ORIGINAL REPORT

Comprehensive Transcriptomic Profiling of Nonatopic Prurigo Nodularis in Korean Patients Reveals Il-22–driven Epidermal Stress and Neuro-immuno-fibrotic Remodelling

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Prurigo nodularis (PN) is a chronic pruritic dermatosis with incompletely defined pathogenesis, and molecular data from East Asian populations are limited. We characterized the transcriptomic signatures of nonatopic PN in Korean patients to identify pathways linked to chronic itch and lesion persistence. RNA sequencing was performed on lesional and nonlesional skin from 17 PN patients and normal skin from 11 controls, followed by differential expression, functional enrichment and correlation analyses. Lesional PN skin showed distinct transcriptional signatures with upregulation of Th22/IL-22–related genes and IL-22–inducible epidermal stress markers (*S100A7/A8/A9, SERPINB4, HRNR*), along with keratinization genes (*KRT6C, KRT16, KRT17*). Itch severity correlated strongly (Spearman's ρ>0.7) with IL-22–inducible stress genes, *IL4R*, profibrotic mediators (*WNT5A*), JAK–STAT regulators (*JAK3, SOCS1/3*), neuromodulatory/epidermal–neural genes (*TRPV3*) and senescence markers (*CDKN1A, CXCL8, PLAUR*). Nonlesional skin showed intermediate expression patterns, consistent with subclinical inflammation. Despite the modest sample size and single-ethnicity design, these findings indicate that nonatopic PN in Korean patients is characterized by IL-22–driven epidermal stress, fibroblast remodelling, neuroimmune signalling and senescence programmes, highlighting therapeutic targets including IL-31RA, IL-4Rα/JAK1, antifibrotic and senescence-directed pathways.

Key words: prurigo nodularis; RNA sequencing; IL-22; IL-31RA; JAK–STAT; fibrosis; senescence; Korean; chronic itch.

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SIGNIFICANCE

This study presents transcriptomic profiling of nonatopic prurigo nodularis (PN) in Korean patients and identifies a dominant IL-22–driven molecular signature that contrasts with the Th2-skewed profiles reported in many Western cohorts. Lesional skin exhibited coordinated activation of epidermal stress, fibroblast remodelling, neuroimmune signalling and senescence pathways, all strongly correlated with itch severity. These findings support PN as a chronic neuro-immuno-fibrotic disorder maintained by IL-22–mediated tissue stress and cytokine–neural coupling. The identification of *IL-22, IL-4Rα/JAK1, IL-31RA, WNT5A* and senescence programmes as potential therapeutic targets highlights opportunities for precision treatment of chronic itch disorders and underscores ethnic-specific immunologic diversity in PN pathogenesis.

Prurigo nodularis (PN) is a chronic, intensely pruritic dermatosis characterized by multiple hyperkeratotic nodules typically located on easily accessible body sites (1, 2). It imposes a profound psychosocial burden, frequently associated with anxiety, depression and sleep disturbance (3), and remains among the most treatment-refractory chronic itch disorders. Lesion persistence is sustained by repetitive scratching, reinforcing the itch–scratch cycle and promoting epidermal and dermal remodelling.(4–7).

Historically regarded as a variant of atopic dermatitis (AD), PN is now recognized as a distinct clinicopathological entity with overlapping but divergent pathogenic pathways (8). Prurigo-like lesions occur in up to one quarter of adults with AD (9), and both conditions exhibit microbial dysbiosis and barrier disruption (10, 11). Increasing evidence supports PN as a heterogeneous disease comprising distinct endotypes that reflect differing degrees of immune activation, neural sensitization and fibrotic remodelling (12, 13). Two major molecular clusters have been proposed: an inflammatory, atopy-associated phenotype dominated by Th2 cytokines (IL-4, IL-13, IL-31), and a neuropathic phenotype characterized by neuroimmune

dysregulation and heightened neuronal remodelling, which may respond preferentially to neuromodulatory approaches (14, 15).

Recent transcriptomic and single-cell studies have expanded the pathogenic framework of PN beyond Th2 polarization to include Th22/IL-22–driven epidermal stress responses, fibroblast activation and cellular senescence programmes (16, 17). IL-22 induces keratinocyte-derived alarmins and stress markers (*S100A7/A8/A9, SERPINB4, HRNR*) that promote epidermal hyperplasia, barrier dysfunction and keratinization (18). In parallel, fibroblasts and immune cells contribute to dermal remodelling and neuroimmune crosstalk through IL-31, oncostatin M and protease signalling that can activate sensory pathways, including via MRGPRX2 (19). These processes converge to establish a self-sustaining inflammatory and neurogenic loop underpinning lesion persistence (6).

Although the molecular landscape of PN has been increasingly delineated in Western populations, data from East Asian cohorts remain limited. Genetic background, environmental exposures and cutaneous microbiota may influence immune phenotypes across populations. While direct comparative evidence is limited, emerging transcriptomic observations suggest that East Asian PN may demonstrate relatively stronger Th22/IL-22 pathway activation, whereas Th2-skewed profiles appear more typical of Western or African American cohorts. Such variation may contribute to differences in disease chronicity and therapeutic responsiveness.

Against this background, the present study sought to characterize the transcriptomic landscape of nonatopic PN in Korean patients to identify molecular pathways linked to chronic itch and lesion persistence. By profiling lesional, nonlesional and normal skin, we aimed to delineate population-relevant molecular signatures, refine pathomechanistic models of PN and highlight potential biomarkers and therapeutic targets, including IL-4Rα/JAK1 signalling, antifibrotic modulation and senescence-associated pathways.

METHODS

Human tissue samples

Skin biopsy specimens were prospectively collected from Korean patients with clinically diagnosed nonatopic PN (n=17). Paired lesional and nonlesional skin samples were obtained using 3 mm punch biopsies; nonlesional samples were taken from clinically uninvolved skin at the same site or contralateral limb, predominantly from the lower extremities. Normal skin samples were collected from age-, sex- and ethnicity-matched healthy Korean volunteers (n=11) without AD or other chronic inflammatory skin diseases, using the same biopsy technique. All procedures were performed under local anaesthesia after written informed consent, with Institutional Review Board approval.

RNA extraction, sequencing and preprocessing

Total RNA was extracted using the RNeasy Mini Kit (Qiagen). Libraries were prepared with the TruSeq RNA Library Preparation Kit v2 (Illumina) and sequenced as paired-end reads (151 bp) on an Illumina NovaSeq 6,000. Reads were quality-filtered with *Trimmomatic v0.38* and aligned to the GRCh38 reference genome using *HISAT2 v2.1.0*. Transcript assembly and quantification were performed with *StringTie v2.1.3b*, generating raw counts and normalized expression values.

Differential expression and functional enrichment

Differential expression analysis was performed using *DESeq2 v1.38.3* with Relative Log Expression normalization. Genes with adjusted p<0.05 (Benjamini–Hochberg) and |fold change|≥2 were considered differentially expressed. Principal component analysis (PCA), multidimensional scaling and hierarchical clustering were conducted using rlog-transformed values. Functional enrichment was performed using *g:Profiler* (Gene Ontology, GO), KEGG pathway analysis and gene set enrichment analysis (GSEA) using *GSEApy* with permutation-based false discovery rate correction.

Data analysis

All statistical analyses and visualisations were performed using *R v4.2.2* and Python. Additional methodological details are provided in Appendix S1.

RESULTS

Study population and global gene expression profiles

The mean age of the PN cohort was 58.1±18.2 years, with a mean disease duration of 18.8±28.7 months. Pruritus severity, measured using the Numerical Rating Scale (NRS), averaged 7.1±2.0 for lesional skin, 1.2±1.9 for nonlesional skin and 0 for healthy controls (Table S1).

PCA demonstrated three distinct transcriptional clusters corresponding to lesional (L, n=17), nonlesional (NL, n=17) and normal control (NC, n=11) skin (**Fig. 1**a). Lesional and control samples showed the greatest separation, while nonlesional samples occupied an intermediate position, consistent with subclinical immune activation.

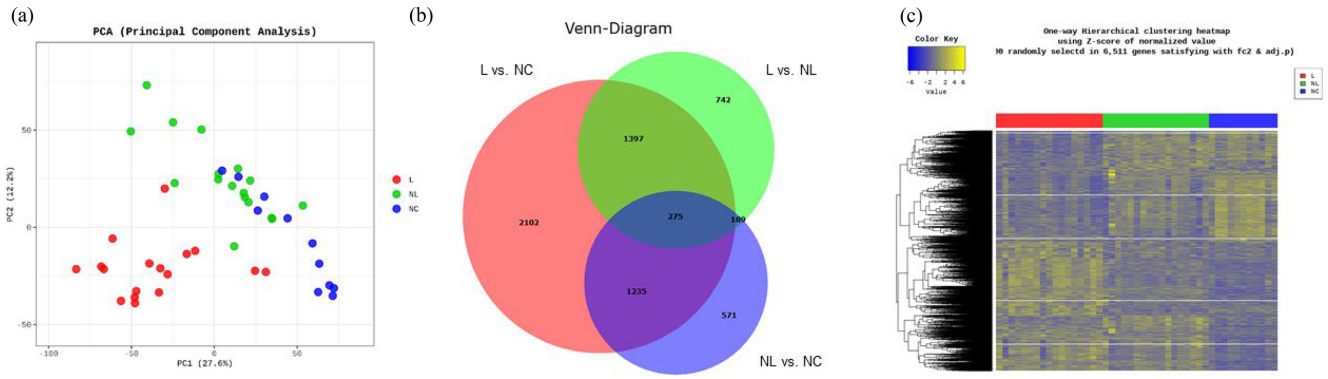

Fig. 1. Global transcriptional differences among lesional, nonlesional and normal control skin in prurigo nodularis (PN). (A) Principal component analysis (PCA) demonstrates distinct transcriptional clustering of lesional (L, *n*=17), nonlesional (NL, *n*=17) and normal control (NC, *n*=11) skin samples. Lesional and control samples show the greatest separation, while nonlesional samples occupy an intermediate position, consistent with subclinical immune activation. (B) Differential expression analysis identified extensive transcriptional changes across comparisons: L vs. NC (*n*=5,009 differentially expressed genes [DEGs]), L vs. NL (*n*=2,603 DEGs) and NL vs. NC (*n*=2,270 DEGs). The Venn diagram illustrates overlap among DEG sets, with DEGs unique to the L vs. NC comparison representing the largest proportion (76.9% of 6,511 unique DEGs), consistent with lesion-specific disease signatures. (C) Hierarchical clustering and heatmap visualization based on rlog-transformed expression values show clear segregation between lesional and control skin, with nonlesional samples displaying an intermediate expression profile.

Distinct gene expression patterns in PN lesions

Differential expression analysis identified extensive transcriptional changes across comparisons: L vs. NC (*n*=5,009 DEGs), L vs. NL (*n*=2,603 DEGs) and NL vs. NC (*n*=2,270 DEGs). DEGs from the L vs. NC comparison accounted for 76.9% of all unique DEGs (*n*=6,511) (Fig. 1b). Hierarchical clustering confirmed a clear separation between lesional and control skin, with nonlesional samples forming an intermediate expression pattern (Fig. 1c).

Functional enrichment analyses

GO and KEGG analyses indicated enrichment of developmental, metabolic and fibroblast-associated signalling pathways in lesional PN skin compared with controls, including TGF-β, Wnt and PI3K-Akt cascades (Fig. S1). These findings support dysregulated tissue remodelling and immune–stromal interactions in PN lesions.

Upregulation of the Th22/IL-22 axis and keratinization-associated genes

Lesional PN skin demonstrated strong upregulation of Th22/IL-22–related genes, including *ARNTL2, BATF, IL22RA1* and *IL22RA2,* together with IL-22–inducible stress markers (*S100A7/A8/A9, SERPINB3/B4/B13, HRNR*) (Fig. S2a, b). These signatures were accompanied by elevated expression of Th2-associated genes (*IL4R, IL10*) and Th1/IL-1 family genes (*IL12RB2, IL12RB1, IL1A, IL1B, IL36G, IL36B*). In contrast, *IL17D* was downregulated, whereas *IL17A* and *IL17F* showed no significant change (Fig. S2b).

Genes associated with keratinization and epidermal hyperplasia (*KRT6A, KRT6C, KRT16, KRT17, LCE3D*) were markedly upregulated in lesional skin. Nonlesional skin showed intermediate expression, consistent with subclinical activation of epidermal repair programmes (Fig. S2c).

Fibroblast activation and cytokine–JAK–STAT signalling

Lesional PN skin showed strong induction of profibrotic and cytokine-signalling pathways. *WNT5A*, a regulator of noncanonical Wnt signalling implicated in fibroblast remodelling, was markedly elevated. IL-6 family cytokines and receptors (*IL6, OSM, OSMR, IL31RA*) and downstream JAK–STAT regulators (*JAK3, SOCS1, SOCS3, PTPRE*) were also enriched (Fig. S3a). *IL31* transcripts showed zero read counts in a subset of samples, precluding reliable differential expression analysis and visualization in boxplots. Accordingly, *IL31* was not included in DEG-based figures. In contrast, *IL31RA* was robustly and consistently upregulated in lesional PN skin, supporting activation of IL-31–responsive signalling pathways despite limited detectability of the ligand at the transcript level. The concurrent increase in *SOCS1* and *SOCS3* without induction of *JAK1* suggests negative-feedback regulation in persistently inflamed tissue.

Neuroimmune signalling and neuromodulatory pathways

Lesional PN skin demonstrated altered expression of genes involved in epidermal–neural and immune–neural crosstalk rather than direct markers of primary afferent neurons. *TRPV3,* a keratinocyte-enriched ion channel implicated in itch amplification, was significantly upregulated, whereas the inhibitory

κ-opioid receptor *OPRK1* and the ion channel *TRPM3* were downregulated (Fig. S3b). Histamine receptors (*HRH1–3*) and the neurotrophin receptor *NTRK1* also showed differential expression, supporting modulation of itch signalling at the epidermal and immune interface rather than direct transcriptional remodelling of primary afferent neurons.

In contrast, canonical neuronal itch receptors, including *TRPV1, TRPA1* and *MRGPRX* family members, did not show statistically significant differential expression in bulk skin RNA sequencing, consistent with the low abundance of sensory nerve terminals in whole-tissue transcriptomic analyses.

Neurotrophic and nerve-sensitizing signals

Genes associated with neurotrophic support and neuronal sensitization, including *NGF, P2RY2* and *ARTN,* were significantly upregulated in lesional PN skin (Fig. S3c). These findings support the presence of a tissue microenvironment that promotes neuronal sensitization through paracrine neurotrophic signalling rather than direct transcriptional remodelling of primary afferent neurons.

Senescence and chronic tissue remodelling

Senescence-associated genes (*CDKN1A, CXCL8, FOSB, SERPINB2, PLAUR*) were enriched in lesional skin, consistent with chronic tissue stress and activation of senescence-associated secretory phenotype (SASP) programmes (Fig. S3d). *PLAUR*, which has been implicated in linking senescence-associated signalling to inflammatory amplification, provides a potential mechanistic connection between persistent tissue stress and chronic pruritus.

Ethnicity-associated itch modulators

Genes implicated in pigmentation and itch modulation in Asian populations (*S100A2*, *SLC24A5*) were significantly upregulated in lesional PN skin (Fig. S3e), suggesting potential population-linked contributions to sensory thresholds and PN phenotype expression.

Antimicrobial/alarmin response and wound healing

Lesional PN skin exhibited upregulation of antimicrobial peptide and alarmin-related genes (*DEFB103A, DEFB103B, PI3* and *IL20*), consistent with an enhanced epidermal defence response. Wound-healing and matrix-remodelling genes, including MMP1 and MMP12, were also significantly elevated, indicating ongoing tissue turnover and repair (Fig. S3e).

Correlation of gene expression with pruritus severity

Correlation analysis between gene expression and itch NRS scores revealed that, among immune-signature genes identified in the differential expression and pathway analyses, Th22/IL-22–associated transcripts accounted for the largest proportion and showed the strongest association with pruritus severity (Spearman's ρ>0.7). These correlations were most prominent for IL-22–inducible epidermal stress markers (*S100A7, S100A8, S100A9, S100A12*), keratinization-associated genes (*KRT6C, KRT16, KRT17*) and *IL4R*. Additional positive correlations were observed across Th22/IL-22,

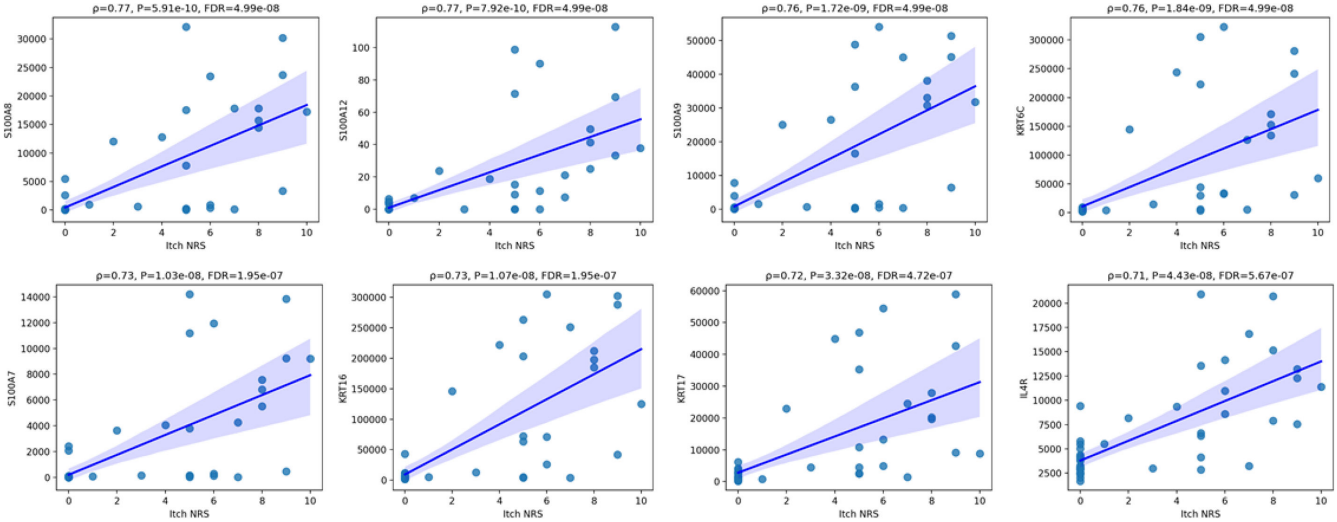

Fig. 2. Correlation of gene expression and pruritus severity in PN. Scatter plots show correlations between gene expression levels and itch NRS scores across all samples (17 lesional, 17 nonlesional, 11 normal control). Among immune-signature genes identified in the differential expression and pathway analyses, the strongest correlations (Spearman's ρ>0.7) were observed for IL-22–inducible epidermal stress and keratinization markers (*S100A7, S100A8, S100A9, S100A12, KRT6C, KRT16, KRT17*) and *IL4R.*

Th1/IL-1, JAK–STAT/IL-6, fibroblast, neuroimmune, antimicrobial/alarmin, wound-healing and senescence-related gene sets (**Fig. 2** and Table SII). These findings support coordinated immune, stromal and tissue-stress response programmes as key correlates of itch severity and lesion persistence in PN.

DISCUSSION

This study provides a comprehensive transcriptomic profile of nonatopic PN in Korean patients, revealing a multifaceted disease network characterized by IL-22–driven epidermal stress, fibroblast activation, neuroimmune sensitization and senescence-associated tissue remodelling. Analysis of paired lesional, nonlesional and control skin demonstrates that nonlesional PN exhibits an intermediate transcriptional state, consistent with subclinical inflammation and immune engagement beyond clinically visible lesions (20, 21). These findings refine current concepts of PN as a multilineage neuro-immuno-fibrotic disorder sustained by dynamic crosstalk between epidermal, dermal and neural compartments.

Lesional skin was dominated by Th22/IL-22–related transcripts and downstream stress markers such as *S100A7/A8/A9, SERPINB4* and *HRNR*, together with upregulation of keratinization-associated genes (*KRT6C, KRT16, KRT17, LCE3D*) (16, 18, 22). Rather than functioning as a direct pruritogen, IL-22 appears to potentiate an "itch-permissive microenvironment" by amplifying keratinocyte stress responses, fibroblast remodelling and cytokine-driven neuroimmune signalling, thereby enhancing pruritic drive through local circuit sensitization. The associated epithelial hyperplasia and barrier disruption are therefore more likely secondary consequences of chronic inflammation and mechanical injury rather than primary disease drivers.

Although Th22 responses predominated, IL-31–responsive pathways also contributed to disease biology. Due to zero read counts in a subset of samples, IL31 transcript levels could not be reliably assessed by differential expression analysis or visualized in boxplots. However, the robust upregulation of *IL31RA* provides molecular evidence for heightened IL-31 signalling competence in lesional skin. Given the known low abundance and spatially restricted expression of IL-31, particularly within immune–neural niches, its transcriptional underrepresentation in bulk RNA sequencing is not unexpected. These findings support a model in which IL-22 conditions an itch-permissive tissue microenvironment, while IL-31 signalling – reflected primarily through receptor upregulation – contributes to neural sensitization. Consistent upregulation of *IL-31RA* provides a molecular link between immune activation and neural excitation, supporting synergistic activity between IL-22, which conditions the tissue milieu, and IL-31, which mediates the pruritic signalling. This cooperative axis offers a mechanistic explanation for clinical response to IL-31RA blockade and its synergy with IL-4Rα and JAK1 inhibition (23).

Our data further revealed strong induction of fibroblast and matrix remodelling programmes, including *WNT5A, COL1A1, ACTA2* and IL-6 family cytokines (*IL6, OSM, OSMR, IL31RA*), implicating fibroblast plasticity and chronic wound-like signalling in nodule persistence. Upregulation of senescence-associated genes (*CDKN1A, CXCL8, PLAUR, SERPINB2*) supports a role for cellular ageing and SASP-driven remodelling in sustaining inflammation and tissue rigidity (24–29). Together, these findings position fibrosis and senescence as active disease processes rather than secondary sequelae, suggesting therapeutic opportunities with antifibrotic and senescence-targeted strategies.

The neuroimmune dimension of PN in this cohort was characterized by altered expression of epidermal- and immune-derived neuromodulatory genes rather than transcriptional changes in classical neuronal itch receptors. *TRPV3,* which is highly expressed in keratinocytes and has been implicated in epidermal–neural crosstalk and itch amplification, was upregulated (19, 30–34), whereas the inhibitory κ-opioid receptor OPRK1 was downregulated. These changes are consistent with a reduced inhibitory tone and enhanced peripheral itch signalling within the epidermal–immune compartment.

Importantly, we did not observe significant differential expression of canonical neuronal pruriceptors, including *TRPV1, TRPA1* or *MRGPRX* family members. This likely reflects the inherent limitation of bulk skin RNA sequencing, which underrepresents sparsely distributed sensory nerve fibres and mast cell–nerve interfaces. Accordingly, our findings should not be interpreted as evidence against neuronal involvement in PN, but rather as indicating that neuronal sensitization is driven predominantly by extrinsic tissue-derived signals.

The upregulation of neurotrophic and nerve-sensitizing mediators, including *NGF, P2RY2* and *ARTN,* supports a model in which chronic inflammation, fibroblast remodelling and epidermal stress create a permissive microenvironment that enhances neuronal excitability through paracrine signalling. Such mechanisms are well aligned with prior histologic and functional studies demonstrating altered nerve architecture and enhanced neuronal sensitization in PN lesions, despite minimal transcriptional signal from neuronal ion channels in bulk tissue analyses.

Collectively, these findings support a model in which itch amplification in PN is driven by epidermal and immune–derived neuromodulatory cues and neurotrophic factors rather than by direct transcriptional remodelling of primary afferent neurons.

Selective dysregulation of the JAK–STAT axis was also observed, with increased *JAK3, SOCS1* and *SOCS3* expression in the absence of *JAK1* induction, consistent with SOCS-mediated transcriptional suppression despite ongoing cytokine activity (35–37). The concurrent elevation of JAK1-linked receptors (*IL4R, IL6R, OSMR*) and their correlation with itch severity suggests preserved functional relevance of JAK1 signalling at the protein level. These findings highlight active cytokine–neural coupling and provide mechanistic rationale for the clinical efficacy of IL-4Rα blockade and selective JAK1 inhibitors in disrupting convergent pruritogenic circuits (35, 38).

Taken together, these transcriptional signatures portray PN as an inflamed, fibrotic and neurosensitized tissue state in which IL-22 establishes an itch-permissive microenvironment, IL-31 and IL-4Rα signalling sustain neural activation and fibroblast-senescence programmes maintain structural persistence (39). Restriction of our cohort to nonatopic Korean patients, while limiting direct generalizability, enabled precise delineation of endotype- and ethnicity-specific features, revealing a Th22/IL-22-dominant profile distinct from the Th2-skewed patterns reported in Western or African American PN. Although direct cross-cohort comparison was not performed, the predominance of IL-22–inducible epidermal stress genes relative to Th2 cytokines contrasts with Western PN transcriptomic studies, including Belzberg et al. (18), which reported stronger systemic and cutaneous Th2 polarization. Consistent with the results, Th22/IL-22–associated transcripts showed the strongest correlations with itch severity, supporting their dominant pathogenic role in Korean nonatopic PN. These population-linked differences may influence therapeutic responsiveness and underscore the importance of population-tailored treatment strategies.

The modest sample size and cross-sectional design represent key limitations, and functional validation at the protein and cellular levels remains necessary. Nevertheless, the internal consistency of our dataset and the inclusion of paired lesional and nonlesional samples enabled robust identification of molecular circuits underpinning itch amplification and lesion persistence.

Taken together, these transcriptional signatures portray PN as an inflamed, fibrotic and neurosensitized tissue state in which IL-22 establishes an itch-permissive microenvironment, IL-31 and IL-4Rα signalling sustain neural activation and fibroblast- and senescence-associated programmes promote lesion persistence. In nonatopic Korean patients, this IL-22–dominant molecular profile was most strongly associated with itch severity, highlighting population-specific pathogenic pathways and supporting IL-22–, IL-31RA–, IL-4Rα/JAK1–, antifibrotic and senescence-directed strategies as rational therapeutic targets.

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Data availability statement: The raw RNA sequencing reads have been deposited in the Sequence Read Archive (SRA) database (Project ID: PRJNA1198666).

Ethical statement: The study protocol was approved by the Institutional Review Board of Incheon St. Mary's Hospital, The Catholic University of Korea (OC21TISI0016). Written informed consent was obtained from all patients before skin biopsy.

Conflict of interest: Dr. Gil Yosipovitch has received funding or grants from Sanofi, Regeneron Pharmaceuticals Inc., Pfizer, Escient Health, Novartis, Eli Lilly, Celldex, and Kiniksa Pharmaceuticals. He has participated in a Data Safety Monitoring/Advisory board and received consulting support from Abbvie, Arcutis, Escient Health, Eli Lilly, Galderma, LEO Pharma, Novartis, Pfizer, Pierre Fabre, Regeneron Pharmaceuticals Inc., Sanofi, Trevi Therapeutics, Vifor, Kamari, Kiniksa, and GSK. Patents include Topical Acetaminophen Formulations for Itch Relief. The remaining authors have no conflicts of interest to declare.

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