pain are closely associated within the epidermis[10,11]. Keratinocytes also express numerous receptors and ion channels capable of activating signaling pathways in response to painful chemical, thermal, and mechanical stimuli[12,13]. They also release soluble molecules capable of directly or indirectly stimulating or modulating pain, including small molecules (e.g., ATP[14,15], PGE_2[16,17] nitric oxide[18,19] and acetylcholine[20]), neurotrophins[21], bioactive peptides[22,23,24], and a variety of chemokines, cytokines and other immunomodulatory proteins (e.g, TSLP[25], IL-1α[26], IL-1β[27], Il-6[28], and TNF[28]). Indeed, transgenic mouse studies have provided evidence that epidermal cell stimulation is sufficient to activate sensory neurons and produce pain-related behaviors in healthy mice, and is required for full responses to mechanical or thermal stimulation[29,30,15].

Based on these findings, it is plausible that PPK pain stems in part from signals emerging from pathologically altered keratinocytes. However, pain is not universal among individuals with PPK, and calluses that form on healthy feet due to prolonged exercise are more likely to suppress pain than cause it[31,32]. Therefore, whereas the specific phenotypic characteristics of keratinocytes in different forms of PPK may influence the predilection towards pain, the existence of keratoderma alone is not sufficient to create pain.

Immune/Inflammatory Cells PPK lesions frequently contain monocytic, granulocytic, and/or lymphocytic infiltrates[33,34,35,36,37]. Skin fissures also trigger inflammatory cell recruitment. Immune cells represent a driving force behind inflammatory pain[38]. This is in part because cytokines and other molecules released by these immune cells can enhance sensitivity to painful stimuli[39], it is also conceivable that mutations causing PPK might directly influence immune cell functions ([40]).

Microorganisms Disruptions of epidermal homeostasis and barrier function, both common in PPK, alter skin commensal organism composition and make skin susceptible to superinfection

with microbial pathogens[41]. Bacteria produce molecules that activate or sensitize nociceptive neurons[42,43], while fungal products can interact with immune cells to produce inflammatory pain[44],[45]. The interplay between immune cells, invading microorganisms, and sensory neurons might therefore shape pain in PPK.

Sensory Neurons and Associated Cells In healthy skin, the perception of pain is triggered by the activation of nociceptors, sensory neurons that are tuned to stimuli that signal or pose a threat of tissue damage. Most nociceptors terminate as free nerve endings in the epidermis[46] or within the walls of dermal blood vessels[47]. Chronic pain is often characterized as inflammatory or neuropathic in origin. Inflammatory pain results from damage to or inflammation within the tissues innervated by nociceptors, whereas neuropathic pain results from injury to the nervous system itself. In both situations, the presence of numerous pro-nociceptive molecules renders nociceptors hypersensitive[48,39]. Inflammatory and neuropathic pain can be associated with either increased[49] or, paradoxically, decreased epidermal nerve fiber density[50-52]. Nerve injury and inflammation also alter the processing of incoming sensory information by spinal cord and brain pain circuits, so that even input from low-threshold mechanoreceptive neurons (LTMRs) that normally convey the perception of nonpainful touch is "inappropriately" perceived as painful (i.e., allodynia)[53].

Diverse Pain Phenotypes in Hereditary PPKs

Pain in Pachyonychia Congenita

One PPK with an especially high prevalence of pain is Pachyonychia Congenita (PC), an autosomal dominant disorder caused by mutations in genes encoding keratin proteins 6a, 6b, 6c, 16, or 17[54-60]**.** The hallmark symptoms of PC include plantar hyperkeratosis, oral leukokeratosis, and thickened nails. The majority of individuals with PC also report pain, most notably at the sites of palmoplantar calluses. A survey conducted using the International Pachyonychia Congenita Research Registry revealed that 89% of individuals with PC and 97% of those over the age of 10 experience plantar pain[61]. This pain has been described as sharp, burning, throbbing, or tingling sensations in the affected areas of the feet, often exacerbated by mechanical force, such as walking or standing[62,63]. The pain seems to be independent of severity of hyperkeratosis. It can be so severe that many individuals will crawl or use a wheelchair to minimize

discomfort[64,59]. The specific keratin gene mutation an individual harbors may determine the severity of their pain[65-67].

Structural skin lesions are important candidate contributors to pain in PC. High-resolution ultrasound studies of individuals with PC revealed what appeared to be subepidermal blisters that were not seen in individuals, with other PPKs, who did not experience pain in their lesions[7]. It is possible that pressure applied to blisters through thickened calluses in affected PC skin activates sensory nerve fibers to produce pain. If these blisters are linked to sweating, this may also explain why pain in some individuals with PC is worse in summertime[68].

There is also growing evidence supporting a neuropathic pain component in PC. In a quantitative cross-sectional survey of 35 individuals with PC using two validated pain questionairres, 62% had results consistent with neuropathic pain, while 20% were found to have mechanical detection threshold abnormalities in quantitative sensory testing[67]. In a subsequent study, 62 individuals with PC completed neuropathic pain questionnaires and were subjected to quantitative sensory testing. Of these, 86% reported pain in the feet, 62% had higher than normal neuropathic pain questionnaire scores, and 55% reported allodynia in the affected region[63]. During quantitative sensory testing, individuals with PC exhibited a higher threshold for detection of both innocuous warm and cool stimuli and mechanical stimuli, and lower thresholds for mechanically evoked pain. A lower threshold for mechanically evoked pain was also observed in a smaller study of 10 patients with PC ([69]). These findings provide evidence for a complex sensory phenotype in PC that may have elements of both inflammatory and neuropathic pain, that includes altered function of nociceptive and non-nociceptive neurons and that might involve perturbations in local and systemic pain processing.

Further evidence for a neuropathic component of PC-associated pain comes from a histological study in which affected PC skin was found to exhibit decreased sweat gland innervation, alterations in the morphology of epidermal nerve fibers, and a trend towards decreased intraepidermal nerve fiber density (IENFD), phenomena characteristic of neuropathic pain conditions[69]. Affected PC skin also exhibited increased blood vessel density within dermal papillae and increased Merkel cell density in the basal epidermis, even compared to skin from

individuals with PPK due to an aquaporin mutation or from subjects with plantar calluses due to frequent running[69]. Merkel cells are epidermal cells derived from keratinocytes that form synaptic contacts with a subset of slow-adapting (SA1) LTMRs. Merkel cells are themselves mechanically sensitive, and help shape the kinetics of SAI responses[70,71,13]. Genetic ablation of Merkel cells decreases mechanical sensitivity and texture discrimination[72,73]. Recent studies reported increased Merkel cell density in rat skin following peripheral nerve injury or repetitive shaving[74,75]. This might explain the increased Merkel cell density in affected PC skin, since PC lesions exhibit many features of injury responses, and since individuals with PC sometimes shave their calluses. One hypothetical sequence of events suggested by these findings is that the neuropathic changes in cutaneous sensory neurons innervating PC lesions lead to abnormal sensitivity of these neurons and consequent spinal sensitization. Mechanically evoked input from the increased number of Merkel cells onto sensitized spinal circuits then produces touch-evoked pain.

Gene expression and proteomics analyses in affected skin of PC individuals and *KRT16* null mice, which exhibit many histological features of PC, have revealed changes in the expression of numerous genes, including some that could be ontologically classified as "nociceptive and neuropathy related[36,76-78]. Another recent study identified exaggerated oxidative stress in PPK lesions in both *KRT16* null mice and individuals with PC due to lower activity of the transcription factor, nuclear-factor erythroid-derived 2 related factor 2 (Nrf2)[79,80], which regulates the expression of antioxidants and anti-inflammatory proteins and has been implicated in pain[81,82]. PC lesions also exhibit reduced keratinocyte expression of Nociceptin/orphanin FQ opioid peptide receptor (NOP-R)[83], a receptor that produces analgesia in multiple animal models of inflammatory and neuropathic pain[84, 83]. All of these changes represent potential mechanistic contributors to PC pain.

Therapeutic approaches to pain in PC.

Avoidance of mechanical stress on palmoplantar surface, topical retinoids, vitamin D treatment, NSAIDs, gabapentin, and opioids are all used to manage pain in individuals with PC, but often do not provide complete relief [85,63,86]. Many individuals shave their calluses to curb their pain,

though this treatment is short-lasting or ineffective and can exacerbate pain if overshaving occurs[85].

Some small studies have reported pain relief and improvement of quality of life in individuals treated off-label with rapamycin or statins[87,88,89]. Consequently, the FDA recently granted fast-track designation for a trial of high-strength topical rapamycin to treat PC. RNA interference to inhibit expression of mutant keratins represents another potential means of treating PC that showed promise in animal studies and in one patient[90,91,92]. In this study the individual exhibited both a reduction in callus size and a reduction in mechanical hypersensitivity at the drug treated site. The apparent coincident reversal of anatomical and sensory symptoms suggest both that PC-associated pain hypersensitivity is reversible and that disease modifying approaches might be effective to treat this pain. Case studies have also reported anecdotal success at alleviating pain by injecting botulinum toxin into the feet of individuals with PC, either alone or in combination with gabapentin. These studies reported a reduction in pain and blistering within a week of treatment and a cessation of symptoms for 6 months[68,93,94,59]. Together with the pain phenotyping results described above, the possible contribution of gabapentin to pain reduction in PC further supports a neuropathic etiology and suggests that other neuropathic pain-oriented therapies may be worth consideration.

Pain in Olmsted Syndrome

Olmsted Syndrome (OS) is another characteristically painful, but rare, hereditary PPK. OS can be caused by a gain of function mutation in the gene encoding the nonselective cation channel Transient Receptor Potential Vanilloid 3 (TRPV3) or a loss of function mutation in the Membrane-Bound Transcription Factor Protease, Site-2 (MBTPS2) gene[95-98]. Symptoms of OS include diffuse and often mutilating palmoplantar hyperkeratosis, periorificial keratotic plaques, leukokeratosis, alopecia, and corneal abnormalities[96,99,100]. In a survey of 50 OS case reports, 21 mentioned pain[99]. This pain results in sleep disturbances, mobility difficulties, and interference with grasping[95,101,102]. Some individuals with OS also experience erythromelalgia, a condition in which the skin becomes intensely red and painful, often in response to warming[34,103].

Home remedies, wet soaks, salicylic acid, urea, tar, shale oil, antibacterial treatment, retinoids,

and corticosteroids have been utilized to treat OS pain[104,105,101]. More extreme measures such as complete removal of the affected skin and subsequent skin graft have also been used[106]. Though some individuals have reported initial relief from this procedure, keratoderma often returns in the grafted tissue[99,107].

One candidate contributor to OS pain is the increased activity of the protein product of the mutated *TRPV3* gene. TRPV3 is a member of the transient receptor potential (TRP) channel family of non-selective cation channels. Many TRP channels are expressed in peripheral sensory neurons, and several have been implicated as initiators or amplifiers of pain[108-111]. TRPV3 is most prominently expressed in skin keratinocytes, but has been detected in other cell types, including nociceptive sensory neurons and immune dendritic cells such as Langerhans cells[112, 113]. Absence of TRPV3 in knockout mice leads to impaired epidermal maturation, a compromised epidermal barrier, and a wavy hair phenotype[114,115]. TRPV3 knockout mice have also been reported to exhibit modest defects in heat evoked pain sensation, though this phenotype is strongly dependent on genetic strain[109,116,117,118]. Two mutant rodent lines, characterized by alopecia, bear autosomal dominant mutations in TRPV3 at the codon encoding Gly573, which is also mutated in some human OS pedigrees[37]. The resulting mutant TRPV3 proteins exhibit constitutive activity and hyperresponsiveness to agonist stimulation[119]. Pain studies have not been reported in the mice bearing OS-alike TRPV3 mutations. However, a similar pattern of constitutive activity has been observed in multiple mutant human TRPV3 proteins encoded by OS alleles[105]. It remains to be determined whether TRPV3 gain of function leads to OS pain solely by virtue of its effects on keratinocyte biology or whether it also reflects TRPV3 hyperfunction in neurons or other cell types. Additional candidate contributors to pain in OS include *Candida* and bacterial infections, which are common in the hands and feet of individuals with this disorder[95,120], as well as immunological/inflammatory cell changes[101,121,105,120]

Another gene linked to OS, *MBTPS2,* encodes a zinc metalloprotease involved in the ER stress response and in the activation of the SREBP transcription factor, which in turn regulates expression of the enzymes involved in cholesterol biosynthesis[95,98]. A defect in the ER stress response in patients with *MBTPS* mutation might alter cellular responses to injury. Alternatively, disruptions in sterol biosynthesis might impair barrier function[122] and pave the way for

superinfection, lesion formation, and consequent pain.

Additional PPKs with Variable Prevalence of Pain

Many other forms of PPK have been associated with pain, albeit with a frequency that varies among conditions. One example is Mal de Meleda (MDM), an autosomal recessive PPK attributable to loss of function mutations in the gene encoding secreted lymphocyte antigen 6/urokinase-type plasminogen activator receptor related protein-1 (SLURP-1)[123], whose diagnostic hallmarks include diffuse palmoplantar hyperkeratosis as well as nail anomalies, perioral erythema, odor, and malignant melanoma[124]. The case reports that describe pain as a symptom of MDM predominately attribute it to secondary fungal or microbial infection or to skin lesions that result from the hyperkeratosis[125,126,35]. However, SLURP1 is also expressed in nociceptive neurons[127], inhibits TNF-α release from macrophages and keratinocytes[128,129], and is necessary for normal T cell activation and function[40]. Pain in MDM might thus arise through both keratinocyte-dependent and -independent mechanisms. Pain has also been reported in some individuals with Vorner disease, a common diffuse epidermolytic PPK caused by a mutation in *KRT9*[130], but has been described predominantly in the context of fissures or blisters in affected skin[3,131,132]. A few additional PPKs in which pain has sometimes been described include Richner-Hanhart syndrome[133], and Papillon–Lefèvre syndrome (PLS)[8] and punctate PPK[134]. However, inconsistencies in reporting pain in PPK make it likely that this list is far from complete.

Summary and Future Directions

Pain severely diminishes quality of life for many individuals with hereditary PPK. Disease modifying therapies aimed at preventing the formation of PPK lesions represent some of the most exciting candidate means of treating PPK-associated pain. However, there is no guarantee that lesion prevention or reversal will be achievable in all forms of PPK or that the drugs used will be tolerated by all patients. Therefore, the field should seek approaches targeted more specifically at the mechanisms that drive pain in a given form of PPK. The development of such approaches would be facilitated by careful phenotypic analysis of pain (presence or absence, quality and quantity) in individuals with PPK along with detailed assessment of relevant immunological, neuroanatomical, and molecular alterations in affected skin and, in parallel, the establishment and mechanistic analysis of animal models that recapitulate PPK-associated pain.

Regardless of how candidate therapies for PPK pain are identified, careful study design, coupled with effective subject engagement, will be important to overcome the inevitably small sizes of clinical trials used to evaluate their safety and efficacy. Finally, the finding of a neuropathic contribution to pain in Recessive Dystrophic Epidermolysis Bullosa [135] another hereditary skin disease, raises questions regarding the prevalence and potential etiology of nerve injury across dermatological conditions and suggests that therapies developed to treat a given condition may benefit individuals suffering from others.

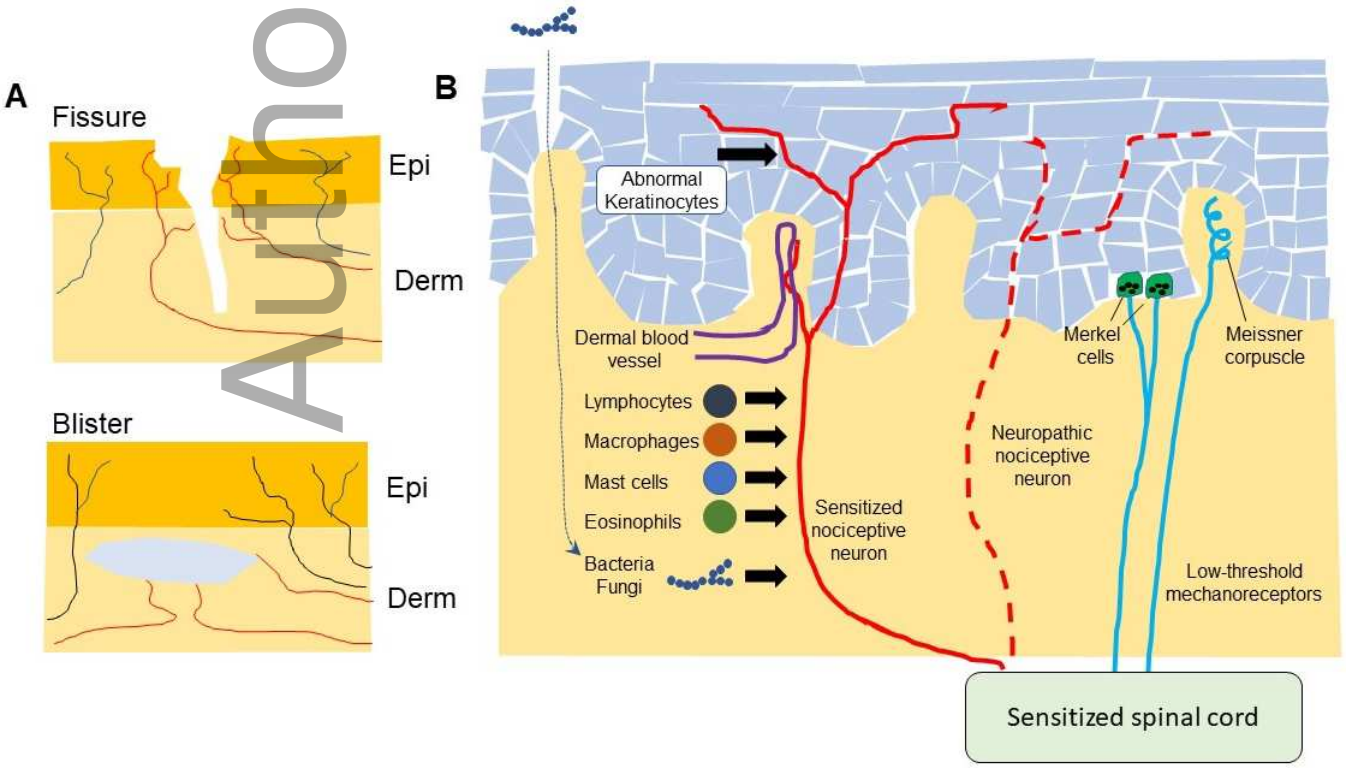

Figure 1. Potential sources of pain in PPK skin. A. Structural lesions seen in some patients with painful PPK. Black fibers represent nociceptors in basal state. Red fibers represent nociceptors sensitized by the injury associated with fissures or blisters. Epi, epidermis. Derm, dermis. B. Cell types that might contribute to either the development of pain or touch-evoked allodynia in PPK skin. Arrows represent soluble factors released by the indicated cell types that could sensitize nociceptive neurons. Nociceptive neurons can be sensitized (to augment pain sensation) or injured (i.e. rendered neuropathic) by either extrinsic factors emanating from the indicated cell types or by intrinsic factors such as PPK-associated gene mutations. Sensitized or neuropathic nociceptors in turn sensitize spinal cord and brain circuits, which make inputs from low-threshold mechanoreceptors feel painful.

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