Pachyonychia congenita – pathogenesis of pain and approaches to treatment

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Learning points

- Pachyonychia congenita is a rare inherited skin condition causing painful palmoplantar keratoderma and dystrophic finger and toenails.
- Both nociceptive and neuropathic pain mechanisms are thought play a role in pathogenesis of pain in pachyonychia congenita.
- There are limited effective treatment options for pachyonychia congenita. Importantly, there is a lack of treatment options which are effective at dealing with the most debilitating feature of pain.
- Clinical trials for pachyonychia congenita are currently limited by lack of a reliable primary outcome which can detect improvement in pain.

Abstract

Pachyonychia congenita is an autosomal dominant genodermatosis characterized by a triad of chronic severe plantar pain, focal palmoplantar keratoderma, and hypertrophic nail dystrophy. Plantar pain can be debilitating and have a profound impact on quality of life. Current therapeutic options for pain in PC are limited to lifestyle adjustment and mechanical techniques, with a small subgroup of patients benefiting from oral retinoids. This review investigates the pathogenesis of pain in pachyonychia congenita and provides a summary of the current and future therapeutic options.

Introduction

Pachyonychia congenita (PC) is a rare autosomal dominant genodermatosis caused by mutations in one of five keratin genes (*KRT6A, KRT6B, KRT6C, KRT16, KRT17)* characterised by a triad of chronic severe plantar pain, focal palmoplantar keratoderma (PPK) and hypertrophic nail dystrophy.[1–5] Other clinical features include oral leukokeratosis, epidermoid cysts, natal teeth, splinter haemorrhages, follicular hyperkeratosis, itch, neurovascular structures and hidradenitis suppurativa.[5–9] PC was historically categorised into two subtypes, PC type 1 and PC type 2, however identification of the genes involved has exposed genotype-phenotype correlations and classification of PC is now based upon molecular analysis (PC-K6a, PC-K6b, PC-K6c, PC-K16, PC-K17).[10–12] There is no known cure for PC and therapeutic options for plantar pain are limited.

To address these issues amongst others, the International Pachyonychia Congenita Research Registry (IPCRR) was founded by the PC Project (www.pachyonychia.org), a US-based charity which supports individuals with PC and connects them to clinicians and researchers. Data from the IPCRR and cases from other registries have demonstrated that painful plantar keratoderma is the most debilitating symptom in PC and has a profound impact on quality of life.[9,13]

Plantar pain was reported by 97% of PC patients over age 10 years in a IPCRR conducted survey of 254 patients. Painful plantar keratoderma affected 94.2% of a cohort of 815 patients, with more than 60% being persistently affected functionally on a daily basis and 24.6% needing medication to handle the pain.[14] Palmar keratoderma is also frequently painful, but is less likely to result in functional impairment.[14] There is a spectrum of pain in PC, with some patients reliant on mobility aids ranging from crutches to wheelchairs.[10] Pain is unrelated to extent of callus and varies between PC subtypes (Figure 1).[14] Pain typically worsens over time; 80% of attendees at one PC Project meeting reported plantar pain had gotten worse with age.[15] Limitations on movement and activities have downstream implications for general health and wellbeing. PC has a profound impact on social activities and mental health in children and adolescents.[16,17] Sedentary lifestyles are a common consequence of plantar pain in PC which can have downstream impacts on physical health including increased all-cause mortality, cardiovascular disease, metabolic disease, and musculoskeletal disease.[18]

The pathogenesis and nature of pain experienced in PC is poorly understood, however in recent years several hypotheses have been developed which may contribute to introduction of new therapeutic interventions for PC. This review aims to summarise hypotheses for the pathogenesis of pain and the current and future treatment options for chronic plantar pain in PC.

Pathogenesis of pain in PC

Physical pain can be divided into nociceptive pain, from actual or threatened tissue damage, and neuropathic pain, from damage or disease to the somatosensory nervous system.[19] Both have been reported in PC.[20,21]

Pain is a subjective phenomenon so is difficult to objectively measure in human or animal research settings. In PC patients, measuring ambulation, a clinically meaningful functional outcome, alongside quality of life measures has been useful. Recent insights have been gained from phenotype/genotype correlations which show that patients with proven *KRT16, KRT6A* and *KRT6B* mutations are significantly more likely than those with *KRT6C* or *KRT17* mutations to require walking aids.[14] Characterisation of genotype-phenotype correlations could allow identification of molecular pathways for mutation-specific therapeutics.

Neuropathic pain has been reported in PC patients, and this may contribute to chronic pain in PC.[20,21] A cross-sectional survey of 35 individuals with PC found that 62% of participants experienced neuropathic pain.[20]

A small cohort study found neuropathic pain most affected quality of life in PC-K17 and PC-K6a patients.[20] A survey-based study identified that patients with PC-K17 and PC-K6a were also significantly more likely to have difficulty wearing socks and shoes.[7] The same study found the presence of neurovascular structures, pinpoint red spots associated with pain suggesting presence of an adjacent nerve, was reported by patients to increase plantar pain. However, they were not significantly more frequently present in PC-K17 or PC-K6a: in fact, they were less frequent in PC-K17.[7] Patients with PC demonstrate mechanical hyperalgesia, allodynia, tingling, and electric shock like sensations compared to control.[21] In addition, PC-affected plantar skin has reduced sweat gland innervation, reduced numbers of Meissner corpuscles and higher Merkel cell densities and blood vessel counts compared to PC-unaffected or anatomically matched control skin.[22] Over time, damage to peripheral sensory nerves may contribute to peripheral sensitisation and the intensification of pain with age.[22]

Nociceptive pain in PC is thought to be stimulated by tissue damage due to abnormal keratinocyte function.[19,20] Keratins are key stress-bearing structural proteins within the cytoplasm of epithelial cells. The keratins associated with PC are predominantly expressed in keratinocytes of palmoplantar skin, mucosal surfaces, and epidermal appendages.[11] Dominant negative mutations in keratin genes result in mechanical fragility and compensatory hyperkeratosis of epithelial tissues.[9]

Structural abnormalities such as fissures and sub-epidermal blistering is observed in many patients with PC and may contribute to chronic pain.[23] High-resolution multifrequency ultrasound of the proximal and distal plantar food calluses demonstrated an anechoic layer interposed between the epidermis and the dermis in all patients with PC compared to none with epidermolytic PPK and mal de Meleda.[24] Pain is often worse in warm weather, which could be hypothesized to be due to blistering caused by increased eccrine gland sweat being trapped under keratoderma.[29] Palmoplantar hyperhidrosis is seen in 50% of PC patients and this is one putative mechanism by which botulinum toxin is reported to help with plantar pain (see below).[29,42]

Nociceptin/orphanin FQ opioid peptide (NOP)-receptor (OP-R) is a member of the opioid receptor family, and activation of this receptor has demonstrated analgesic effects. In one study, plantar biopsies

from 10 PC patients were performed on PC-affected skin (the ball of the foot) and PC-unaffected skin (the arch of the foot). OP-R expression was reduced in PC-affected plantar skin compared with PC-unaffected skin.[25] This suggests the OP-R could represent a target for neuropathic pain in PC.

Mouse models of PC have been used to investigate the pathogenesis of PC pain, although their use in studying pain is limited as pain is a perceptual phenomenon and mouse footpads differ to human skin. *KRT16* null mouse strains which develop footpad skin lesions mimicking non-epidermolytic PPK show transcriptional hyperactivation of damage-associated molecular patterns (DAMPs) and cytokines in response to chemical or mechanical irritation to skin.[26] This suggests *KRT16* is important in the progression of cutaneous inflammation in response to trauma. *KRT17* is thought to have a role as a pro-inflammatory immunomodulator and in contrast to *KRT16*, *KRT17* knockout mice do not show altered DAMP expression in response to trauma. This is consistent with patients with PC-K17 being less likely to require walking aids.[14,20,27] The increased expression of DAMPs in PC has been linked to oxidative stress and impaired glutathione synthesis in *KRT16* knockout mouse footpad skin. *KRT16* expression may be associated with nuclear factor erythroid derived 2 related factor 2 (Nrf2) activation. Genetic ablation of Nrf2 results in earlier onset of PPK in KRT16 knockout footpad skin, and Nrf2 demonstrates low activity in the plantar skin of individuals with PC.[28]

Transient Receptor Potential cation channel subfamily V, member 3 (TRPV3) is a heat-sensitive calcium ion channel which forms a signaling complex with TGF-alpha and EGFR controlling keratinocyte proliferation, differentiation, and apoptosis.[29,30] PC-lesional skin shows EGFR signaling overactivity and increased TRPV3 activity.[31]

The current mechanisms for the causes of pain in PC are summarised in Figure 2.

Current treatment options

Therapeutic options for pain management in PC can be categorised into non-invasive techniques, topical, pharmacological, and surgical treatments. At present, most patients control their PC-related pain using lifestyle adjustments and mechanical techniques;[15] targeted therapies are limited to clinical trials.

Non-invasive

Lifestyle measures to minimize pain include using comfortable footwear and orthotics, limiting movement and activities on feet and the use of walking aids.[15,32] Many patients opt for comfortable footwear with or without insoles or orthotics, while some patients opt for wicking socks. Nearly 20% of patients use walking aids either through devices, such as walking sticks, crutches, four-wheeled walkers, and wheelchairs, or improvise by leaning on furniture, crawling, or holding onto another person.[14,15,33] Maintaining ideal body weight can reduce pressure and friction at callus sites, though this can be challenging due to pain limiting exercise tolerance.[33,34]

Mechanical techniques reported by PC patients including filing, grinding, cutting, and clipping are the best available treatment for calluses. However, over-trimming can worsen plantar pain, particularly if there is resulting neurovascular structure exposure.[32] Tools used to pare calluses include razor blades, clippers, paring knives, emery boards, pumice stones and specialist foot files[33]. Patients find this of varying benefit, with older and female patients more likely to describe mechanical techniques as beneficial.[32]

Surgical

Reports of successful surgical techniques utilised in pain management of PC are limited.[35] Techniques have included excision of cysts, electrofulguration and deep curettage.[33] Excision, followed by autologous grafting of skin from an unaffected site, results in recurrence of keratoses on transplanted skin on the soles.[33] Subsequently, there is a limited role for surgical procedures in reducing plantar pain in PC.

Pharmacological therapies

Topical therapies, such as emollients, retinoids and keratolytics, have no impact on pain although they may be used to soften and facilitate removal of the outer layer of keratoderma.[33,34]

Symptomatic relief of pain with oral analgesics including simple analgesia (paracetamol, non-steroidal anti-inflammatories) and neuropathic agents are an underused option in alleviating pain in PC patients.[20] However, these do not treat the underlying PPK.[36]

Oral vitamin A derivatives (retinoids), such as acitretin and isotretinoin, are of limited benefit. Though they result in thinning of hyperkeratosis which may benefit some, others report increased blistering and plantar pain.[37] In addition, systemic retinoids are of limited use in women of childbearing potential due to teratogenicity and are poorly tolerated due to adverse events including dryness of the mouth, skin and eyes, skin peeling, headaches, and liver enzyme abnormalities.[37,38]

Future treatment options

There is a significant unmet need for successful treatments for patients with PC. Clinical trials are exploring future options for pain in PC, but have been limited by intolerable adverse effects, variable efficacy, and drug delivery difficulties.

Statins have been shown to downregulate *KRT6A* expression via Stat1 transcription factor, through the geranylgeranylation pathway.[39] They have also been shown to activate Keap1-Nrf2 signaling in rat models.[40] Case-reports have demonstrated reduction in callus formation and plantar pain with simvastatin and rosuvastatin in paediatric patients with *KRT6A* mutations but results in adult patients have been mixed.[41–45] Its efficacy has not yet been proven through a placebo-controlled clinical trial and benefit must be balanced with risks of myalgia and potentially diabetes in the long-term.[46]

Botulinum toxin (Btx) type A injections have been shown to be effective at treating plantar pain in case series, though the mechanism is contested.[47] Some patients have reported poor efficacy of Btx but patients with the painful PC subtypes K6a and K16 have demonstrated positive impact on plantar keratoderma, possibly related to reduction in eccrine gland sweating (and thus blistering) via inhibition of acetylcholine release at the neuromuscular junction.[48,49] An alternative mechanism is the effect of Btx on sensory nerve function through reduction in neurotransmitter release from sensory nerve axons, and inhibit neurogenic flare.[47,50–52] Finally, Btx may inhibit vasodilation and neurogenic inflammation.[49] Intradermal Btx injections are associated with significant pain, requiring repeated administrations and local anaesthetic nerve block or general anaesthesia for administration, which limits Btx's practical use. Current research is limited by small sample sizes. Larger, multi-centre placebo-controlled studies and improved understanding of the long-term impact of Btx is required.[47]

Short interfering RNAs (siRNA) can potently and specifically inhibit gene expression.[53–56] Targeting mutant keratin alleles in PC has shown positive effects both in pre-clinical studies on organotypic skin models and on pain and appearance of callus in PC patients with intralesional administration of siRNAs in an off-label study of 3 patients and a stage Ib study.[53,54,56,57] However, large-scale trials of intradermal siRNAs have not been performed due to the intense pain with injection of large volumes into PC lesions.[56,58] Topical siRNA treatment for PC is limited by difficulties with delivery of siRNA through the stratum corneum and uptake by keratinocytes.[53] siRNA technologies with good penetration of the stratum corneum may be facilitated by development of microneedle arrays,[59] and dissolving microneedles show promise in targeting STAT3 in melanoma.[59,60] The development of these more 'patient-friendly' delivery mechanisms is required to facilitate utilisation of this technology in PC.[58] Capsaicin is a TRPV1 agonist which desensitises sensory nerves. The off-label use of cutaneous 8% capsaicin patches in one patient demonstrated a transient small-to-moderate improvement in pain. However, this did not result in a change in quality of life and has not been explored in large-scale clinical trials.[61,62]

The mTOR inhibitor rapamycin (sirolimus) selectively downregulates expression of *KRT6a* in cell culture, reducing proliferation and hyperkeratosis seen in PC.[36,57,63] Rapamycin may also have therapeutic potential in reducing neuropathic pain, as demonstrated in patients with spinal cord injury.[64] Oral rapamycin has shown subjective improvement in plantar pain and quality of life in four PC patients over two uncontrolled and unblinded studies, with one patient reporting regression of neurovascular structures which may account for the reduction in pain.[57,65] However, treatment limiting severe side effects including gastrointestinal upset, aphthous ulcers, infections and acneiform follicular eruptions caused all patients to cease treatment, preventing it from being a long-term treatment for PC.[57] Topical rapamycin, which avoids side effects associated with systemic administration, may be a therapeutic option for PC. A case report detailed reduced plantar pain with regular topical rapamycin in two PC-K6a patients.[63] A recent Phase IIIb study (NCT05180708), investigated the efficacy and safety of topical rapamycin in PC. Intention to treat analyses did not show a treatment effect on primary endpoint when compared to placebo.[66,67]

Pre-clinical studies demonstrating mTOR role in regulation of PC-K6a expression, resulted in exploration of targeting the mTOR pathway in other ways.[31,57] mTOR is a primary target of EGFR which regulates cell growth, survival, proliferation, and differentiation. Case reports of the oral EGFR inhibitors erlotinib and lapatinib demonstrated reduced pain, callus size and improved quality of life in patients with PC.[31,68] Similar improvement of keratoderma, plantar pain and quality of life in patients with Olmsted syndrome have been demonstrated with oral erlotinib.[69,70] Given the safety profile of oral EGFR inhibitors,[71] the development of topical EGFR inhibitors has become of interest, and a recent case report showed clinical improvement in patients with PC-K16 with topical erlotinib in combination with salicylic acid.[72] Large scale, placebo controlled clinical trials are required to further explore the efficacy and safety of topical EGFR inhibitors in all subtypes of PC. Other targeted therapies include topical selective TRPV3 antagonists, which are in the early stages of clinical trials (NCT05435638).

Sulforaphane, in its pure form or as broccoli sprout extract, acts as a pharmacological inducer of Nrf2.[28] In *KRT16* null male mice (but not female), topical application prevented PPK-like lesions and normalized redox balance, offering a potential pathway for targeted therapies for PC.[73,74] Interestingly, the effects seen in male mice were replicated in female mice after dual treatment with sulforaphane and oestrogen receptor agonist diarylpropionitrile. Human clinical trials are required to explore the role of Nrf2 as a targeted therapy for pain in PC and to investigate sexual dimorphism in humans.[36,73,74]

Gene editing using CRISPR based therapies can target single-gene conditions. Pre-clinical studies of CRISPR technology in genodermatoses largely focus on recessive dystrophic epidermolysis bullosa, and clinical trials utilizing this technology have been started in cancer and chronic infections.[75] Gene editing targeting of keratin genes using CRISPR/Cas technology may be explored as a future therapeutic option for PC in the future.

One limitation to clinical studies of pain in PC the lack of a validated scoring tool for measurement of pain and keratoderma. Self-reported electronic diaries are limited by recall bias,[67] therefore there is a movement towards using electronic devices such as monitoring step counts[76] or vital signs as a surrogate for pain.[67] Developing a validated scoring mechanism remains a top research priority, as recognised by the recent PC research agenda produced by PC experts in investigative and clinical dermatology, convened by the PC Project.[62,67] This lists six high-priority areas for PC research: organizing PC research–related resources, investigating major clinical manifestations (painful PPK, nail dystrophy, and cysts), focusing on better harnessing the power of omics studies; optimizing new laboratory models, devices, and other emerging technologies, promoting molecular therapies and drug repurposing in PC, and developing novel regular and technology-based outcome measures.[62]

Rare genetic disease previously has been under-represented in the research capacity although this is improving.[77] Better understanding of the pathogenesis of PC will improve the treatment options. The IPCRR brings together a community of PC patients which facilitates research and recruitment for clinical trials.

Conclusion

Plantar pain is the most debilitating symptom of PC. Current therapeutic options for PC plantar pain provide limited relief, with mechanical/surgical options being preferred over medical therapies. Delineation of genotype-phenotype correlations is now possible through collaboration with patient registries such as PC Project. With improved understanding of pain in PC, particularly improved understanding of the molecular pathways involved, recognition of a significant neuropathic component to the pain and adopting new gene editing techniques, targeted therapies are being developed which hold promise for the future.

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Figure legends

Figure 1: Proportion of patients of each genotype requiring the use of mobility aids (out of 815 patients). From Samuelov L, *et al*. Revisiting pachyonychia congenita: a case-cohort study of 815 patients. British Journal of Dermatology [Internet]. 2020; 182(3):738–46. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/bjd.18794

Figure 2: Features of pachyonychia congenita (PC) lesional skin (b) compared to normal skin (a). Mechanical causes of pain include sub-epidermal blisters, fissures, and neurovascular structures. Keratinocytes demonstrate mechanical fragility and a compensatory hyperkeratosis. On a microscopic level, studies have demonstrated decreased sweat gland nerve fibre density and a reduced number of Meissner's corpuscles. Several pathways have been identified as potential targets for the development of therapeutics for pain in PC. NRF2 (nuclear factor erythroid derived 2 related factor 2) is a key regulator of cellular responses to oxidative stress and epidermal homeostasis. Under physiological conditions, chemical or mechanical stress causes phosphorylation of Nrf2 and synthesis of glutathione (GSH). However, this pathway is disrupted in pachyonychia congenita and *KRT16* knockout mice demonstrate upregulated but hypoactive NRF2, decreased GSH synthesis and increased oxidative stress. Nociceptin opioid peptide receptor (OP-R) is expressed in epidermal keratinocytes and activation of the receptor has demonstrated analgesic effects. PC-lesional skin has reduced expression of OP-R, which suggests this could be a target for treatment of neuropathic pain in PC. Transient Receptor Potential cation channel subfamily V, member 3 (TRPV3) is a heat-sensitive calcium ion channel which forms a signaling complex with TGF-alpha and EGFR controlling keratinocyte proliferation, differentiation, and apoptosis. PC affected skin shows EGFR signaling overactivity and increased TRPV3 activity.

CPD Questions

Question 1. Mutations in which of the following keratin genes is not associated with pachyonychia congenita?

(a) KRT5.
(b) KRT6A.
(c) KRT6B.
(d) KRT6C.
(e) KRT16.

Question 2. How is pachyonychia congenita (PC)-6A inherited?

(a) Autosomal recessive.
(b) X-linked recessive.
(c) Autosomal dominant.
(d) X-linked dominant.
(e) Semi-dominant

Question 3. What are the classic features of pachyonychia congenita?

(a) Mutilating bilateral palmoplantar keratoderma and periorificial keratotic plaques.
(b) Triad of anonychia, plantar pain and hidradenitis suppurativa.
(c) Triad of focal keratoderma, dystrophic nails and cysts
(d) Triad of plantar pain, focal palmoplantar keratoderma, and hypertrophic nail dystrophy.
(e) Triad of plantar pain, itch, and follicular hyperkeratosis.

Question 4. Which of the following is not suggested to cause pain in pachyonychia congenita?

(a) Fissures and sub-epidermal blistering.
(b) Increased oxidative stress.
(c) Increased TRPV3/ EGFR signalling.
(d) Neurovascular structures.
(e) Sedentary lifestyle.

Question 5. How do most people with pachyonychia congenita manage their pain at present?

(a) Botulinum toxin injections.
(b) Keratolytics
(c) Mechanical paring and lifestyle adjustment.
(d) Retinoids.
(e) Surgical techniques.

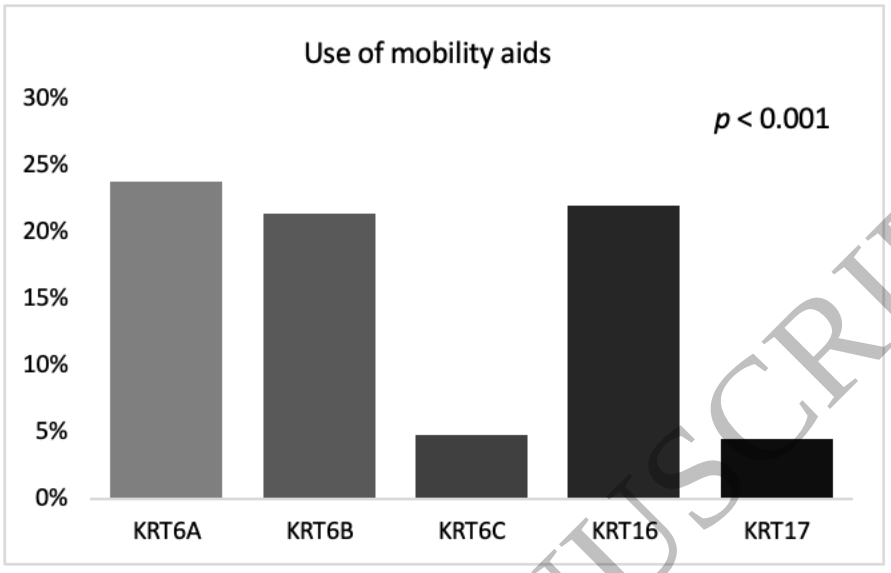

Figure 1
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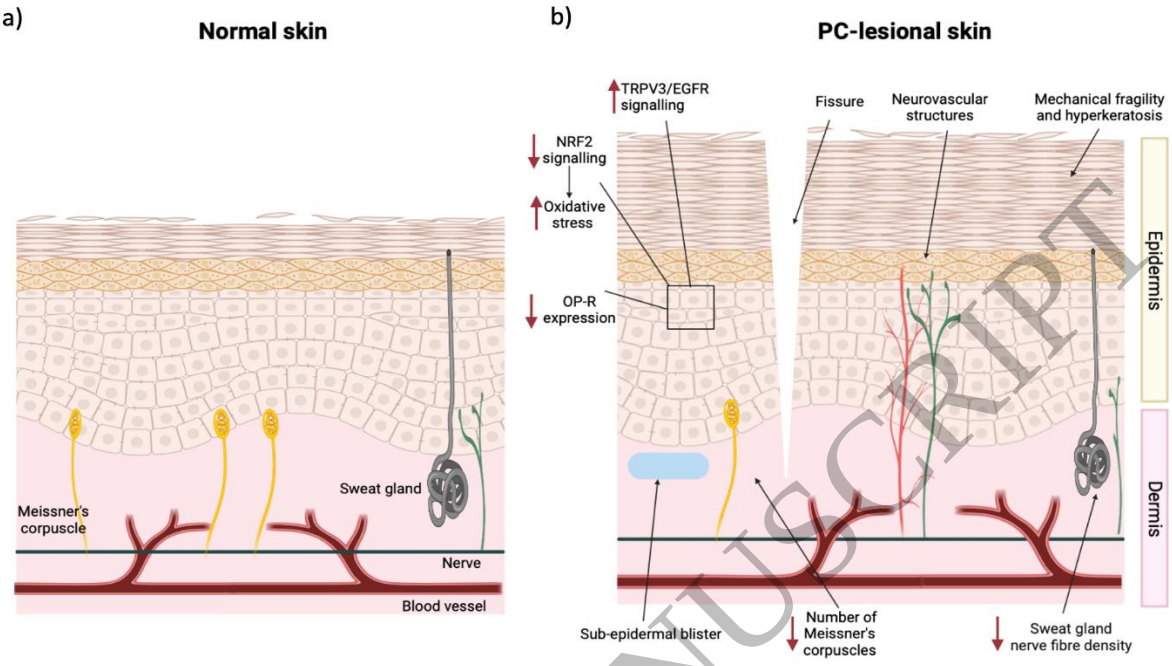

Figure 2
417x222 mm (x DPI)