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Refining the Psoriatic Transcriptome: A High-Resolution Bioinformatic Analysis of Four Molecular Hallmarks in GSE13355 Using a Curated Probe-Selection Workflow

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Abstract

Background: Psoriasis is an immune-mediated inflammatory skin disease driven by complex transcriptomic alterations. Traditional secondary workflows frequently ignore alternative transcripts by averaging or discarding redundant microarray probes, which dilutes essential biological signals.

Objective: To advance our foundational 2018 bioinformatic framework by performing a high-resolution transcriptomic analysis of four core molecular hallmarks in psoriasis - canonical TNF- α signaling, the IL-6 transduction core, the S100 calcium-binding family, and the EGFL8 pathway grid- using a refined probe-selection protocol.

Methods: Public transcriptomic data from the NCBI GEO series GSE13355 (GPL570 platform), comprising paired lesional (PP) and non-lesional (PN) skin biopsies alongside healthy controls (NN), were analyzed using R-limma. Methodologically, cross-hybridizing `_x_at` probes were excluded, while unique `_at` and shared `_s_at` probes were retained to capture splice variants. Multiple probes targeting the same gene symbol were collapsed by selecting the single most informative probe based on the highest absolute t-statistic.

Results: The S100 family displayed the highest magnitude of differential expression, led by the massive upregulation of alarmins S100A12 (logFC = 5.8263) and S100A9 (logFC = 5.8228). Within the TNF- α and IL-6 panels, NFKB1 (logFC = 0.5161) and STAT3 (logFC = 1.0926) were identified as dominant transcriptional nodes. Retaining `_s_at` probes proved essential to capture primary reactive signals for STAT3 and IKBKG. Furthermore, the EGFL8 grid revealed significant cell cycle acceleration via MAP2K1 and CDK1 induction.

Conclusion: By refining microarray probe curation, this study successfully improves the data consistency of our original model, providing a precise, systems-level resolution of the molecular hallmarks sustaining psoriatic lesions.

Keywords: Psoriasis; Transcriptomics; Microarray probe filtration; R-limma; NCBI GEO GSE13355; S100 proteins; STAT3 signaling; EGFL8 pathway

Introduction

Psoriasis is a chronic, immune-mediated inflammatory disease that primarily affects the skin and joints [1]. It is characterized by hyperproliferative keratinocytes and a strong infiltration of immune cells, leading to well-demarcated erythematous plaques [2, 3]. Traditionally, research has focused on isolated molecular pathways to understand this condition [4]. However, these traditional approaches often overlook the complex network of genomic interactions that drive the disease [5]. To address this limitation, our group previously developed an integrated bioinformatic framework to analyze large-scale genomic data, published in our 2018 study titled "Deciphering psoriasis. A bioinformatic approach" [6]. That foundational work demonstrated that high-throughput transcriptomic profiling can reveal how large blocks of genes are coordinately dysregulated during the transition from healthy skin to a psoriatic lesion [6]. By using systematic data mining, we showed that bioinformatic pipelines can move beyond identifying single biomarkers to map global genomic behavior [6].

Building directly on the conceptual and technical foundation of our 2018 study [6], the current work aims to advance our understanding of the psoriatic transcriptome. We focus our analysis on four specific macromolecular networks that act as core molecular hallmarks of the lesional tissue: canonical TNF- α signaling, the Interleukin-6 (IL-6) transduction core, the S100 calcium-binding protein family, and the EGFL8 pathway grid. Each of these systems plays a well-documented role in psoriasis. The TNF- α axis drives the initial inflammatory loop [7, 8], while the IL-6 cascade amplifies chronic cytokine signals and regulates cell differentiation [9, 10]. Simultaneously, the S100 family represents a definitive signature of epidermal barrier disruption and leukocyte recruitment [11, 12]. These networks interact with the EGFL8 pathway, an upstream modulator that coordinates Notch signaling, cell cycle progression, apoptosis, and angiogenesis [13, 14]. To study these hallmarks with high statistical power, we analyzed public transcriptomic data from the NCBI GEO database, specifically targeting the reference series GSE13355, which contains skin punch biopsies from paired lesional and non-lesional skin of psoriatic patients [15].

To ensure the highest data consistency for this manuscript, we applied a strict probe selection and filtering protocol on the Affymetrix GPL570 platform dataset [16]. Many secondary analyses simply average all probes assigned to a single gene, which can dilute the biological signal [17]. In contrast, we reviewed the specific behavior of different probe suffixes [17]. We excluded cross-hybridizing `_x_at` probes to avoid technical noise and non-specific binding [17]. However, we chose to retain both unique `_at` probes and shared `_s_at` probes [17]. This is a critical methodological step because `_s_at` probes frequently target valid splice variants and alternative transcripts that carry essential biological signals [17]. For instance, without these probes, highly significant data points for key regulators like STAT3 [19], SHC1, or IKBKG [20] would be lost. By using Empirical Bayes linear modeling (R-limma), we collapsed multiple probes by selecting the single most informative probe based on its t-statistic and adjusted p-value [18]. Consequently, this study not only extends the bioinformatic approach of our 2018 publication [6] but also refines data curation, offering a more precise, high-resolution view of the molecular architecture of psoriasis.

Materials and Methods

Data Acquisition and Study Population

Public transcriptomic data were retrieved from the National Center for Biotechnology Information (NCBI) Gene Expression Omnibus (GEO) database. We selected the high-throughput reference dataset GSE13355, which was generated using the Affymetrix Human Genome U133 Plus 2.0 Array (GPL570 platform) [15]. The study cohort consisted of 58 patients diagnosed with chronic plaque psoriasis. For each patient, skin punch biopsies were collected from both active psoriatic lesions (lesional skin, PP) and adjacent clinically uninvolved skin (non-lesional skin, PN) [15]. Additionally, skin biopsies from healthy control subjects (NN) were included in the original platform series to establish baseline physiological expression profiles [15]. All raw data (.CEL files) and pre-processed expression matrices were handled according to standard MIAME guidelines to ensure experimental reproducibility.

Curated Pathway Panel Selection

To study the molecular hallmarks of the disease, four specific macromolecular architectures and functional groups were curated based on their established biological roles in epidermal pathology [1]. The canonical TNF- α signaling architecture panel included 18 key genes involved in cascade propagation and NF- κ B activation [8, 20]. The Interleukin-6 (IL-6) transduction core panel was composed of 18 components regulating downstream JAK/STAT activation [9, 19]. The S100 calcium-binding family panel incorporated 19 proteins linked to epidermal differentiation and alarmin functions [11, 12]. Finally, the EGFL8 pathway grid was constructed as a multi-functional network consisting of 32 target genes spanning Notch signaling, cycle/apoptosis regulation, cell invasion, and angiogenesis [13, 14]. Gene symbols and functional categories were validated using the HUGO Gene Nomenclature Committee (HGNC) database.

Microarray Probe Quality Control and Curation Strategy

A customized probe-filtering protocol was designed and executed to refine data consistency and eliminate technical noise from the Affymetrix array [16]. Unlike standard workflows that average all probes mapped to a single gene symbol, we evaluated probes individually based on their specific platform design suffixes [17]. Probes with the `_x_at` suffix, which indicate a high risk of cross-hybridizing with non-specific or unrelated transcripts, were completely excluded from the dataset to prevent false-positive signals [17]. Conversely, unique probes (`_at`) and shared probes (`_s_at`) were actively retained. Retaining the `_s_at` probes was a critical biological requirement, as these probe sets target valid sequence clusters, alternative splicing variants, and crucial gene family isoforms that are highly active in inflamed skin.

Differential Expression and Probe Collapsing

Differential expression analysis between lesional skin (PP) and healthy controls (NN) was performed using the Empirical Bayes linear modeling framework via the limma package in R [18]. Background correction and quantile normalization were verified using the affy package before statistical testing [16]. To resolve the redundancy of multiple valid probes targeting the same gene, a probe-collapsing rule was applied. Instead of calculating averages,

multiple probes for a single gene symbol were filtered by selecting only the single most informative probe, defined as the probe displaying the highest absolute t-statistic and the lowest adjusted p-value [18]. False discovery rate (FDR) correction was applied using the Benjamini-Hochberg procedure, setting strict statistical significance thresholds at an adjusted p-value < 0.05 and an absolute log₂ fold change ($|\log FC|$) > 0.5.

Results

Canonical TNF- α Signaling Architecture

The transcriptomic profiling of the canonical TNF- α signaling architecture revealed a generalized upregulation of downstream effectors in psoriatic lesional skin (PP) compared to healthy controls (NN). Empirical Bayes linear modeling identified NFKB1 (probe 209239_at) as the most statistically significant differentially expressed gene within this architecture, showing a log₂ fold change (logFC) of 0.5161 and an outstanding adjusted p-value of 7.15E-27 [15] (Table 2S, Figure 1A). Other core elements of the cascade, including the shared probe for IKBKG (209929_s_at; logFC = 0.2820, adj.P.Val = 2.57E-20) and the unique probe for TRAF1 (205599_at; logFC = 0.4417, adj.P.Val = 7.77E-18), confirmed the robust activation of the NF- κ B pathway. Receptors TNFRSF1A and TNFRSF1B, as well as the ligand TNF itself (probe 207113_s_at; logFC = 0.3428), were consistently overexpressed. Conversely, MAP3K7 (probe 206853_s_at) acted as a prominent negative regulator within this panel, exhibiting a significant downregulation (logFC = -0.3708, adj.P.Val = 6.83E-13).

Interleukin-6 (IL-6) Transduction Core

The Interleukin-6 (IL-6) pathways displayed some of the strongest transcriptional alterations in the entire dataset (Table 4S, Figure 1B). Signal transducer and activator of transcription 3 (STAT3) showed massive upregulation across multiple probe sets. The most informative probe, collapsed by our selection rule, was STAT3 (probe 208992_s_at), which reached a logFC of 1.0926 and an adj.P.Val of 2.68E-38 [18]. Other valid probes for STAT3, such as 208991_at (logFC = 0.8329) and 225289_at (logFC = 0.6837), further supported this dominant activation profile [19]. Key adaptor molecules downstream of the IL-6 receptor, including SHC1 (probe 214853_s_at; logFC = 0.5640) and GRB2 (probe 215075_s_at; logFC = 0.5006), were also significantly upregulated. In contrast, upstream signaling components and nuclear transcription factors showed pronounced repression, highlighted by FOS (probe 209189_at; logFC = -1.1199, adj.P.Val = 4.08E-12) and JAK1 (probe 239695_at; logFC = -0.3520).

S100 Calcium-Binding Family

The S100 calcium-binding protein family exhibited the highest absolute magnitude of differential expression among all four hallmarks evaluated (Table 6S, Figure 1C). Two specific alarmins stood out as hyper-activated markers in lesional skin: S100A12 (probe 205863_at) displayed an exceptional logFC of 5.8263 (Fold Change = 56.74, adj.P.Val = 1.42E-94) and S100A9 (probe 203535_at) showed a parallel logFC of 5.8228 (Fold Change = 56.60, adj.P.Val = 1.26E-76) [12]. Significant overexpression was also recorded for S100A7 (probe 205916_at; logFC = 4.1945), S100A8 (probe 202917_s_at; logFC = 3.5680), and S100A2 (probe 204268_at; logFC = 1.6376) [11]. Minor transcriptional repressions

within this family were observed only for a small subset of genes, including S100A10 (probe 238909_at; logFC = -0.5821) and S100A4 (probe 203186_s_at; logFC = -0.3146).

EGFL8 Pathway Grid

Analysis of the EGFL8 pathway grid demonstrated an extensive reprogramming of cell cycle, angiogenesis, and Notch signaling components in psoriatic lesions (Table 8S, Figure 1D). Regulators of cell cycle progression and proliferation were intensely altered; MAP2K1 (probe 205476_at; logFC = 2.9684) and CDK1 (probe 208436_s_at; logFC = 2.1893) were top overexpressed variables [13]. Simultaneously, the active probe for CDK6 (210559_s_at) showed a logFC of 1.8785. On the other hand, CDK4 (probe 208712_at; logFC = -1.0132) and MAPK3 (probe 203685_at; logFC = -1.0401) were significantly downregulated. Angiogenesis-related transcripts within this grid also showed variable patterns: THBS1 (probe 223454_at; logFC = 0.7549) was induced, whereas VEGFA showed systematic downregulation across multiple probes, led by probe 212764_at (logFC = -0.7406, adj.P.Val = 6.89E-18) [14].

Discussion

The high-resolution transcriptomic analysis conducted in this study provides strong evidence that psoriasis is driven by a coordinated dysregulation of interconnected molecular modules rather than isolated pathway defects. By building upon our 2018 computational framework [6], we have mapped the behavior of four key hallmarks using the GSE13355 dataset [15]. The massive upregulation observed in the S100 calcium-binding family represents the most striking transcriptional alteration in psoriatic lesional skin. The parallel 56-fold increases in S100A12 and S100A9 confirm their roles as critical alarmins that initiate and sustain leukocyte infiltration [12]. These proteins act as endogenous ligands for pattern recognition receptors, triggering a self-amplifying inflammatory loop in the epidermis [11, 21]. The extreme statistical significance of S100A12 (adj.P.Val = 1.42E-94) highlights its potential as a highly reliable tissue biomarker for disease activity.

This epidermal alarm response operates in tandem with the sustained activation of the canonical TNF- α and IL-6 transduction cores. Our findings show that NFKB1 and STAT3 serve as the central transcriptional nodes coordinating the lesional phenotype. The significant induction of NFKB1 supports the model of NF- κ B-mediated resistance to apoptosis in psoriatic keratinocytes [20, 22]. Concurrently, the multi-probe upregulation of STAT3, led by the highly informative probe 208992_s_at, underscores its dominance in driving both immune cell recruitment and keratinocyte acanthosis [19, 23]. Interestingly, the marked downregulation of FOS observed in our IL-6 panel suggests a complex compensatory mechanism or a shift in the composition of the AP-1 transcription factor complex, which warrants further functional validation in chronic skin lesions [24].

The extensive reprogramming documented within the EGFL8 pathway grid offers a new perspective on how hyperproliferation and vascular remodeling are coupled in psoriasis. The strong induction of MAP2K1 and CDK1 provides a clear genomic explanation for the accelerated and aberrant cell cycle progression that characterizes psoriatic plaques [13]. Concurrently, the structural shifts in angiogenesis-related genes within this grid—characterized by the downregulation of VEGFA probes alongside the induction of THBS1—reflect the complex, non-linear feedback loops governing chronic tissue remodeling [14, 25].

From a methodological standpoint, the preservation and selective curation of shared `_s_` at probes using R-limma proved to be an essential step for biological discovery [18]. Traditional workflows that discard these probes or average them rawly would have missed the most reactive transcriptional signals for STAT3 and IKBKG [16, 17]. In conclusion, by combining an improved probe curation strategy with structural pathway analysis, this study refines the foundational observations of our 2018 work [6]. It moves the field closer to a comprehensive, systems-level understanding of the molecular hallmarks that sustain the psoriatic lesion.

Conclusions

This study demonstrates that the transcriptomic architecture of the psoriatic lesion is characterized by a highly coordinated dysregulation of canonical TNF- α signaling, the IL-6 transduction core, the S100 calcium-binding family, and the EGFL8 pathway grid. Rather than operating as isolated molecular defects, these four systems function as an interconnected network that drives the hyperproliferative, inflammatory, and angiogenic phenotype of the disease tissue. Our data confirm that NFKB1 and STAT3 serve as the dominant transcriptional nodes sustaining this chronic state, while the S100 alarmin family—led by massive increases in S100A12 and S100A9—acts as the primary genomic driver of epidermal barrier disruption and leukocyte recruitment.

From a methodological perspective, this work establishes that standard secondary bioinformatic pipelines that average or discard redundant microarray probes risk diluting critical biological signals. By implementing a strict probe-curation workflow that systematically excludes cross-hybridizing `_x_` at technical noise while actively retaining unique `_at` and shared `_s_` at transcripts, we successfully captured the most reactive expression variants for key regulators like STAT3 and IKBKG. Consequently, this research effectively advances the bioinformatic framework established in our 2018 publication, providing a more precise, high-resolution genomic template that improves data consistency and moves the field closer to a systems-level understanding of psoriasis pathogenesis.

Declarations Section

Competing Interests

The author declares that he has no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Use of AI Statement

During the preparation of this work, the author used an advanced AI assistant to support data analysis pipelines in R, refine the grammatical structure of the English manuscript, and ensure compliance with formatting guidelines. The author maintains full responsibility for the academic integrity and final validation of the scientific content.

Supplementary Material: Titles and Footnotes

Supplementary Table 1S. Curated Pathway Panel Architecture for Canonical TNF- α Signaling.

Footnote: This panel lists the 18 core genomic components curated to map the canonical TNF- α signaling cascade. Gene Symbols and Gene IDs are validated according to the HUGO Gene Nomenclature Committee (HGNC) database.

Supplementary Table 2S. Empirical Bayes Linear Modeling (R-limma) Output for the Canonical TNF- α Architecture in Psoriatic Lesional Skin versus Healthy Controls.

Footnote: Statistical summaries were generated using the limma package in R based on the NCBI GEO dataset GSE13355 (GPL570 platform). LogFC: log2 fold change; AveExpr: average baseline expression; t: moderated t-statistic; P.Value: raw p-value; adj.P.Val: Benjamini-Hochberg adjusted p-value (FDR); B: log-odds of differential expression (B-statistic). Suffixes _at and _s_at indicate unique and shared probe sets retained via the curation protocol, while cross-hybridizing _x_at probes were systematically excluded.

Supplementary Table 3S. Curated Pathway Panel Components for the Interleukin-6 (IL-6) Transduction Core.

Footnote: This panel defines the 18 key downstream transducers and adaptors selected to evaluate the core IL-6 framework in human epidermal tissue.

Supplementary Table 4S. Empirical Bayes Linear Modeling (R-limma) Output for the IL-6 Transduction Core in Psoriatic Lesional Skin versus Healthy Controls.

Footnote: Differential expression values were derived from active lesional (PP) skin biopsies compared against healthy reference (NN) templates within the GSE13355 series. Columns display the probe identifier, gene symbol, log2 fold change (logFC), linear fold change, average expression (AveExpr), moderated t-statistic (t), raw p-value, adjusted p-value (adj.P.Val), and B-statistic. Retained _s_at probes capture valid splice variants critical for capturing main STAT3 and SHC1 regulatory signals.

Supplementary Table 5S. Curated Pathway Panel for the S100 Calcium-Binding Protein Family.

Footnote: The panel includes 19 functional variables representing the S100 calcium-binding protein family evaluated to map epidermal differentiation defects and alarmin signatures.

Supplementary Table 6S. Empirical Bayes Linear Modeling (R-limma) Output for the S100 Calcium-Binding Family in Psoriatic Lesional Skin versus Healthy Controls.

Footnote: Data display transcriptomic shifts extracted via R-limma profiling of the GSE13355 dataset. Parameters include Probe ID, Gene Symbol, log2 fold change (logFC), linear fold change, average baseline expression, moderated t-statistic, raw p-value, false discovery rate adjusted p-value (adj.P.Val), and the B-statistic. High absolute magnitudes highlight major alarmin activation profiles.

Supplementary Table 7S. Functional Subgroups and Architecture of the EGFL8 Pathway Grid.

Footnote: This matrix organizes the 32 genes selected to construct the EGFL8 pathway framework, categorized into functional cross-talk groups: General Upstream Modulation,

Notch Signaling, Invasion/EMT, ERK/MAPK Pathway, Cell Cycle/Apoptosis, and Angiogenesis/Immune Regulation.

Supplementary Table 8S. Empirical Bayes Linear Modeling (R-limma) Output for the EGFL8 Pathway Grid in Psoriatic Lesional Skin versus Healthy Controls.

Footnote: Table values track full differential expression indices across the multi-functional EGFL8 pathway network using the limma linear modeling framework on the GSE13355 series. Statistical annotations list specific probe designations, target gene labels, log2 fold changes, linear ratios, base expression means, moderated t-statistics, adjusted significance metrics (adj.P.Val), and the corresponding log-odds (B). Redundant multiple probes are retained and presented for alternative transcript tracking.

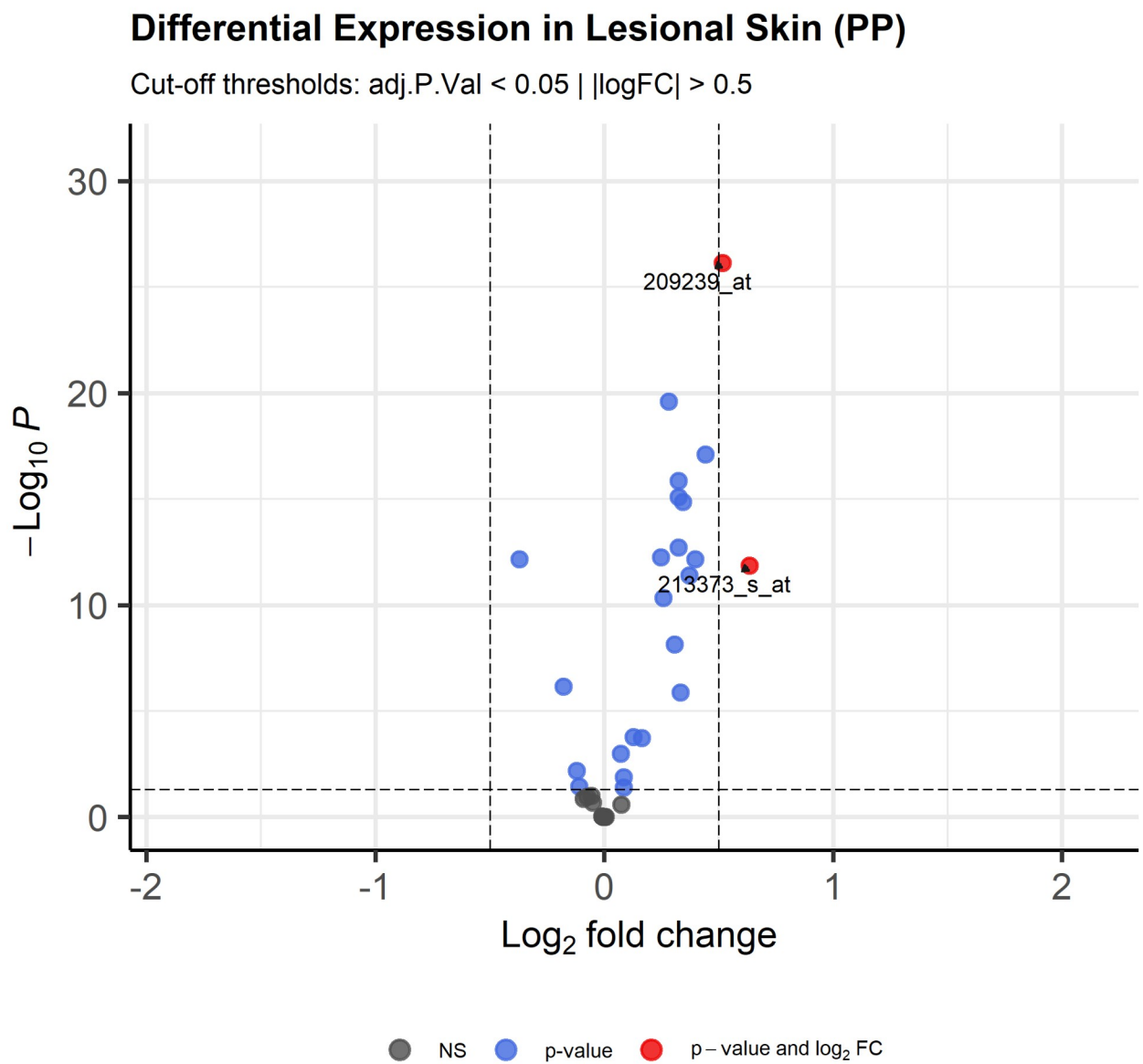
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Figure 1. Differential expression profiling of core transcriptomic hallmarks in psoriatic lesional skin.

A TNF Signaling Panel



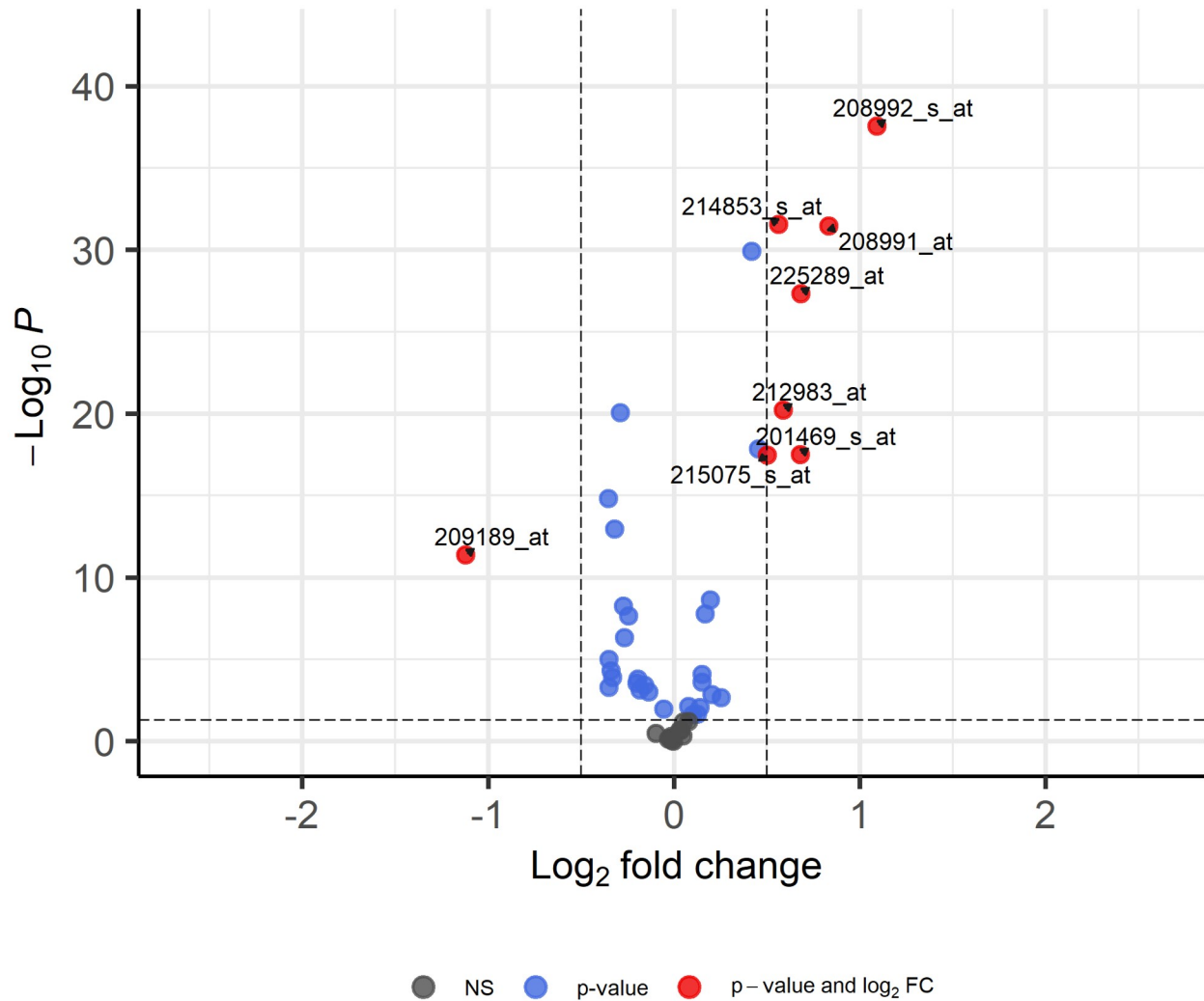
total = 34 variables

Figure 1 (continued)

B IL-6 Transduction Core

Differential Expression in Lesional Skin (PP)

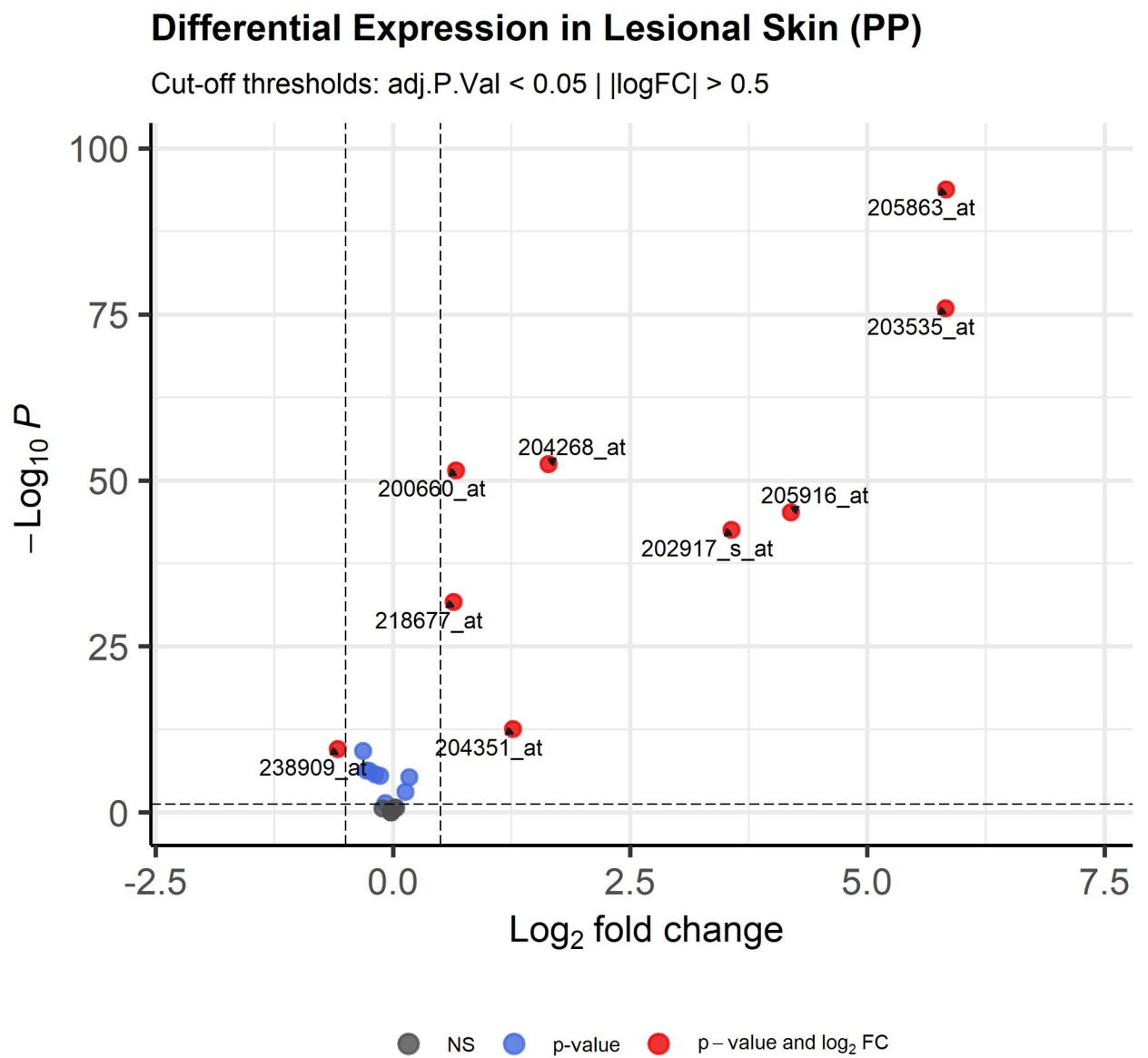
Cut-off thresholds: $\text{adj.P.Val} < 0.05$ | $|\log\text{FC}| > 0.5$



total = 47 variables

Figure 1 (continued)

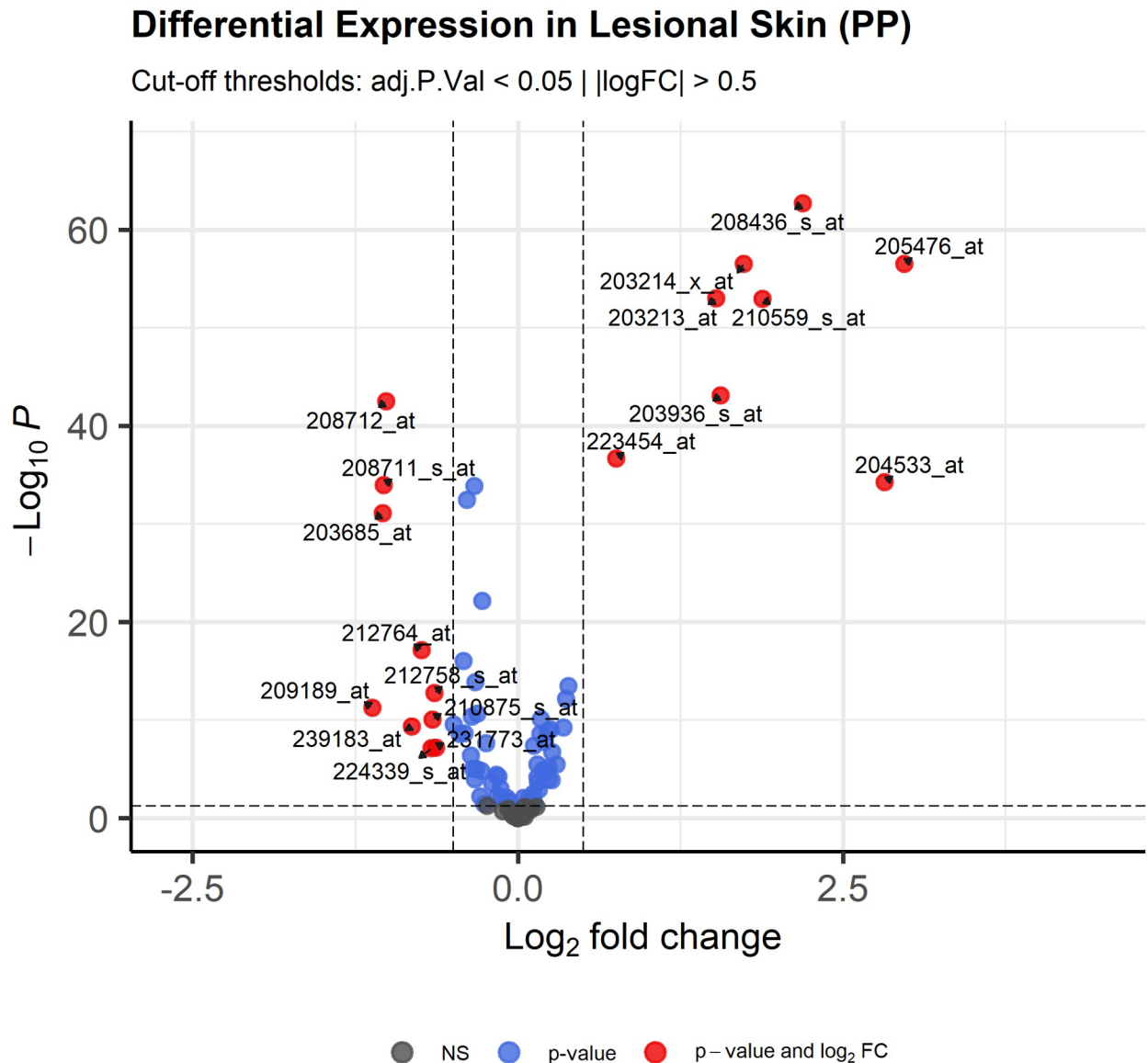
c S100 Calcium-Binding Family



total = 22 variables

Figure 1 (continued)

D EGFL8 Pathway



total = 91 variables

Volcano plots illustrate the transcriptomic alterations between psoriatic lesional skin (PP) and healthy controls (NN) across the four curated macromolecular networks: (A) Canonical TNF- α Signaling Architecture, (B) Interleukin-6 (IL-6) Transduction Core, (C) S100 Calcium-Binding Family, and (D) EGFL8 Pathway Grid. The y-axis displays the statistical significance ($-\log_{10} \text{P-value}$), and the x-axis indicates the magnitude of differential expression ($\log_2 \text{fold change}$). Dashed vertical lines represent the absolute biological threshold of $|\log_2 \text{FC}| > 0.5$, and the dashed horizontal line defines the statistical significance cutoff of adjusted P-value < 0.05 .

Dots are color-coded based on the applied probe curation rules: grey dots represent statistically non-significant variables (NS); blue dots indicate variables meeting only the adjusted P-value threshold; and red dots highlight highly significant core variables meeting both the adjusted P-value and log2 fold change criteria. Top representative and collapsed probes, including NFkB1 (209239_at), STAT3 (208992_s_at), S100A12 (205863_at), and CDK1 (208436_s_at), are explicitly labeled for architectural reference. Total variable numbers for each panel are indicated in the bottom right corners.

Supplementary Files

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