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Coexistence of pachyonychia congenita and hidradenitis suppurativa: more than a coincidence*

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Abstract

Background The coexistence of pachyonychia congenita (PC) and hidradenitis suppurativa (HS) has been described in case reports. However, the pathomechanism underlying this association and its true prevalence are unknown.
Objectives To determine the genetic defect underlying the coexistence of PC and HS in a large kindred, to delineate a pathophysiological signalling defect jointly leading to both phenotypes, and to estimate the prevalence of HS in PC.
Methods We used direct sequencing and a NOTCH luciferase reporter assay to characterize the pathophysiological basis of the familial coexistence of HS and PC. A questionnaire was distributed to patients with PC registered with the International Pachyonychia Congenita Research Registry (IPCRR) to assess the prevalence of HS among patients with PC.
Results Direct sequencing of DNA samples obtained from family members displaying both PC and HS demonstrated a missense variant (c.275A>G) in *KRT17*, encoding keratin 17. Abnormal NOTCH signalling has been suggested to contribute to HS pathogenesis. Accordingly, the *KRT17* c.275A>G variant resulted in a significant decrease in NOTCH activity. To ascertain the clinical importance of the association of HS with PC, we distributed a questionnaire to all patients with PC registered with the IPCRR. Seventy-two of 278 responders reported HS-associated clinical features (25·9%). Disease-causing mutations in *KRT17* were most prevalent among patients with a dual phenotype of PC and HS (43%).
Conclusions The coexistence of HS and *KRT17*-associated PC is more common than previously thought. Impaired NOTCH signalling as a result of *KRT17* mutations may predispose patients with PC to HS.

What is already known about this topic?

- The coexistence of pachyonychia congenita (PC) and hidradenitis suppurativa (HS) has been described in case reports.
- However, the pathomechanism underlying this association and its true prevalence are unknown.

What does this study add?

- A dual phenotype consisting of PC and HS was found to be associated with a pathogenic variant in *KRT17*.
- This variant was found to affect NOTCH signalling, which has been previously implicated in HS pathogenesis.

- HS was found to be associated with PC in a large cohort of patients with PC, especially in patients carrying *KRT17* variants, suggesting that *KRT17* variants causing PC may also predispose to HS.

What is the translational message?

- These findings suggest that patients with PC have a higher prevalence of HS than previously thought, and hence physicians should have a higher level of suspicion of HS diagnosis in patients with PC.

Hidradenitis suppurativa (HS) is a chronic inflammatory disease of the hair follicle unit. It manifests with relapsing subcutaneous nodules resulting in scarring and sinus tracts involving mainly the axillae, groin and perianal and/or inframammary regions.[1] Most cases of HS are sporadic; however, autosomal dominant familial HS (MIM 142690) has been found to be associated with variants in several genes, including *PSENEN*, *NCSTN* and *PSEN1*, encoding critical components of the γ-secretase complex.[1–5]

Pachyonychia congenita (PC) refers to a group of inherited autosomal dominant disorders that result from heterozygous mutations in one of five keratin genes (*KRT17*, *KRT16*, *KRT6C*, *KRT6B* and *KRT6A*; MIM 148069, 148067, 612315, 148042 and 148041), encoding keratins 17, 16, 6c, 6b and 6a, respectively.[6–12] Patients with PC display palmoplantar keratoderma often associated with debilitating plantar pain, toenail and fingernail dystrophy, oral leucokeratosis, natal teeth, follicular hyperkeratosis, and various pilosebaceous cysts, including steatocystoma multiplex. Cysts are most commonly associated with *KRT17* mutations[6,7,9,13–15] and tend to rupture with associated pain and residual scarring. This condition has occasionally been termed steatocystoma multiplex suppurativa[16,17] and shares clinical features with HS. An association of HS with PC was first described by McDonald and Reed in 1976[18] and has since been further confirmed in several case reports.[19–22] The molecular basis for this association and its magnitude are currently not known.

Here we present data suggesting that the association of HS with PC may be more significant than initially thought and may result from abnormal NOTCH signalling.

Patients and methods

Patients

All patients provided written informed consent according to a protocol reviewed and approved by our institutional review board and by the Israel National Committee for Human Genetic Studies, in adherence with the Declaration of Helsinki principles. Patient consent was received for publishing identified information and photographs.

Mutation analysis

Genomic DNA was extracted from peripheral blood leucocytes using the Gentra Puregene Blood Kit (Qiagen, Hilden, Germany) or from saliva samples collected using the OG-500 saliva collection kit (DNA Genotek Inc., Ottawa, ON, Canada) according to the manufacturer's instructions. Genomic DNA was polymerase chain reaction (PCR) amplified using oligonucleotide primer pairs spanning the entire coding sequence of *KRT17*, *PSEN*, *PSENEN* and *NCSTN* (Table S1; see Supporting Information) and Taq polymerase (Qiagen). Cycling conditions were as follows: 94 °C for 2 min; then 94 °C for 40 s, 61 °C for 40 s, 72 °C for 50 s, for three cycles; then 94 °C for 40 s, 59 °C for 40 s, 72 °C for 50 s, for three cycles; then 94 °C for 40 s, 57 °C for 40 s, 72 °C for 50 s, for 34 cycles. Gel-purified amplicons (QIAquick gel extraction kit, Qiagen) were subjected to bidirectional DNA sequencing with the BigDye Terminator system (Thermo Fisher Scientific Inc., Waltham, MA, USA) on an ABI Prism 3100 sequencer (Applied Biosystems, Foster City, CA, USA).

Cell cultures and reagents

Primary keratinocytes (KCs) were obtained from three healthy individuals and from index patient III-2 (Figure 1a) after written informed consent was given by the donors according to a protocol reviewed and approved by our institutional review board, as previously described.[23] KCs were maintained in KC Growth Medium (Lonza, Walkersville, MD, USA). HaCaT cells, a spontaneously immortalized human skin KC cell line, were maintained in modified Eagle's medium supplemented with 10% fetal calf serum, 1% L-glutamine, 1% streptomycin and 1% amphotericin (Biological Industries, Beit-Haemek, Israel).

Expression vectors

The human *KRT17* expression vector (RC201619) was purchased from Origene (Rockville, MD, USA). The c.275A>G mutation was introduced using the Q5® Site-Directed Mutagenesis Kit (New England Biolabs, Ipswich, MA, USA). Mutagenesis primers were designed with the NEBaseChanger® tool (http://nebasechanger.neb.com). Mutagenesis was confirmed by direct sequencing. Wildtype or mutant *KRT17* overexpression was achieved by transient transfection into HaCaT cells grown to 70% confluence using Lipofectamine 2000 transfection reagent (Invitrogen, Carlsbad, CA, USA) and incubation for 24 h. Overexpression of *KRT17* was ascertained using quantitative reverse-transcriptase (qRT)-PCR.

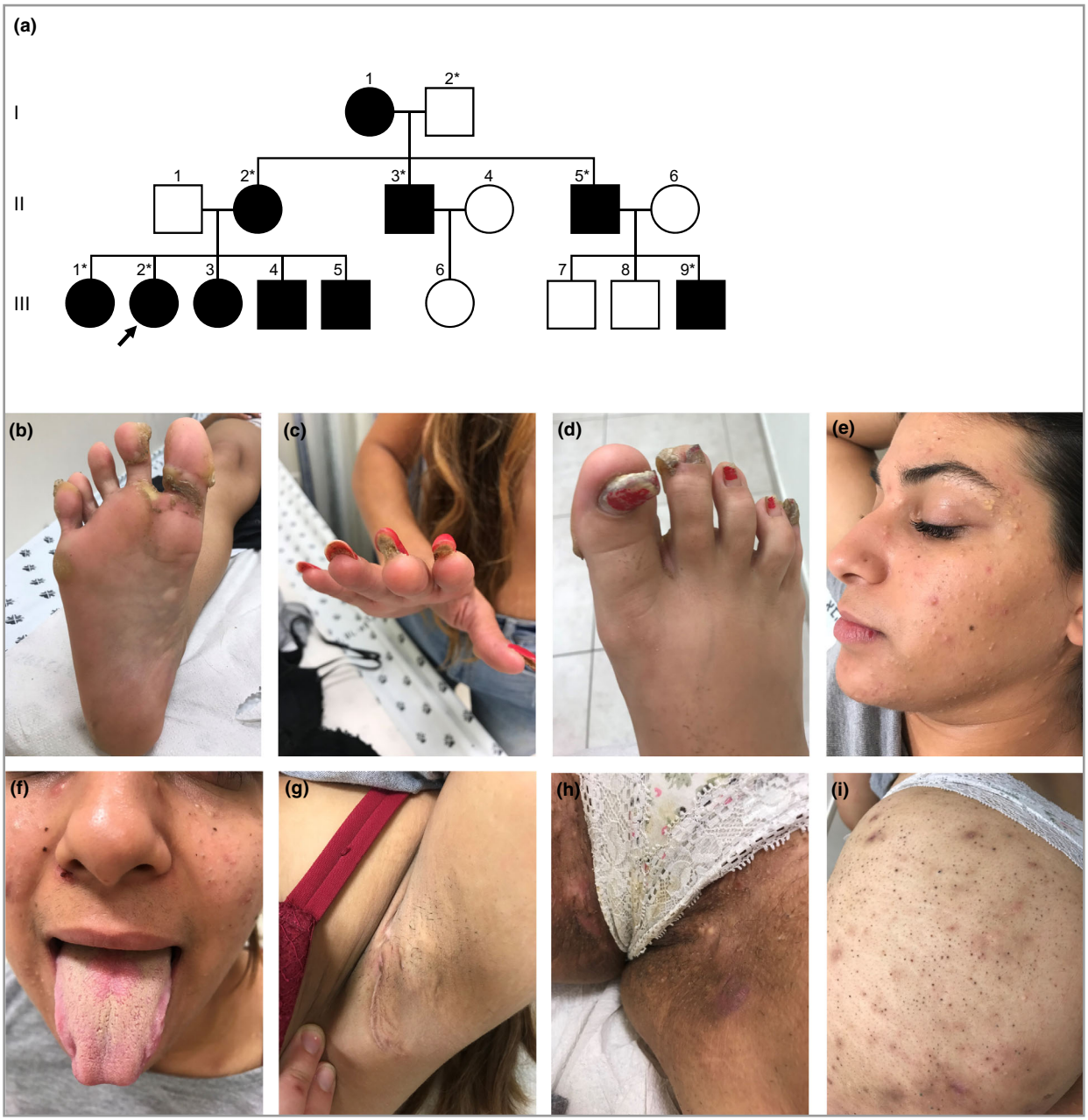

Figure 1 Clinical features of a large kindred with KRT17-associated pachyonychia congenita and hidradenitis suppurativa. (a) Pedigree of a large kindred carrying the KRT17 c.275A>G mutation. The index patient is denoted with an arrow. Family members sequenced for the c.275A>G KRT17 mutation are denoted with an asterisk (other patients' DNA samples were not available for molecular analysis). Affected individuals display plantar keratoderma (b), nail dystrophy (c, d), facial cysts (e), oral leucokeratosis (f) and features typical of hidradenitis suppurativa, including flexural scarring (g, h) and multiple black comedones (i).

NOTCH reporter assay

Cells were seeded on 96-well plates (15 000 cells per well). Forty-eight hours following seeding, cells were transfected with a NOTCH response element containing a luciferase reporter construct, kindly provided by Dr David Sprinzak (Biochemistry Department, The George S. Wise Faculty of Life Sciences, Tel Aviv University), as well as a *Renilla* expression vector, using Lipofectamine 2000. Twenty-four hours following transfection, luciferase activity was read using a dual luciferase assay (Promega, Madison, WI, USA). Luciferase activity was normalized to *Renilla* luciferase.

Quantitative reverse-transcriptase polymerase chain reaction

For qRT-PCR, cDNA was synthesized from 500 ng of total RNA using a qScript kit (Quanta Biosciences, Gaithersburg,

MD, USA). cDNA PCR amplification was carried out with the PerfeCTa SYBR Green FastMix (Quanta Biosciences) on a StepOnePlus system (Applied Biosystems) with gene-specific intron-crossing oligonucleotide pairs (Table S1). Cycling conditions were as follows: 95 °C for 20 s; then 95 °C for 3 s and 60 °C for 30 s for 40 cycles. Each sample was analysed in triplicate. For each set of primers, standard curves were obtained with serially diluted cDNAs. Results were normalized to *GAPDH* mRNA levels.

Cytokine secretion measurement

Supernatant collected from normal human epidermal KCs and patients' KCs was evaluated using the Human TNF alpha ELISA Kit (ab181421; Abcam, Cambridge, MA, USA). All enzyme-linked immunosorbent assays were read and quantified using a Tecan Infinite M200 device (Tecan Group, Männedorf, Switzerland).

Data collection from the International Pachyonychia Congenita Research Registry

The International Pachyonychia Congenita Research Registry (IPCRR) (WCG IRB #20040468; www.pachyonychia.org) includes clinical data of patients with PC collected through a comprehensive questionnaire, clinical photos and a telephone interview, as previously reported.[13] All patients are offered genetic testing. In total, 815 participants were enrolled in the registry between May 2004 and June 2018.[13] In order to assess the prevalence of HS among patients with PC, a short questionnaire aimed at identifying HS-defining features was electronically sent to all patients with PC registered in the IPCCR. The full questionnaire is available in Figure S1 (see Supporting Information).

Results

A *KRT17* variant causes a phenotype combining pachyonychia congenita and hidradenitis suppurativa

An 18-year-old woman was referred to our clinic for the evaluation of abnormal fingernails and toenails, and thickened palmoplantar skin associated with significant pain while walking, since early childhood. In addition, multiple cysts were evident over her back, face and scalp. She also reported recurrent bilateral painful abscesses in the axillae and inguinal folds that appeared at 11 years of age. She denied any other symptoms, including natal teeth. Nine additional family members displayed similar symptoms (Figure 1a).

Skin examination revealed focal palmoplantar keratoderma (Figure 1b) and markedly thickened and dystrophic toenails and fingernails (Figure 1c, d). Numerous cysts were present over her face (Figure 1e) and trunk. Oral leucokeratosis was observed over the dorsum of her tongue (Figure 1f). Scarring was present over the axillae and inguinal folds, with multiple black comedones present on the thighs (Figure 1g, i), suggesting the diagnosis of HS rather than steatocystoma multiplex typically seen in patients with PC.

Seven additional affected family members were examined (Table 1). These affected individuals demonstrated palmar keratoderma, painful plantar keratoderma and multiple cysts. Thickened nails were variably present. Three of the 10 affected family members had a history of recurrent abscesses involving the axillae and groin (Table 1).

Using direct sequencing, we identified a previously reported heterozygous missense mutation in *KRT17*,[13] c.275A>G, in all affected family members for whom DNA was available. The mutation is predicted to result in the substitution of asparagine with serine (p.N92S).[24] The mutation was not identified in DNA obtained from an unaffected family member for whom DNA was available (I-2, Figure 1a). No mutations were identified in genes previously reported to be associated with HS, including *PSEN*, *PSENEN* and *NCSTN* (not shown).[1–5]

Abnormal NOTCH signalling associated with a pachyonychia congenita-causing *KRT17* variant

The c.275A>G (p.N92S) *KRT17* mutation, which results in a combined phenotype of both PC and HS, as described above, is the most common PC-associated *KRT17* mutation[13,24] and is responsible for 40% of cases of *KRT17*-associated PC. Given the fact that abnormal NOTCH signalling has been found to contribute to the pathogenesis of both familial and sporadic HS,[25,26] we ascertained the effect of the PC-causing *KRT17* variant c.275A>G on NOTCH signalling.

We transfected primary KCs obtained from the index patient (III-2, Figure 1a) and control primary KCs with a NOTCH luciferase reporter construct. The patient's transfected KCs demonstrated significantly reduced NOTCH activity compared with controls (Figure 2a). We then cotransfected HaCaT cells with wildtype *KRT17* cDNA or *KRT17* c.275A>G-carrying expression vectors, together with the NOTCH luciferase reporter. Luciferase activity in HaCaT cells transfected with the mutant *KRT17* expression vector was significantly decreased

Table 1 Clinical characteristics of pachyonychia congenita and hidradenitis suppurativa (HS) among affected family members (Figure 1)

	II-2	II-3	II-5	III-1	III-2 (index)	III-3/4/5
PPK (palms/soles)	−/+	+/+	+/+	−/+	−/+	−/+
Nail dystrophy (fingers/toes)	+/+	−/−	+/+	+/+	+/+	+/+
Cysts[a]	+	++	+	++	+	+
Leucokeratosis	+	−	NA	+	+	NA
Natal teeth	−	−	NA	+	−	−
HS[a]	−	−	+	+	++	−
KRT17 c275A>G[b]	−/+	−/+	−/+	−/+	−/+	NA

NA, not available; PPK, palmoplantar keratoderma. [a]Increasing severity from − to + to ++. [b]−/+ indicates autosomal inheritance.

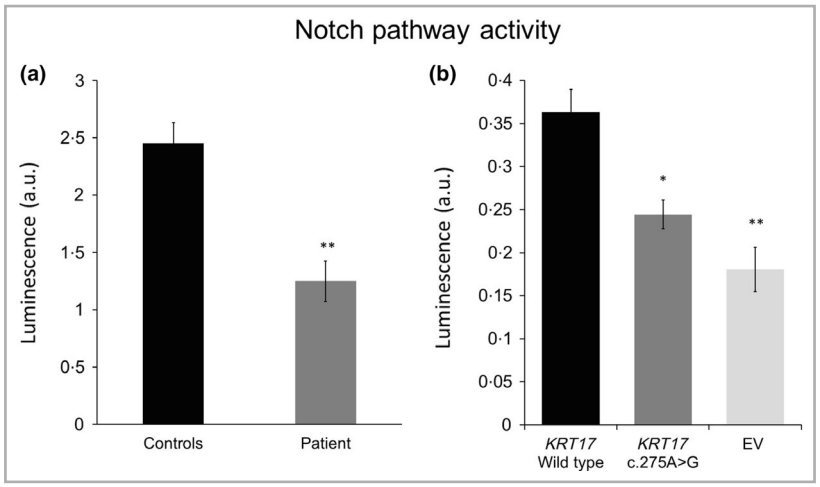

Figure 2 Functional studies. (a) NOTCH luciferase activity in the index patient's primary keratinocytes (KCs) compared with control KCs (n = 3) (**P < 0·01, two-sided t-test). The data represent the mean (SE) of three independent experiments. (b) NOTCH luciferase activity in HaCaT cells transfected with a wildtype *KRT17* expression vector compared with a mutant *KRT17* expression vector harbouring the c.275A>G mutation or empty vector (EV, pCMV6-Entry vector) (*P < 0·05, **P < 0·01; one-way ANOVA followed by Tukey's post hoc test for multiple comparisons). The data represent the mean (SE) of three independent experiments.

compared with the wildtype (Figure 2b), further supporting an association between the *KRT17* c.275A>G mutation and abnormal NOTCH activity.

The KRT17 c.275A>G variant is associated with increased expression of inflammatory cytokines

As elevated levels of inflammatory cytokines were previously demonstrated in HS lesional skin,[27] we next investigated the mRNA expression of key cytokines in the patient's KCs compared with control KCs. *IL1B*, *TNF* and *IL23A* gene expression was markedly elevated in KCs derived from the patient with the combined PC and HS phenotype compared with KCs derived from healthy controls (Figure 3a). In line with the gene expression profile, upregulated expression of tumour necrosis factor (TNF)-α was observed in the patient's KCs compared with control KCs (Figure 3b).

Hidradenitis suppurativa is prevalent among patients with pachyonychia congenita and is associated with *KRT17* variants

Given previous results[19–22] supporting an association between *KRT17* variants and the propensity to develop HS, we circulated a questionnaire among a cohort of 815 patients with PC (Figure S1). In total, 278 patients with PC replied, with the distribution of keratin gene mutations being similar to that in previous reports based on the IPCRR[13] (Figure 4a, b). Twenty-nine patients reported being previously diagnosed with HS. An additional 43 patients reported repeated outbreaks of skin lesions typical for HS (painful subcutaneous nodules, abscesses, sinuses and scarring) involving at least two regions characteristic of HS (groin, buttocks, genitals, perianal, inframammary and abdominal folds or armpits) (Table 2). Accordingly, 72 out of 278 PC patients demonstrated clinical features of HS (25·9%) (Table 2, Figure 4a).

KRT17 mutations were most commonly associated with HS, followed by mutations in *KRT6A* and *KRT6B* (43%, 29% and 19%, respectively) (Figure 4c). Most patients with PC carrying *KRT17* mutations who completed the questionnaire reported an HS phenotype (31 of 36, 86%), with the *KRT17* c.275A>G (p.N92S) mutation being most common (Table S2; see Supporting Information). This is in contrast to 21 of 97 (22%) and 14 of 29 (48%) patients with PC carrying *KRT6A* and *KRT6B* mutations, respectively, who completed the questionnaire and reported an HS phenotype (Table S2).

Discussion

Taken collectively, the data presented in this study point to a high prevalence of HS among patients with PC, especially those carrying *KRT17* mutations.

PC and HS have previously been reported to coexist,[19–22] but it is unclear to date whether this association is serendipitous or reflects a common pathogenesis. The high prevalence of HS among patients with PC demonstrated in this study (25·9%), which is significantly higher than the prevalence of HS in the general population,[28] argues in favour of a specific association. Accordingly, the fact that a PC-causing mutation in *KRT17* was found to interfere with NOTCH signalling, which has been implicated in HS pathogenesis, suggests that both conditions may result from a common pathophysiological defect.

Keratin 17 belongs to the type I intermediate filament family and is mainly expressed in the epithelial appendages, such as hair follicles and sebaceous gland epithelium.[29,30] In the

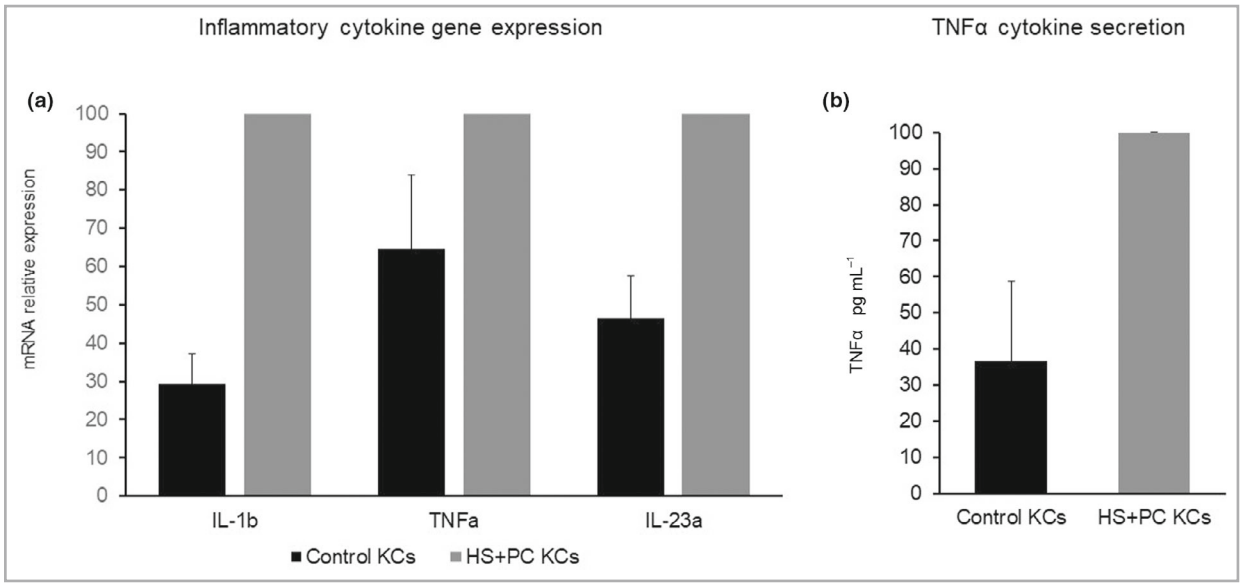

Figure 3 The *KRT17* c.275A>G variant is associated with increased expression of inflammatory cytokines. (a) Inflammatory cytokine gene expression in keratinocytes (KCs) obtained from the patient presenting with the combined pachyonychia congenita (PC) and hidradenitis suppurativa (HS) phenotype compared with KCs derived from healthy controls (n = 3). The results are expressed as the percentage of RNA expression relative to expression in the patient's KCs. The results represent the mean (SE) of three independent experiments. IL, interleukin; TNF, tumour necrosis factor. (b) TNF-α expression in culture medium was measured using enzyme-linked immunosorbent assay. The results are expressed as the percentage of protein expression levels relative to expression in the patient's KCs. The results represent the mean (SE) of two independent experiments.

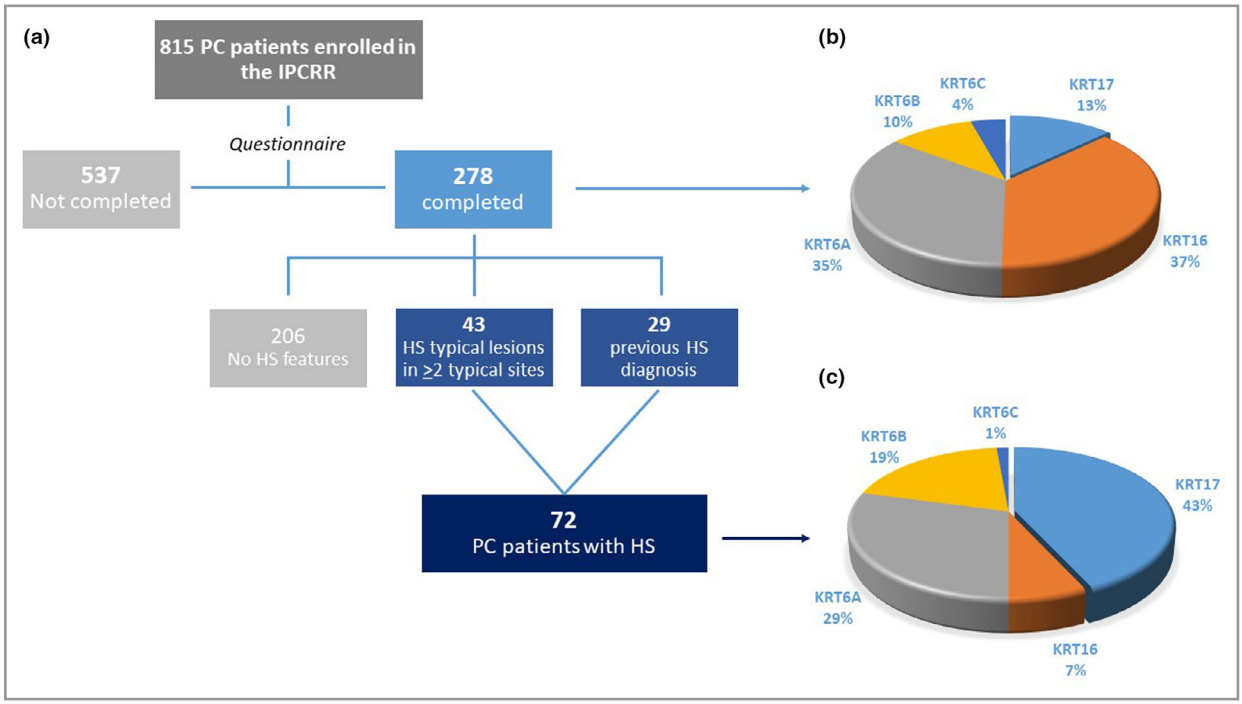

Figure 4 The prevalence of hidradenitis suppurativa (HS) among patients with pachyonychia congenita (PC). (a) Distribution of the combined PC–HS phenotype among patients with PC who completed the questionnaire. (b) Distribution of PC-associated keratin gene mutations among patients with PC who completed the questionnaire. (c) Distribution of PC-associated keratin gene mutations among patients with PC presenting with a phenotype of HS. IPCRR, International Pachyonychia Congenita Research Registry.

Table 2 Hidradenitis suppurativa (HS): clinical features among patients with pachyonychia congenita (PC)

HS diagnosis or associated clinical features in patients with PC	Number (%)
Previously diagnosed with HS[a]	29 (10·4)
Patients fulfilling HS-defining criteria[a,b,45,46]	43 (15·5)
Total PC patients demonstrating HS manifestations[a]	72 (25·9)
Involved regions[c]	
Groin	60 (83)
Buttocks	37 (51)
Armpits	69 (96)
Genitals	49 (68)
Anal region	26 (36)
Inframammary folds	22 (31)
Abdominal folds	14 (19)
More than two outbreaks during the last 6 months[c]	
Yes	52 (72)
No	20 (28)
Has undergone previous surgery for HS[c]	
Yes	14 (19)
No	58 (81)

[a]Out of 278 patients with PC. [b]Subcutaneous nodules, abscesses, sinuses and scarring affecting at least two body sites: groin, buttocks, armpits, genitals, perianal region, and inframammary and lower-abdominal folds. [c]Out of 72 patients with both PC and HS.

hair follicle unit, keratin 17 is expressed in the outer root sheath, medulla and hair follicle matrix, suggesting a role played by keratin 17 in hair shaft formation and hair follicle cycling.[31–34] In the epidermis, keratin 17 expression is induced upon skin injury,[35] viral infections,[36] psoriasis[37] and acne.[38] Keratin 17 is a structural protein that contributes to the formation of the cell cytoskeleton, but it also regulates major additional biological processes such as cell proliferation, cell growth and inflammation, as well as nuclear morphology, chromatin organization, gene expression and epigenetic modifications.[34,39] It may also regulate NOTCH signalling, possibly through mammalian target of rapamycin,[40] as shown in previous studies.[40–42] Inhibition of NOTCH signalling results in hair follicle cycle arrest, conversion of hair follicles into cysts, and inhibition of sebaceous gland differentiation,[43] which may therefore explain the clinical manifestations seen in patients displaying both HS and PC. Loss of *KRT17* was shown to downregulate *Hes1* (an effector NOTCH pathway gene) in cervical tissue of HPV16$^{tg/+}$ Krt17$^{-/-}$ mice.[41]

TNF-α has previously been implicated in HS pathogenesis. TNF levels are elevated in skin[27] and serum[44] of patients with HS, while TNF-α inhibitors are approved by the US Food and Drug Administration for moderate-to-severe HS. Accordingly, increased expression of TNF-α, as well as other inflammatory cytokines, was observed in KCs of patients with the combined PC and HS phenotype, supporting the double-phenotype hypothesis.

A main limitation of this study is the fact that the questionnaire we used was self-administered, suggesting a self-reporting bias. In addition, patients affected with significant HS may have been more inclined to fill in the questionnaire, so we cannot exclude the possibility that the prevalence of HS was overestimated.

In conclusion, the coexistence of HS and *KRT17*-associated PC is more common than previously thought. Impaired NOTCH signalling as a result of *KRT17* mutations may predispose patients with PC to HS. A long-term prospective study may be needed to confirm the present results.

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Funding sources

A donation from the Ram family.

Conflicts of interest

The authors declare they have no conflicts of interest.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics statement

All patients provided written informed consent according to a protocol reviewed and approved by our institutional review board and by the Israel National Committee for Human Genetic Studies, in adherence with the Declaration of Helsinki principles. Patient consent was received for publishing identified information and photographs.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Figure S1 Hidradenitis suppurativa questionnaire.

Table S1 Primers used for direct sequencing.

Table S2 Mutated genes in patients with hidradenitis suppurativa and pachyonychia congenita.

Video S1 Author video.