Transcriptomic Profiling of Psoriatic Arthritis and Psoriasis Skin Lesions Reveals Shared and Distinct Gene Expression Signatures

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Introduction

About 30% of psoriasis (PsO) patients develop psoriatic arthritis (PsA), a systemic disease affecting immune responses and inflammation in skin and joint tissue. PsO is typically diagnosed with a skin biopsy, however, PsA requires blood sampling, traditional imaging (e.g. MRI), or synovial fluid samples. Often, patients with PsA are not diagnosed until they are symptomatic (joint aches, severe cartilage loss, painful inflammation, immobility, etc.) If PsA can be detected with a skin biopsy, patients may be diagnosed and treated before the onset of these debilitating symptoms. Our research design compares expression levels of genes in PsO and PsA skin biopsies to determine if there are differentially expressed genes (DEGs) between sample groups. Furthermore, these DEGs would be analyzed to evaluate their potential involvement in PsA-specific pathways. The significance of these findings would support the possibility of diagnosing PsO patients with PsA earlier than current research allows based on non-invasive skin biopsy samples.

Background

Psoriasis is a genetically based chronic autoimmune disease that targets the skin of an affected person. Previous notions suggest that psoriasis was derived from the existence of two recessive genes; later revelations show that the development of psoriasis is more complex and contains polygenic attributes. This modern understanding suggests that the disease is caused by a combination of genetic and environmental factors (Delin Ran, 2019). Currently, there are five known variations of psoriasis, with each type also varying in susceptibility. Plaque psoriasis is the most common form, totaling 90% of all cases. Plaque psoriasis causes the skin to have red patches around the forearms, stomach, and scalp. Guttate psoriasis creates drop-shaped lesions, while pustular psoriasis creates pus-filled blisters on the skin (NIAMSD, 2019). Other forms of psoriasis, such as inverse and erythrodermic, highlight the condition's variability—inverse psoriasis causes red patches in skin folds, while erythrodermic psoriasis leads to widespread rashes (NIAMSD, 2019). There is also a form of psoriasis called psoriatic arthritis (PsA), which can emerge and develop among normal PsO patients. Psoriatic arthritis affects the joint and skin tissues, causing limited mobility and articular pain. Although PsO is a genetically induced disease, skin lesions are often triggered by numerous environmental factors.

Environmental factors include both climate and psychological responses. Colder temperatures can worsen symptoms due to drier air conditions, and high levels of stress can lead to flare-ups (Boehncke & Schön, 2015; Menter & Bhushan, 2008). Certain medications can also lead to flare-ups. Beta-blockers or NSAIDS have a history of causing symptoms of PsO to worsen (Boehncke & Schön, 2015).

Significance

Understanding how Psoriasis (PsO) progresses into Psoriatic Arthritis (PsA) is important because the mechanisms behind PsA development remain poorly understood. Unlike PsO, PsA cannot be diagnosed through a routine skin biopsy. Rather, patients with symptomatic PsA often undergo blood sampling, synovial fluid aspirations, and MRI testing to reach a diagnosis. These diagnostic procedures are more invasive, costly, and frequently result in increased patient discomfort. This underscores the need to further understand PsA molecular pathways, as well as the necessity for diagnostic biomarkers to identify and prevent unnecessary disease progression.

Current Knowledge

As an autoimmune disease, psoriasis causes the immune system to hyperactivate in healthy skin cells. This attack leads to an inflammatory response, causing the proliferation and buildup of skin cells (hyperkeratinization) (Deng & Qianjin, 2016). The rapid buildup of skin cells causes the formation of plaques and scaly patches of skin associated with the disease (Deng & Qianjin, 2016). This is due to T helper 17 (Th17) producing pro-inflammatory cytokine cells, like IL-22, that stimulate and progress the keratinization. Keratinization depends on the expression of specific differentiation markers in skin cells programmed to undergo premature death. In psoriasis patients, only the early differentiation markers: involucrin, small proline-rich proteins (SPRR), cystatin A, and transglutaminase l, are expressed while the late differentiation markers are turned off (Iizuka & Ishida‐Yamamoto, 2004). This causes skin cells to react by rapidly producing late differentiation markers. The rapid production of late differentiation markers increases the presence of keratohyalin granules (profilaggrin) throughout the skin, creating the keratinized phenotype in psoriasis patients' skin (Iizuka & Ishida‐Yamamoto, 2004).

Experimental Design

Samples are from publicly available high-throughput sequencing data of paired-end RNA reads of skin biopsies extracted from GSE186063 (Deng et. al., 2022). Biopsies were taken from a cohort of fifteen patients (TABLE 1). Five patients had a dermatologist-confirmed diagnosis of psoriasis without concurrent psoriatic arthritis (PsO), five patients with diagnosed psoriatic arthritis (PsA), and five patients with ankylosing spondylitis and no history of psoriasis as a reference group (AS/CTL).

TABLE 1

Design matrix of selected samples from GSE186063. Fifteen total samples were selected with five from each sample group.

GEO Accession	Sex/Age	Disease	Tissue	SRR ID	Sample ID
GSM5629992	male, 47	PsA	skin lesion	SRR16468298	PsA_298
GSM5629994	male, 52	PsA	skin lesion	SRR16468300	PsA_300
GSM5629989	male, 29	PsA	skin lesion	SRR16468302	PsA_302
GSM5630002	male. 54	PsA	skin lesion	SRR16468333	PsA_333
GSM5630026	male, 48	PsA	skin lesion	SRR16468350	PsA_350
GSM5630010	male, 48	PsO	skin lesion	SRR16468325	PsO_325
GSM5630020	male, 26	PsO	skin lesion	SRR16468356	PsO_356
GSM5630008	male, 50	PsO	skin lesion	SRR16468327	PsO_327
GSM5630031	male, 26	PsO	skin lesion	SRR16468344	PsO_344
GSM5630018	male, 33	PsO	skin lesion	SRR16468358	PsO_358
GSM5629988	male, 32	AS	normal skin	SRR16468303	CTL_303
GSM5629985	male, 49	AS	normal skin	SRR16468305	CTL_305
GSM5629974	male, 26	AS	normal skin	SRR16468317	CTL_317
GSM5629973	male, 46	AS	normal skin	SRR16468322	CTL_322
GSM5630030	male, 47	AS	normal skin	SRR16468345	CTL_345

The original study aimed to better understand molecular profiles and gene expression among PsO and PsA patients. Lesional and non-lesional skin samples were collected via 4-mm punch full-depth biopsies. Clinical participants included thirteen PsO patients, 15 PsA patients, and 12 AS/CTL patients. RNA from samples was isolated using a QIAGEN Universal Kit and sequenced using Illumina NovaSeq 6000. A core network of genes was discovered and associated with neutrophil activation, epidermal cell differentiation, and response to bacteria. This study bolstered understanding on the inflammation and hyperkeratinization pathways in psoriatic pathogenesis (Deng et al., 2022).

Methods

Paired-end RNA-seq FASTQ files were retrieved from the Sequence Read Archive (SRA) under BioProject PRJNA772258, corresponding to the study indexed in the Gene Expression Omnibus (GEO) under accession GSE186063 (Leinonen et al., 2011; Deng et al., 2022). SRA accession numbers for the relevant samples were submitted to the Galaxy platform (Abueg et al, 2024) to facilitate downstream quality assessment and alignment procedures.

Raw sequence reads underwent initial quality checks using FastQC, with outputs subsequently compiled into a unified summary via MultiQC (Andrews, 2019; Ewels et al, 2016). To enhance read quality, adapters and low-quality ambiguous reads were removed using Trimmomatic with default parameters for paired-end reads (Bolger et al., 2014). The GRCh38.p14 version of the human genome reference sequence (FASTA) and its corresponding gene annotation file (GTF) were downloaded from Ensembl and uploaded to Galaxy (Harrison et al., 2023; Morales et al., 2022). Trimmed reads were aligned to the reference genome using HISAT2, yielding BAM alignment files for each sample (Kim et al., 2015).

Aligned reads were quantified using HTSeq-count, in which BAM files were paired with the Ensembl GTF annotation to generate gene-level read counts (Anders et al., 2014). The resulting count tables were extracted from Galaxy and imported into RStudio for statistical analysis (R Core Team, 2024; RStudio Team, 2023). Individual tables were merged into a single matrix for uniform processing.

Genes with fewer than 10 reads across all samples were excluded to minimize noise from low expression. Exploratory analysis was conducted via pairwise scatter plots

(SUPPLEMENTARY FIGURE 1) and principal component analysis (PCA) to evaluate sample similarity, detect outliers, and assess clustering patterns (SUPPLEMENTARY FIGURE 2).

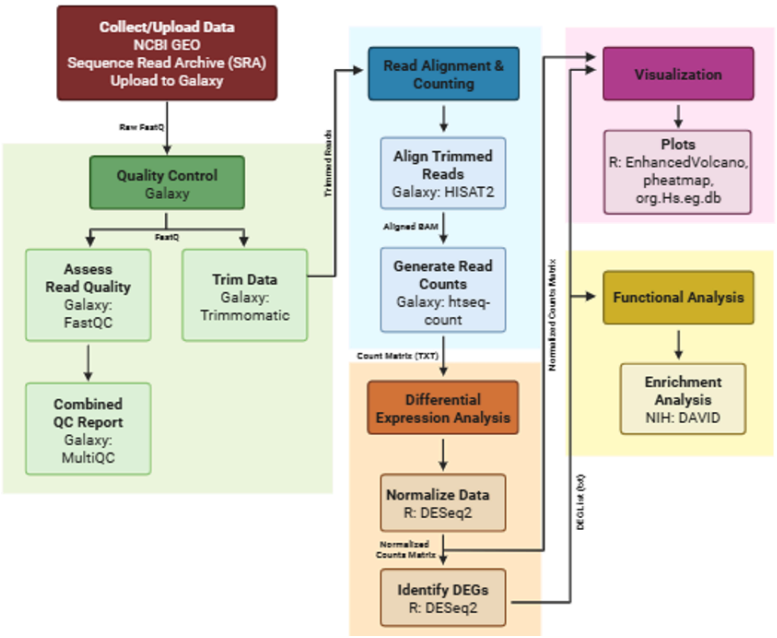
Normalized counts and differential expression testing were performed using the DESeq2 package (Love et al., 2014). Comparisons were made between three groups: PsA vs CTL, PsO vs CTL, and PsA vs PsO. Significant results were visualized using MA plots for each pairwise contrast to display the relationship between expression strength and statistical significance.

Gene Ensembl IDs were annotated with gene symbols and supplemented with metadata. Volcano plots were generated using the EnhancedVolcano package in conjunction with org.Hs.eg.db to annotate gene functions and significance levels (Blighe et al., 2025; Carlson, 2024). Candidate gene sets were used to construct heatmaps using the *pheatmap* package in R (Kolde, 2019).

Differentially expressed gene lists were exported from the R environment and uploaded to the Database for Annotation, Visualization, and Integrated Discovery (DAVID) for functional enrichment analysis. This included Gene Ontology (GO) terms, KEGG pathway associations, and protein domain over-representation (Sherman et al., 2022; Huang et al., 2009). Results were cross-validated with findings from previous literature.

The complete analysis workflow, including all tools and decision points, was visually summarized using BioRender (FIGURE 1). The R analysis pipeline can be found as a supplementary RMarkdown script.

FIGURE 1



Results

A principal component analysis (PCA) revealed distinct transcriptomic clustering among sample groups (SUPPLEMENTARY FIGURE 2). Though PsO and PsA groups had similar clustering patterns, they were graphically distinct from AS control tissue.

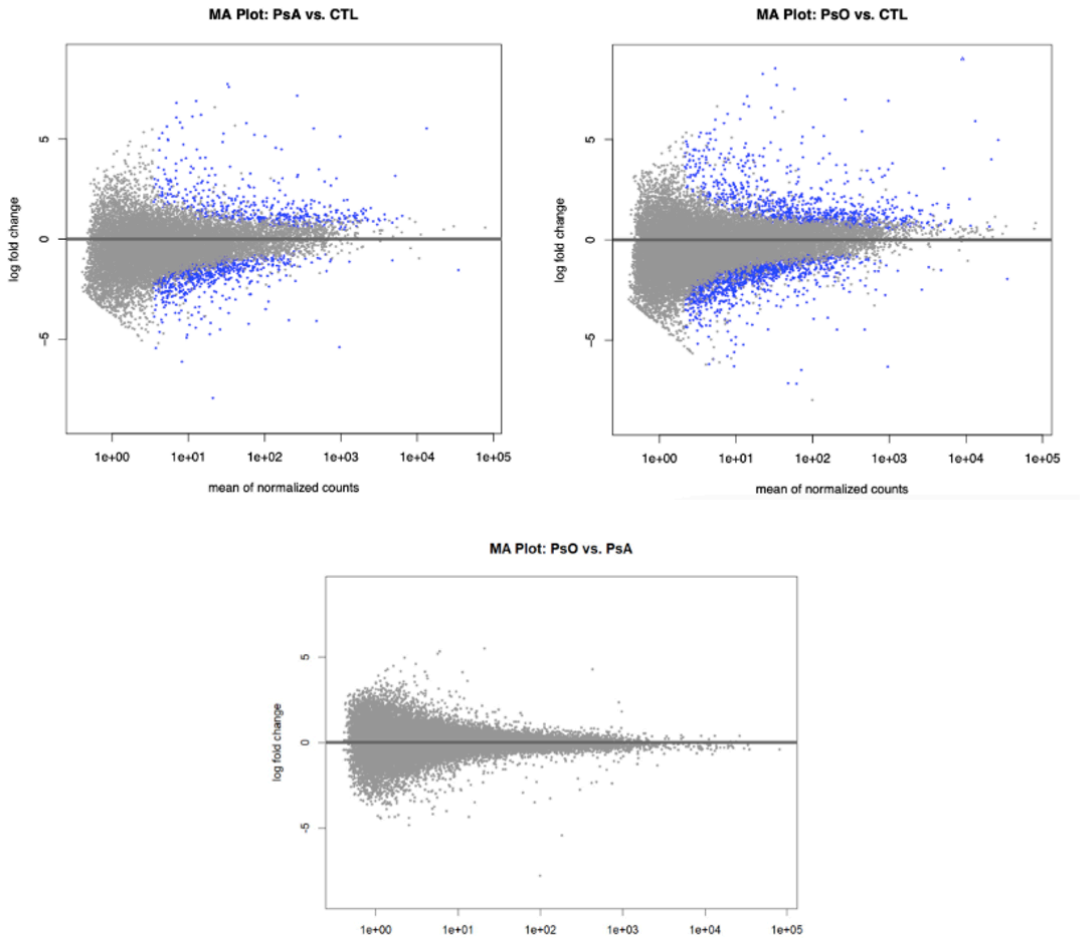
Differential gene expression analysis was conducted for the following three pairwise comparisons between sample groups: PsO vs CTL, PsA vs CTL, and PsO vs PsA (TABLE 2). 1,490 and 1,250 differentially expressed genes (DEGs) were identified in PsO vs. CTL and PsA vs. CTL comparisons, respectively (FDR < 0.05). In contrast, no DEGs were detected in the PsO vs. PsA comparison under the same significance threshold. The skin expression profiles of PsA and PsO lesions are highly similar and thus inconclusive for distinguishing them at the transcriptional level for this study.

TABLE 2
Number of statistically significant differentially expressed genes in different comparison groups

	DEGs (FDR < 0.05)		
Comparison	**Total**	**Upregulated**	**Downregulated**
PsO vs CTL	1490	664	826
PsA vs CTL	1250	621	629
PsO vs PsA	0	0	0

For all three pairwise comparisons, statistically significant up-regulated and down-regulated differentially expressed genes are represented in MA plots. There are clear DEGs expressed in both PsO and PsA groups when compared to the control, however, no DEGs are visualized between PsO and PsA (FIGURE 2).

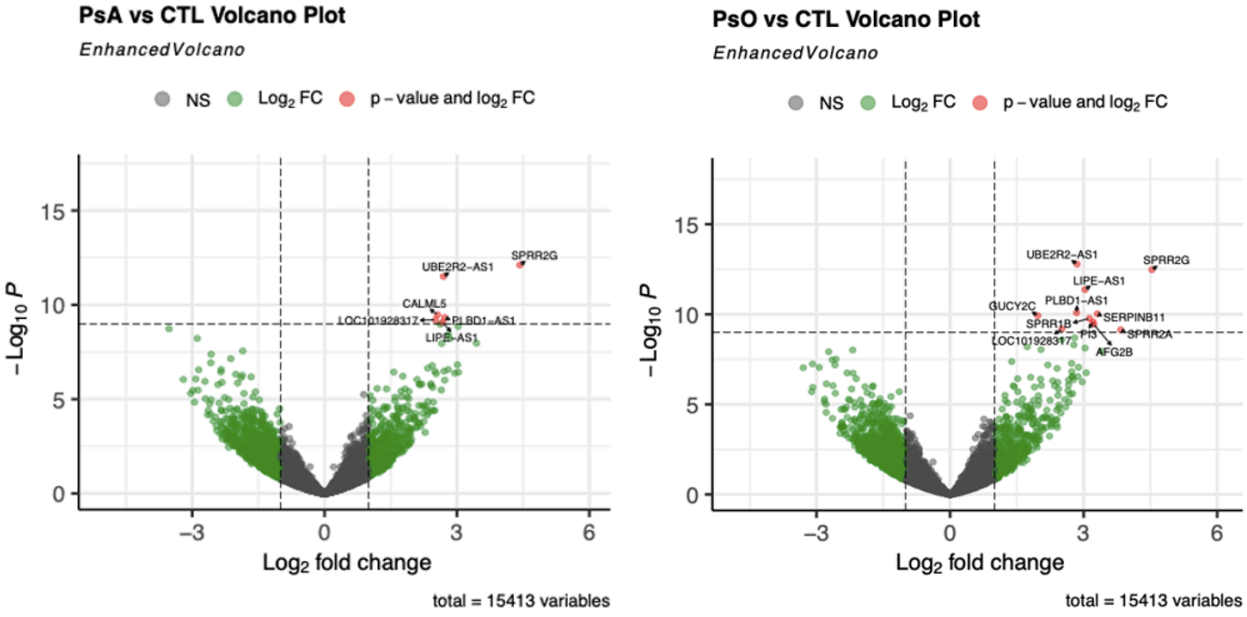
FIGURE 2



A ranked table displaying the top ten upregulated and downregulated genes was developed for PsO vs CTL and PsA vs CTL groups (SUPPLEMENTARY TABLE 1). Results are ranked by log2 fold change and only include significant DEGs (FDR < 0.05). Rankings include non-protein coding genes and protein-coding genes. Highly upregulated genes include peptidase inhibitor-3 (PI3), S100 calcium-binding proteins (S100A9, S100A7A), and small proline-rich proteins (SPRR2A, SPRR2B, SPRR2G). These genes are congruent with known involvement in keratinization and IL-17 signaling pathways central to psoriasis pathogenesis (Guo et al, 2023). Highly downregulated genes include NADH:ubiquinone oxidoreductase subunit C2 (NDUFC2), fatty acid desaturase 1 (FADS1), and forkhead box protein A1 (FOXA1) (SUPPLEMENTARY TABLE 2).

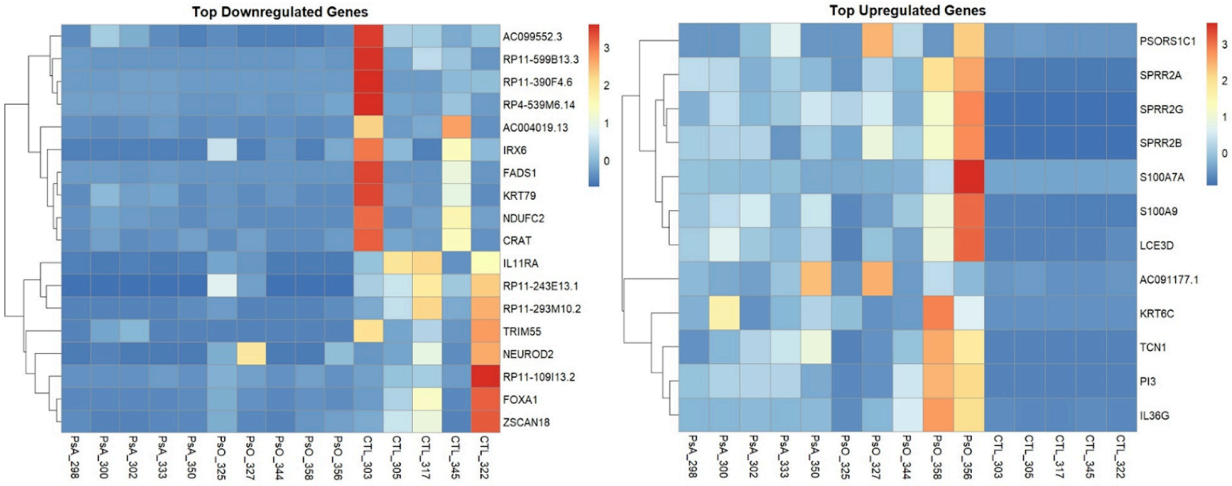
To further visualize gene expression changes, volcano plots were constructed for comparison groups that produced statistically significant DEGs. A substantial number of genes are not only significantly altered (FDR < 0.05) but also display notable changes in expression magnitude. Genes like SPRR2G, PI3, and CALML5 were among those with both high fold change and statistical significance, appearing prominently in the upper quadrants of the plots (FIGURE 3).

FIGURE 3



To explore trends in gene expression across sample groups, the most upregulated and downregulated genes across PsO and PsA groups were combined into heatmaps. This approach utilized Z-score normalized rlog-transformed counts, helping to identify consistent group-level differences and potential molecular signatures. Genes were more highly upregulated in PsO than PsA, however, both psoriatic groups displayed overall elevated expression levels in selected genes relative to AS controls. The opposite is true for selected downregulated genes, showing uniform downregulation across PsA and PsO samples relative to the AS controls (FIGURE 4).

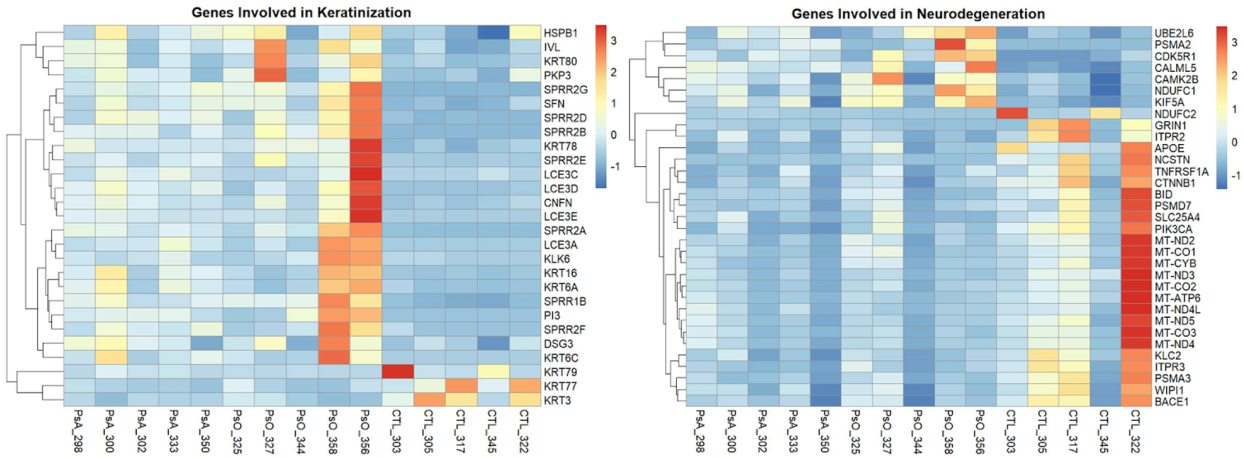
FIGURE 4



Functional enrichment analysis in DAVID revealed shared and distinct gene expression signatures in PsO and PsA groups. Both groups showed significant association with the "keratinization" and "cornified envelope" GO terms (Benjamini adjusted p-value < 0.05). This result is highly predicted for hyperproliferative epidermal changes in psoriatic pathology (Deng et al, 2022). Genes mapped to these pathways were extracted from DAVID and visualized in a heatmap to observe expression patterns across samples (FIGURE 5). Genes were more highly expressed in psoriatic samples relative to AS control tissue, except for KRT79, KRT77, and KRT3, which exhibited reduced expression.

The PsO group showed significant enrichment in the KEGG pathways for Parkinson's disease, Alzheimer's disease, and Prion disease (Benjamini-adjusted $p < 0.05$), all of which share common neurodegenerative mechanisms as identified in the DAVID annotation clusters. These pathways were not significant for the PsA group. Genes mapped to these neurodegenerative annotation terms for the PsO group were visualized in a heatmap to observe notable expression patterns across all sample groups (FIGURE 5). A small cluster of genes shows elevated expression in psoriatic lesion samples compared to controls, notably CALML5, CDK5R1, and CAMK2B. These genes are involved upstream in the phosphorylation of the Tau protein, a key factor in neurofibrillary tangle pathways and neurodegenerative diseases (Lee & Leugers, 2012).

FIGURE 5



Discussion

We did not identify any DEGs between the PsO lesion and PsA lesion group, which aligns with the findings of the original study. The original study analyzed the lesion samples from combined PsO and PsA groups against the non-lesion samples of these groups. The study also analyzed the lesion samples from combined PsO and PsA groups against non-lesional and healthy skin samples from all three groups. We analyzed the lesion PsO samples against the control group and the lesion PsA samples against the control group separately, which the original study did not perform. DEGs identified between each sample group and the control group with a p-adjusted value <0.05 were analyzed with DAVID. The top gene ontology (GO) biological process term for both groups was “keratinization”, followed by “keratinocyte differentiation” and “epidermal cell differentiation”. These processes coincide with the type of samples we analyzed, which were lesional only. This finding also agrees with the original study as the authors were able to identify overexpression of keratinocyte differentiation markers.

In our enrichment analysis, DAVID detected a cluster of genes in the PsO patients linked to the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways for Alzheimer’s disease (AD) and Parkinson's disease (PD). These pathways contribute to the accumulation of misfolded protein aggregates responsible for these diseases through a series of processes that lead to a deficiency of the ubiquitin-proteasome-autophagy system, oxidative stress and free radical

formation, endoplasmic reticulum stress, mitochondrial dysfunction, and disruptions of axonal transport (Kenehisa et al., 2000, 2019, 2025).

A subset of these pathways involves the hyperphosphorylation of tau protein, a process closely related to the pathogenesis of AD and dementia. Hyperphosphorylation of tau protein leads to the formation of paired helical filaments (PHFs) that form neurofibrillary tangles between neurons. (Iqbal et al., 2005). The tangles disrupt microtubule formation, which directly impacts the structure and function of neurons, ultimately resulting in the degeneration of the cell (Sferra et al., 2020). CALML5 encodes for calmodulin-like skin protein (CLSP) and is expressed in epidermal tissues. Although expressed in the epidermis, the protein has been documented to cross the blood-brain barrier, entering the central nervous system. CLSP has been shown to inhibit cell death through its binding to the heterotrimeric Humanin receptor (htHNR) (Yashimoto et. al, 2013). Humanin has a preventative effect on neurons against AD by countering the formation of amyloid plaques. The expression and circulation of humanin decrease as humans age and measured levels of humanin are also decreased in AD patients. Since CLSP is an agonist of the htHNR, overexpression of CLSP may have the same protective effects as humanin in AD patients (Alqahtani et al., 2025). CALML5 was highly upregulated in our PsO sample group. CALML5 is upstream of CAMK2B in the KEGG neurodegeneration pathway, which encodes calcium/calmodulin-dependent protein kinase II. CAM2KB has been shown to be essential for healthy learning abilities and synaptic strength in mice and may have similar roles in human brain development (Küry et al., 2017). In opposition to these findings, another track of this pathway involves CDK5R1, which encodes for p35, an activator of cyclin-dependent kinase 5. The hyperactivation of the complex is related to the pathogenesis of AD (Spreafico et al., 2018). However, overexpression of CDK5R1 also plays a role in pain management and is related to the functional recovery of neurons impacted by injury (Xia et al., 2023). CDK5R1 was upregulated in the PsO sample group, suggesting a potentially complex relationship with psoriasis and neurodegenerative disease, given the protective properties of CLSP and calcium/calmodulin-dependent protein kinase II paired with the upregulation of a gene involved with neural recovery. If these genes are contributing to the hyperphosphorylation of tau protein, they may instead be a precursor to the development of a neurodegenerative disorder, such as AD or PD. We would propose exploration expression levels to determine if these have an impact on therapeutic effects.

Proposal for Experimental Validation

Further validation of our findings on DEGs associated with AD and PD could be achieved through a larger analysis of the original study. Due to computational power and time constraints, a small subset of lesional samples was selected for our present research. Our findings suggest that there may be a potential link between the upregulation of protein-coding genes associated with PsO and neurodegenerative disease; however, these genes were not as highly upregulated in the PsA patients. The proteins coded by these genes are related to new epidermal growth and healing, processes that lesional skin undergoes as it is constantly irritated and broken. The original study totaled 66 samples, made up of both lesional and nonlesional samples from the PsO and PsA patients. To verify whether a relationship potentially exists between the diseases, a future experiment could be expanded to include all samples from the original study. Since CALML5 encodes for a circulating protein, we would also expect to find it upregulated in the healthy skin of PsO patients. Per our current knowledge, we would expect the genes of interest to be upregulated in PsA patients, but to a lesser extent than the PsO patients.

We hypothesize that there may be therapeutic benefits to PsO patients concerning the prevention of AD and PD development, which may be diminished with the onset of PsA. A longitudinal cohort study could be used with PsO and PsA patients to record if they develop neurodegenerative symptoms as they age. These studies are difficult to establish links between disease, as the pathogenesis of neurodegenerative disease is highly complex due to environmental and genetic factors, and is difficult to study in human subjects. Additionally, longitudinal studies require large populations to infer significant data from and may be difficult to implement. Another option for study might include collecting samples from non-epidermal tissues. The genes of interest are expressed in the skin but travel to other tissues. If they have potential impacts on brain tissue, it may be beneficial to collect samples from post-mortem brain tissue in human subjects with AD and PsO, AD and PsA, and AD with healthy skin. This would be another difficult approach to implement. The subject requirements are highly specific, and consent for the use of this type of tissue sample would be difficult to obtain for a significant population. For these reasons, bioinformatics analysis of more diverse studies with publicly available data would be the best non-invasive approach to validate our findings.

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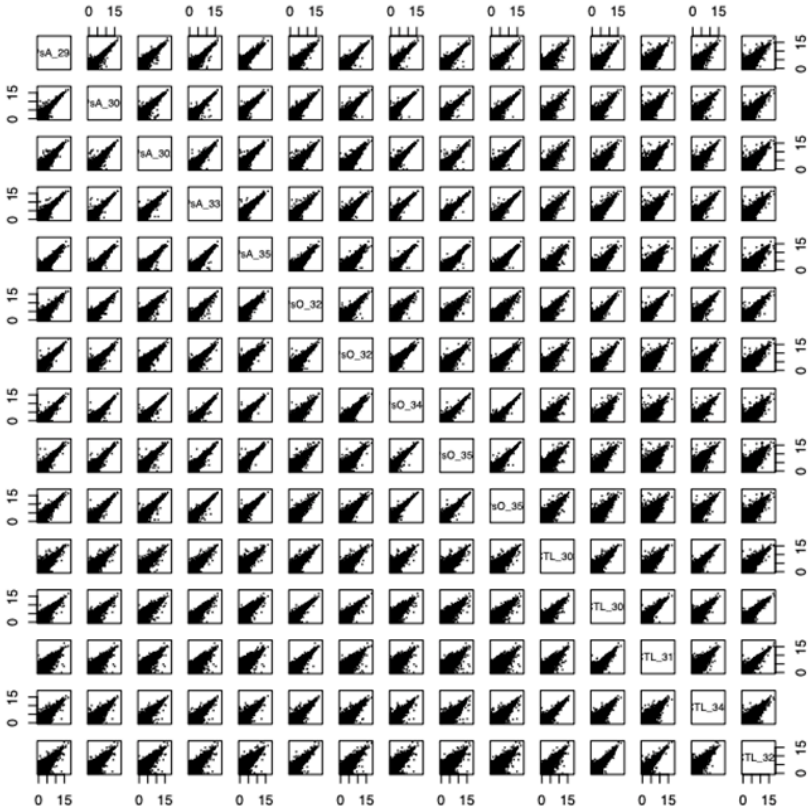
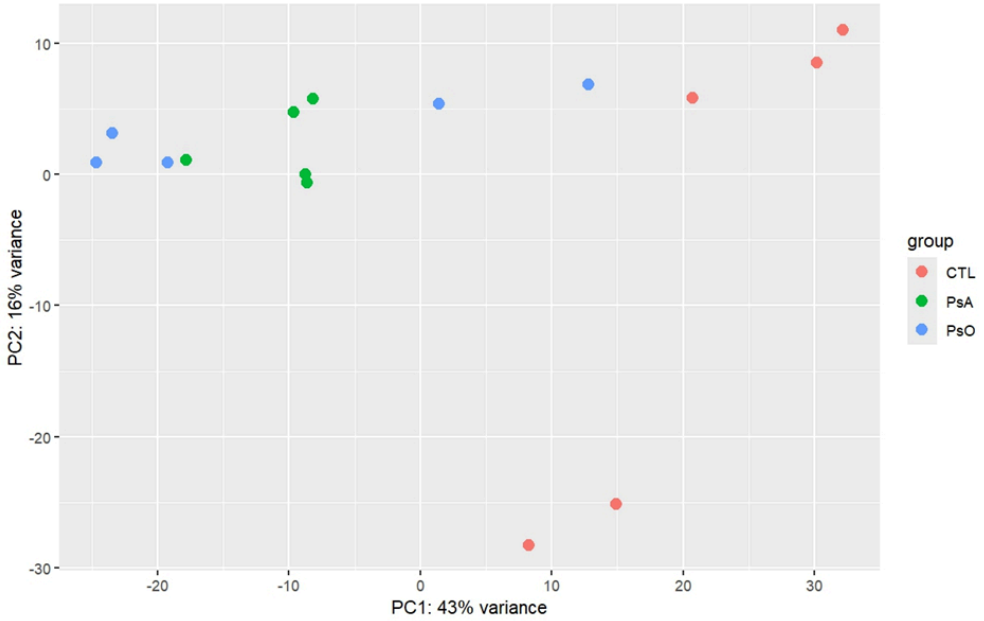
Supplementary Figures and Tables

SUPPLEMENTARY FIGURE 1



SUPPLEMENTARY FIGURE 2



SUPPLEMENTARY TABLE 1

Top ten up-regulated differentially expressed genes in psoriasis (PsO) and psoriatic arthritis (PsA) lesional biopsies vs healthy skin

	Gene Symbol	LFC	Biotype	p-adj
PsO vs CTL	PI3	+8.54	protein_coding	3.62E-07
	SPRR2G	+7.70	protein_coding	1.80E-09
	S100A7A	+7.51	protein_coding	4.76E-06
	S100A9	+6.99	protein_coding	1.98E-06
	PSORS1C1	+6.92	protein_coding	2.81E-03
	KRT6C	+6.76	protein_coding	6.96E-03
	SPRR2A	+6.65	protein_coding	6.47E-07
	IL36G	+6.58	protein_coding	7.64E-05
	SPRR2B	+6.27	protein_coding	6.17E-06
	LCE3D	+6.02	protein_coding	1.25E-04
PsA vs CTL	PI3	+7.74	protein_coding	8.12E-06
	SPRR2G	+7.60	protein_coding	3.74E-09
	S100A9	+7.16	protein_coding	1.56E-06
	KRT6C	+6.90	protein_coding	6.58E-03
	AC091177.1	+6.32	antisense	9.11E-04
	SPRR2A	+6.21	protein_coding	8.12E-06
	LCE3D	+6.13	protein_coding	1.19E-04
	TCN1	+6.07	protein_coding	7.43E-03
	SPRR2B	+5.83	protein_coding	7.51E-05
	S100A7A	+5.79	protein_coding	1.16E-03

SUPPLEMENTARY TABLE 2

Top ten down-regulated differentially expressed genes in psoriasis (PsO) and psoriatic arthritis (PsA) lesional biopsies vs ankylosing spondylitis healthy skin biopsies (CTL)

	Gene Symbol	LFC	Biotype	p-adj
PsO vs CTL	NDUFC2	-7.16	protein_coding	1.56E-04
	FADS1	-6.32	protein_coding	3.17E-05
	RP11-390F4.6	-6.30	lincRNA	1.82E-02
	TRIM55	-6.19	protein_coding	2.08E-04
	RP11-599B13.3	-5.95	lincRNA	3.58E-02
	KRT79	-5.79	protein_coding	2.47E-02
	AC004019.13	-5.59	antisense	6.78E-03
	RP4-539M6.14	-5.22	antisense	7.10E-03
	CRAT	-5.21	protein_coding	2.30E-02
	AC0099552.3	-5.00	lincRNA	2.29E-04
PsA vs CTL	RP11-243E13.1	-7.94	lincRNA	1.90E-03
	FOXA1	-6.13	protein_coding	2.10E-04
	IRX6	-5.45	protein_coding	4.53E-02
	FADS1	-5.40	protein_coding	7.31E-04
	RP11-109I13.2	-5.04	processed_transcript	4.05E-03
	RP11-293M10.2	-4.95	antisense	2.00E-03
	AC004019.13	-4.92	antisense	1.96E-02
	ZSCAN18	-4.79	protein_coding	5.52E-04
	IL11RA	-4.75	protein_coding	2.08E-06
	NEUROD2	-4.64	protein_coding	9.24E-03