Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Epigenetic Dysregulation and H19 Suppression in Psoriasis: An SEM Approach

Antonio Romeu

antonioramon.romeu@iubilo.urv.cat

University Rovira i Virgili https://orcid.org/0000-0002-3898-061X

Lluís Arola

University Rovira i Virgili

Research Article

Keywords: Structural Equation Modeling (SEM), Psoriasis, Epigenetics, H19 long non-coding RNA, Genomic Imprinting, lavaan R package

Posted Date: July 24th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10459725/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: The authors declare no competing interests.

Epigenetic Dysregulation and *H19* Suppression in Psoriasis: An SEM Approach

Lluís Arola[1], Antoni Romeu[2,3,]

1. Department of Biochemistry and Biotechnology. University Rovira i Virgili. Tarragona. Spain
2. University Rovira i Virgili. Tarragona. Spain
3. Corresponding author. Email: antonioramon.romeu@iubilo.urv.cat

Abstract

Background: Psoriasis is characterized by widespread transcriptomic alterations, but traditional bioinformatic pipelines identify individual genes without evaluating multi-layered, network-level structures. We previously hypothesized that the coordinated activation and suppression of gene clusters on human chromosomes in psoriatic skin resemble a loss of genomic imprinting controls. Here, we present the first application of Structural Equation Modeling (SEM) in psoriasis genomics to evaluate this structural relationship.

Methods: Genome-wide transcriptomic data from 180 skin biopsy profiles were obtained from the public NCBI GEO dataset GSE13355. Core gene families involved in epigenetic machinery and psoriasis pathology were curated using Gene Ontology and KEGG databases. Differential expression analysis was performed using the limma R package, selecting the top five most statistically significant genes as indicators per category. Expression profiles were Z-score normalized, and a two-latent SEM structure (Epigenetics and Psoriasis) was estimated via the lavaan R package.

Results: The structural model demonstrated an excellent statistical fit (CFI = 0.973, TLI = 0.964, SRMR = 0.034, RMSEA = 0.087). A significant structural path coefficient of 1.00 ($p < 0.001$) connected the Epigenetics latent variable to the Psoriasis variable. The long non-coding RNA H19 exhibited a strong negative loading (-0.63), aligning with the suppression of the Wnt antagonist WIF1 (-0.88), the downregulation of CCL27 (-0.88), and the induction of the inflammatory driver CCL20 (0.93).

Conclusion: Our structural findings support the hypothesis of altered imprinting-like controls in psoriatic tissue, closely linked to H19 downregulation. This study establishes SEM as a robust methodology for modeling complex, multi-latent genomic hypotheses.

Keywords. Structural Equation Modeling (SEM), Psoriasis, Epigenetics, H19 long non-coding RNA, Genomic Imprinting, lavaan R package

Introduction

Psoriasis is a chronic, immune-mediated inflammatory dermatosis characterized by sharply demarcated erythematous plaques, epidermal hyperproliferation, and aberrant keratinocyte differentiation [1-4]. Data mining of genome-wide microarrays, such as the NCBI Gene Expression Omnibus (GEO) [5,6] specifically public baseline series like GSE13355 [7-9], has catalogued significantly dysregulated transcripts in lesional tissue [10].

We previously addressed this transcriptomic complexity by developing a dedicated computational pipeline to explore genome-wide variations in psoriatic skin [10]. Our baseline study uncovered systemic alterations affecting multiple biological pathways across all chromosomes, including the coordinated up-regulation of cell cycle genes and the synchronized suppression of core antioxidant systems. A critical conclusion of that work was that the stable, mitotically inheritable nature of the psoriatic phenotype, combined with its profound environmental sensitivity, pointed directly to an epigenetic origin. Furthermore, we hypothesized that the localized "awakening" and silencing of large, physically grouped multi-locus gene clusters on human chromosomes closely mirrored the behavioral patterns of genomic imprinting (monoallelic gene expression). Nevertheless, our 2018 framework relied on standard differential expression analysis, a method that captures individual downstream end-products but lacks the structural capability to mathematically model the upstream regulatory forces driving these coordinated domain actions.

In complex biological systems, traditional univariate linear models or multiple regression strategies fall short because they assume that predictor transcripts act independently. In reality, the epigenetic machinery operates as a highly integrated network where individual writers, erasers, and non-coding transcripts share underlying variance. To resolve this statistical limitation, this study introduces Structural Equation Modeling (SEM) to the field of psoriasis genomics [11]. While SEM is a rigorous reference methodology widely validated in fields like econometrics, psychometrics, and sociology to evaluate relationships between latent (unobserved) constructs [11-13], its application to molecular dermatology remains virtually unexplored. SEM provides a transformative analytical advantage by clustering observed variables -such as Z-normalized gene expressions- into multi-indicator latent variables (Epigenetics and Psoriasis). This approach models measurement error explicitly and evaluates multi-layered, directional causal hypotheses simultaneously, offering a direct statistical analogue to the complex network structure of living cells.

The primary objective of this study is to advance our previous bioinformatic baseline by validating a parsimonious, two-latent SEM architecture that directly tests whether the upstream expression of the epigenetic machinery explains the downstream phenotypic gene network in lesional skin cells. Using the NCBI GEO GSE13355 dataset as a robust testing matrix, we curated using Gene Ontology and KEGG databases top-ranked differentially expressed indicators via the limma R package, focusing heavily on the long non-coding RNA H19 -a master structural regulator of genomic imprinting domains. By deploying the lavaan package from the empirical covariance matrix, we provide structural verification for our chromosome-cluster hypothesis, presenting a novel methodological framework capable of scaling into increasingly complex, multi-latent genomic designs for inflammatory dermatoses.

Methodology

Rationale for Structural Equation Modeling (SEM)

Traditional univariate regression and standard linear models are inherently limited when analyzing complex biological systems, as they evaluate single gene-to-gene interactions in isolation. In the context of psoriasis, the transcriptomic phenotype is characterized by massive, non-linear, and coordinated cascades of gene activation and suppression. Standard regression methods cannot capture the multiplicative effects or the shared variance of underlying regulatory machineries.

To overcome these limitations, we employed Structural Equation Modeling (SEM). SEM offers a distinct mathematical advantage by grouping individual observed variables (gene transcripts) into unobserved, functional latent constructs (Epigenetics and Psoriasis). This methodology accounts for measurement error within the indicators and evaluates directional, causal-effect pathways between the latent constructs simultaneously. By utilizing SEM, we could test the systemic hypothesis that upstream epigenetic dysregulation directly dictates the downstream inflammatory and hyperproliferative phenotype in psoriatic skin, establishing a network-level reference framework for genomic analysis.

Data Source and Preprocessing

Transcriptomic data were obtained from the public NCBI GEO database, under the reference series GSE13355 (GDS4602). The dataset comprises genome-wide expression profiles from 180 skin biopsy samples processed on the Affymetrix Human Genome U133 Plus 2.0 microarray platform (GPL570). Raw data files are normalized and log2-transformed using the Robust Multichip Average (RMA) method to ensure consistency across arrays.

Indicator Selection and Differential Expression

To identify the manifest indicators for each structural latent construct, a comprehensive list of candidate genes mapping to epigenetic machinery and psoriatic pathogenesis was initially curated from the Gene Ontology (GO) and KEGG pathway public databases.

To isolate the most transcriptomically robust markers for modeling, we performed a rigorous differential expression analysis comparing involved psoriatic lesional skin against healthy control skin. The computational analysis was executed using the limma package in R, applying an empirical Bayes linear modeling framework. Transcripts were ranked and filtered using strict statistical criteria (Adjusted p-value < 0.05) via Benjamini-Hochberg false discovery rate control, and a minimum $\log_2$Fold Change > 1. Following this filtering step, the top 5 most statistically significant genes per functional dimension were established as the final measurement indicators to define the Epigenetics and Psoriasis latent variables within the SEM architecture (Table 1). Prior to structural modeling, the $\log_2$-transformed expression values of these 10 core genes were Z-score normalized (mean = 0, standard deviation = 1) across all samples to eliminate scale discrepancies and ensure baseline statistical comparability (Table 2)

Structural Equation Modeling Estimation

The structural model was specified, estimated, and evaluated using the lavaan package (version 0.6-21) in R. Because gene expression data can exhibit non-normal distributions, parameters were estimated using maximum likelihood with robust standard errors (MLR). To ensure full reproducibility of the mathematical structure, standard errors, and fit statistics, the computation was executed directly from the empirical covariance matrix of the Z-normalized indicators. Model fit was comprehensively assessed using multiple established criteria: the Comparative Fit Index (CFI),

the Tucker-Lewis Index (TLI), the Root Mean Square Error of Approximation (RMSEA), and the Standardized Root Mean Square Residual (SRMR).

Results and Discussion

The structural SEM model demonstrated an excellent fit to the NCBI GEO GSE13355 dataset (N = 180). Figure 1 shows the SEM diagram demonstrating the causal pathway between epigenetic dysregulation and the psoriatic transcriptomic phenotype. Table 3 shows the SEM fit Statistics and global parameter assessment. The Comparative Fit Index (CFI = 0.973) and the Tucker-Lewis Index (TLI = 0.964) both surpassed the standard 0.95 threshold for good model fit. The Standardized Root Mean Square Residual (SRMR = 0.034) further supported the adequacy of the model structure, as values below 0.05 indicate a minimal discrepancy between the observed and predicted correlation matrices. Although the Root Mean Square Error of Approximation (RMSEA = 0.087) was slightly elevated, the overall robust fit indices justify the structural pathways proposed.

An analysis of the specific factor loadings within the Epigenetics latent variable highlights a coordinated transcriptional shift. The histone deacetylase HDAC1 (0.93) and the polycomb repressive complex subunit EZH2 (0.78) show strong positive loadings, and their residual variances exhibit a significant positive covariance of 0.319 ($p = 0.003$). This statistical covariance aligns with biological evidence demonstrating that HDAC1 and EZH2 physically interact and co-operate to silence tumor suppressor genes and regulatory pathways through histone methylation and deacetylation [14-16]. In contrast, BRD4 has a negative loading (-0.67). This shows that as gene-silencing complexes become highly active, certain epigenetic readers and writers like BRD4 are downregulated [17]. This upstream dysregulation directly mirrors the downstream Psoriasis phenotype profile. The chemokine CCL20, a known driver of Th17 cell recruitment [18], shows a critical positive loading of 0.93. Simultaneously, the Wnt pathway antagonist WIF1 presents a strong negative loading of -0.88. The down-regulation of WIF1 implies a loss of control over Wnt signaling, which promotes the characteristic epidermal hyperproliferation seen in psoriatic lesions [19], demonstrating how the model successfully pairs epigenetic repression with phenotypic activation.

Within the Epigenetics construct (Figure 1), the long non-coding RNA H19 exhibits a distinct negative factor loading (-0.63). In our model, the negative factor loading of H19 ($\lambda = -0.63$). Its severe downregulation in lesional tissue correlates with the loss of growth control in psoriatic epidermis, which is associated with increased keratinocyte proliferation [20,21]. The measurement model shows prominent positive loadings for the pro-inflammatory chemokine CCL20 ($\lambda = 0.93$) within the Psoriasis latent variable (Figure 1). This strong statistical indicator reflects the established role of CCL20 in recruiting pathogenic Th17 cells to psoriatic lesions [22]. Similarly, the transcription factor STAT3 shows a strong positive factor loading ($\lambda = 0.82\)$) within the same latent construct. This high value is consistent with the established role of STAT3 as a central transcriptional driver of keratinocyte proliferation and immune activation in psoriatic tissue [23]. Conversely, the model identifies heavily suppressed negative factor loadings for WIF1 ($\lambda = -0.88$), CCL27 ($\lambda = -0.88$), and S100A7 ($\lambda = -0.86$) (Figure 1). The negative loading of WIF1 reflects its epigenetic silencing via promoter hypermethylation [24], while the suppression of CCL27 aligns with the breakdown of homeostatic immune regulatory axes in chronic psoriatic lesions [25]. Finally, the inverse behavior of S100A7 is consistent with its established role as a potent negative regulator of normal human epidermal differentiation under inflammatory stress [26]. Biologically, the SEM model (Figure 1) revealed a definitive structural path coefficient of 1.00 from the boths epigenetic and psoriasis phenotype latent variables.

The integration of the long non-coding RNA H19 as a significant negative indicator (-0.63) bridges a critical conceptual gap previously hypothesized in our baseline study [10]. In that work, we suggested that the massive, coordinated activation and silencing of specific chromosomal gene clusters in psoriasis strongly resembled the behavior of genomic imprinting (monoallelic expression patterns). The SEM results provide empirical, structural verification for this hypothesis. H19 is a classic master regulator of genomic imprinting, known to orchestrate the higher-order chromatin conformation and monoallelic expression of imprinted gene domains via its Imprinting Control Region (ICR) [27].

Concluding Remarks

In conclusion, this study presents a novel structural equation modeling (SEM) framework that connects epigenetic dysregulation with the transcriptomic phenotype of psoriasis. Utilizing the GSE13355 dataset, the model shows an excellent fit (CFI = 0.973, SRMR = 0.034), indicating that gene expression shifts in psoriatic skin operate as a coordinated network. Notably, the negative loading of the imprinted lncRNA H19 supports our previous hypothesis regarding altered imprinting-like controls in this pathology (Melero et al., 2018). This architecture transitions the analysis from single genes to network-level interactions, offering a validated template to interpret complex genomic structures in inflammatory dermatoses.

Competing interests

The authors declare no competing interest

Acknowledgements

This work has not been awarded grants by any Institution. The authors acknowledges NCBI GEO database contributors

References

1. Gayathri K Perera, Paola Di Meglio, Frank O Nestle. Psoriasis. Annu Rev Pathol 7:385-422.2012. PMID: 22054142.doi: 10.1146/annurev-pathol-011811-132448.
2. Francesca Capon. The Genetic Basis of Psoriasis. Int J Mol Sci18(12):2526.2017. PMID: 29186830. doi: 10.3390/ijms18122526.
3. Adriana Rendon, Knut Schäkel. Psoriasis Pathogenesis and Treatment. t J Mol Sci 20(6):1475.2019. PMID: 30909615. oi: 10.3390/ijms20061475.
4. Izabela Sieminska, Monika Pieniawska, Tomasz M Grzywa. The Immunology of Psoriasis-Current Concepts in Pathogenesis. Clin Rev Allergy Immunol 66(2):164-191.2024. PMID: 38642273. doi: 10.1007/s12016-024-08991-7.
5. Ron Edgar, Michael Domrachev, Alex E Lash. Gene Expression Omnibus: NCBI gene expression and hybridization array data repository. Nucleic Acids Res 30(1):207-10.2002. PMID: 11752295. doi: 10.1093/nar/30.1.207.
6. Tanya Barrett, Dennis B Troup, Stephen E Wilhite, Pierre Ledoux, Carlos Evangelista, Irene F Kim, Maxim Tomashevsky, Kimberly A Marshall, Katherine H Phillippy, Patti M Sherman, Rolf N Muertter, Michelle Holko, Oluwabukunmi Ayanbule, Andrey Yefanov, Alexandra Soboleva.

NCBI GEO: archive for functional genomics data sets--10 years on. Nucleic Acids Res 39(Database issue):D1005-10.2011. PMID: 21097893. doi: 10.1093/nar/gkq1184.
7. Rajan P Nair, Kristina Callis Duffin, Cynthia Helms, Jun Ding, Philip E Stuart, David Goldgar, Johann E Gudjonsson, Yun Li, Trilokraj Tejasvi, Bing-Jian Feng, Andreas Ruether, Stefan Schreiber, Michael Weichenthal, Dafna Gladman, Proton Rahman, Steven J Schrodi, Sampath Prahalad, Stephen L Guthery, Judith Fischer, Wilson Liao, Pui-Yan Kwok, Alan Menter, G Mark Lathrop, Carol A Wise, Ann B Begovich, John J Voorhees, James T Elder, Gerald G Krueger, Anne M Bowcock, Gonçalo R Abecasis. Genome-wide scan reveals association of psoriasis with IL-23 and NF-kappaB pathways. Nat Genet 41(2):199-204.2009. PMID: 19169254. doi: 10.1038/ng.311.
8. William R Swindell, Andrew Johnston, Steve Carbajal, Gangwen Han, Christian Wohn, Jun Lu, Xianying Xing, Rajan P Nair, John J Voorhees, James T Elder, Xiao-Jing Wang, Shigetoshi Sano, Errol P Prens, John DiGiovanni, Mark R Pittelkow, Nicole L Ward, Johann E Gudjonsson. Genome-wide expression profiling of five mouse models identifies similarities and differences with human psoriasis. PLoS One Apr 4;6(4):e18266.2011. PMID: 21483750. doi: 10.1371/journal.pone.0018266.
9. Jun Ding, Johann E Gudjonsson, Liming Liang, Philip E Stuart, Yun Li, Wei Chen, Michael Weichenthal, Eva Ellinghaus, Andre Franke, William Cookson, Rajan P Nair, James T Elder, Gonçalo R Abecasis. Gene expression in skin and lymphoblastoid cells: Refined statistical method reveals extensive overlap in cis-eQTL signals. Am J Hum Genet87(6):779-89.2010. PMID: 21129726. doi: 10.1016/j.ajhg.2010.10.024.
10. Juan L Melero, Sergi Andrades, Lluís Arola, Antoni Romeu. Deciphering psoriasis. A bioinformatic approach. J Dermatol Sci 89(2):120-126.2018. PMID: 29239787. doi: 10.1016/j.jdermsci.2017.11.010. Epub 2017 Nov 22.
11. Piotr Tarka. An overview of structural equation modeling: its beginnings, historical development, usefulness and controversies in the social sciences. Qual Quant 52(1):313–354.2017. PMID: 29416184. doi: 10.1007/s11135-017-0469-8.
12. Lisa D Wijsen, Denny Borsboom, Anna Alexandrova. Values in Psychometrics. Perspect Psychol Sci 17(3):788–804.2021. PMID: 34846952. doi: 10.1177/17456916211014183.
13. Douglas Gunzler, Tian Chen, Pan Wu, Hui Zhang. Introduction to mediation analysis with structural equation modeling. Shanghai Arch Psychiatry 25(6):390-4.2013. PMID: 24991183. doi: 10.3969/j.issn.1002-0829.2013.06.009.
14. J van der Vlag, A P Otte. Transcriptional repression mediated by the human polycomb-group protein EED involves histone deacetylation. Nat Genet 23(4):474-8.1999. PMID: 10581039. doi: 10.1038/70602.
15. Amy E Schade, Ryan Kuzmickas,. arrie L Rodriguez, Kaia Mattioli, Miriam Enos, Alycia Gardner, Karen Cichowski. Combating castration-resistant prostate cancer by co-targeting the epigenetic regulators EZH2 and HDAC. PLoS Biol Apr 27;21(4):e3002038.2023. PMID: 37104245. doi: 10.1371/journal.pbio.3002038.
16. Taichi Takashina, Ichiro Kinoshita, Junko Kikuchi, Yasushi Shimizu, Jun Sakakibara-Konishi, Satoshi Oizumi, Masaharu Nishimura, Hirotoshi Dosaka-Akita. Combined inhibition of EZH2 and histone deacetylases as a potential epigenetic therapy for non-small-cell lung cancer cells. Cancer Sci 107(7):955-62.2016. PMID: 27116120.doi: 10.1111/cas.12957.
17. Xiaohui Sun, Pengfei Yang. Inhibition of BRD4 inhibits proliferation and promotes apoptosis of psoriatic keratinocytes. Biomed Eng Online 20(1):107.2021. PMID: 34674702. doi: 10.1186/s12938-021-00943-y.
18. Erin G Harper, Changsheng Guo, Heather Rizzo, Joseph V Lillis, Stephen E Kurtz, Iliyana Skorcheva, David Purdy, Erin Fitch, Mihail Iordanov, Andrew Blauvelt. Th17 cytokines stimulate CCL20 expression in keratinocytes in vitro and in vivo: implications for psoriasis

pathogenesis. J Invest Dermatol 129(9):2175-83.2009. PMID: 19295614. doi: 10.1038/jid.2009.65.
19. Johann E Gudjonsson, Andrew Johnston, Stefan W Stoll, Mary B Riblett, Xianying Xing, James J Kochkodan, Jun Ding, Rajan P Nair, Abhishek Aphale, John J Voorhees, James T Elder. Evidence for altered Wnt signaling in psoriatic skin. J Invest Dermatol130(7):1849-59.2010. PMID: 20376066. doi: 10.1038/jid.2010.67. Epub 2010 Apr 8.
20. Chun-Xiao Li, Hua-Guo Li, Lin-Ting Huang, Yu-Wei Kong, Fu-Ying Chen, Jian-Yin Liang, Hong Yu, Zhi-Rong Yao. H19 lncRNA regulates keratinocyte differentiation by targeting miR-130b-3p. Cell Death Dis 8(11):e3174.2017. PMID: 29192645. doi: 10.1038/cddis.2017.516.
21. Yuexi He, Xiran Yin, Jianjun Yan, Xue Li, Qing Sun. The lncRNA H19/miR-766-3p/S1PR3 Axis Contributes to the Hyperproliferation of Keratinocytes and Skin Inflammation in Psoriasis via the AKT/mTOR Pathway. Mediators Inflamm 2021:9991175.2021. PMID: 34992498. doi: 10.1155/2021/9991175. eCollection 2021.
22. Kazuhisa Furue, Takamichi Ito, Gaku Tsuji, Takeshi Nakahara, Masutaka Furue. The CCL20 and CCR6 axis in psoriasis. Scand J Immunol 91(3):e12846.2020. PMID: 31692008. doi: 10.1111/sji.12846.
23. Limin Li, Lu Chen, Cai Zhang, Wenchao Yao, Zhengxiao Li, Faming Tian. Role of the STAT3 Signaling Pathway in Cell Proliferation and Inflammation in Psoriasis and Approaches for Targeted Therapies: A Review. Med Sci Monit 32:e952449.2026. PMID: 42015469. doi: 10.12659/MSM.952449.
24. Jing Ma, Lu Gan, Hongying Chen, Lihao Chen, Yu Hu, Chao Luan, Kun Chen, Jiaan Zhang. Upregulated miR-374a-5p drives psoriasis pathogenesis through WIF1 downregulation and Wnt5a/NF-κB activation. Cell Signal 119:111171.2024. PMID: 38604345. doi: 10.1016/j.cellsig.2024.111171.
25. Masaru Karakawa, Mayumi Komine, Yasushi Hanakawa, Hidetoshi Tsuda, Koji Sayama, Kunihiko Tamaki, Mamitaro Ohtsuki. CCL27 is downregulated by interferon gamma via epidermal growth factor receptor in normal human epidermal keratinocytes. J Cell Physiol 229(12):1935-45.2014. PMID: 24710735. doi: 10.1002/jcp.24643.
26. Eui Dong Son, Hyoung-June Kim, Kyu Han Kim, Bum Ho Bin, Il-Hong Bae, Kyung-Min Lim, Seok Jong Yu, Eun-Gyung Cho, Tae Ryong Lee. S100A7 (psoriasin) inhibits human epidermal differentiation by enhanced IL-6 secretion through IκB/NF-κB signalling. Exp Dermatol 25(8):636-41.2016. PMID: 27060579. doi: 10.1111/exd.13023. Epub 2016 Jun 20.
27. Sreenivasulu Kurukuti, Vijay Kumar Tiwari, Gholamreza Tavoosidana, Elena Pugacheva, Adele Murrell, Zhihu Zhao, Victor Lobanenkov, Wolf Reik, Rolf Ohlsson. CTCF binding at the H19 imprinting control region mediates maternally inherited higher-order chromatin conformation to restrict enhancer access to Igf2. Proc Natl Acad Sci U S A 103(28):10684-9.2006. PMID: 16815976. doi: 10.1073/pnas.0600326103.

Table 1. Manifest indicators selected for the *Epigenetics* and *Psoriasis* latent variables in the SEM architecture.

Probe_ID*	GENE_ID	Symbol	Gene.Title	Latent
201697_s_at	1786	DNMT1	DNA (cytosine-5-)-methyltransferase 1	Epigenetics
203358_s_at	2146	EZH2	enhancer of zeste 2 polycomb repressive complex 2 subunit	Epigenetics
238612_at	23476	BRD4	bromodomain containing 4	Epigenetics
201209_at	3065	HDAC1	histone deacetylase 1	Epigenetics
224997_x_at	283120	H19	H19 imprinted maternally expressed transcript (non-protein coding)	Epigenetics
208991_at	6774	STAT3	signal transducer and activator of transcription 3	Psoriasis
205476_at	6364	CCL20	chemokine (C-C motif) ligand 20	Psoriasis
205916_at	6278	S100A7	S100 calcium binding protein A7	Psoriasis
207955_at	10850	CCL27	chemokine (C-C motif) ligand 27	Psoriasis
204712_at	11197	WIF1	WNT inhibitory factor 1	Psoriasis

*: Probe ID Platform GPL570: [HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array. NCBI GEO GDS4602. Reference Series: GSE13355

Transcriptomic profile markers were derived from the public **NCBI GEO GDS4602 / GSE13355** reference series. Gene selection was initiated using baseline functional families from the **Gene Ontology (GO)** and **KEGG pathway** repositories. Indicators represent the top 5 most statistically significant differentially expressed genes per category, determined via the empirical Bayes linear modeling framework in the **limma R package** comparing psoriatic lesional skin against healthy controls (see Methodology)

Table 2. Empirical covariance and correlation matrix of the Z-normalized SEM model indicators.

	DNMT1	EZH2	BRD4	HDAC1	H19	STAT3	CCL20	S100A7	CCL27	WIF1
DNMT1	1	0.6948	-0.501	0.7303	-0.4914	0.6252	0.7361	0.7392	-0.7372	-0.6965
EZH2	0.6948	1	-0.4783	0.8009	-0.4625	0.5809	0.7268	0.7201	-0.6931	-0.6769
BRD4	-0.501	-0.4783	1	-0.5796	0.5735	-0.6378	-0.5833	-0.6162	0.6196	0.6016
HDAC1	0.7303	0.8009	-0.5796	1	-0.5648	0.7592	0.8716	0.7846	-0.8219	-0.825
H19	-0.4914	-0.4625	0.5735	-0.5648	1	-0.5611	-0.556	-0.5581	0.5539	0.5359
STAT3	0.6252	0.5809	-0.6378	0.7592	-0.5611	1	0.7752	0.6858	-0.7234	-0.6928
CCL20	0.7361	0.7268	-0.5833	0.8716	-0.556	0.7752	1	0.8005	-0.7944	-0.8296
S100A7	0.7392	0.7201	-0.6162	0.7846	-0.5581	0.6858	0.8005	1	-0.7397	-0.7414
CCL27	-0.7372	-0.6931	0.6196	-0.8219	0.5539	-0.7234	-0.7944	-0.7397	1	0.8041
WIF1	-0.6965	-0.6769	0.6016	-0.825	0.5359	-0.6928	-0.8296	-0.7414	0.8041	1

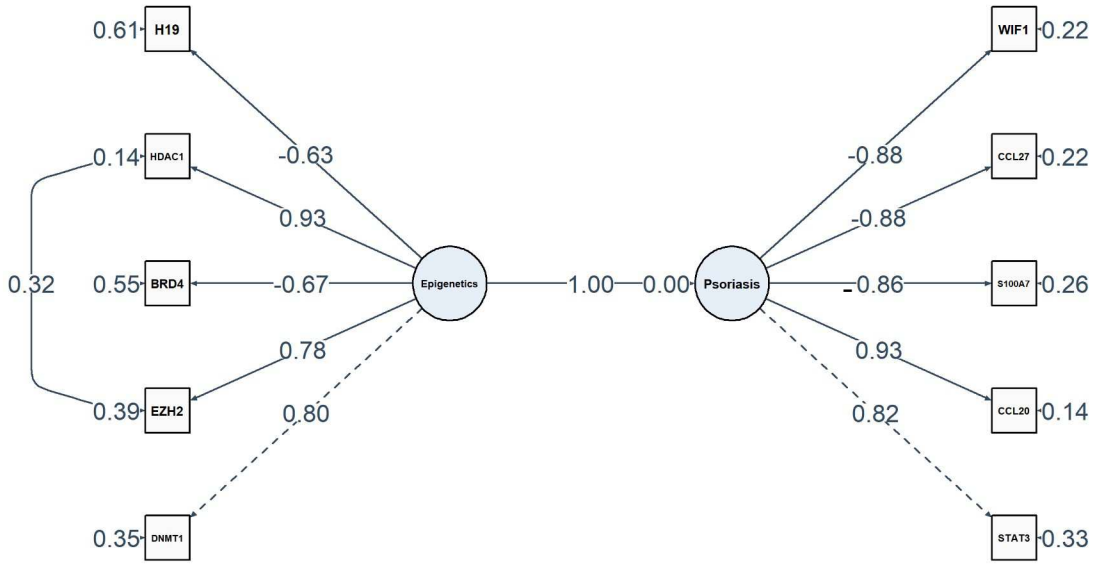
Values represent the Pearson correlation coefficients r derived from the Z-normalized expression data (N = 180) skin biopsies from dataset GSE13355). Because the data are Z-score normalized, the correlation matrix is mathematically equivalent to the variance-covariance matrix used as the primary input for the lavaan structural equation modeling engine, provided here to guarantee complete computational reproducibility of the paths and fit indices reported. All correlation coefficients are statistically significant ($p < 0.001$).

Table 3. Structural Equation Modeling (SEM) Fit Statistics and Global Parameter Assessment

Fit Index/Criterion	Value (Standard/ Unscaled)	Value (Robust/ Scaled)	Threshold for Good Fit
Sample Siza (N)	180	180	-
Estimator Type	Maximum Likelihood (ML)	Robust ML (MLR)	-
Model Chi-Square (χ^2)	80.602	83.792	-
Degrees of Freedom (*df*)	34	34	-
χ^2 P-value	0.000	0.000	> 0.05 (Often Significant in Large N)
Comparative Fit Index (CFI)	**0.973**	**0.972**	>= 0.95
Tucker-Lewis Index (TLI)	**0.964**	**0.963**	>= 0.95
Standardized Root Mean Square Residual (SRMR)	**0.034**	**0.034**	< 0.08 (Excelent if < 0.05)
Root Mean Square Error of Approximation (RMSEA)	0.087	0.088	Ideally <= 0.05; Reasonable <= 0.06 to <= 0.08
RMSEA 90% Confidence Interval	(0.063 - 0.112)	(0.065 - 0.113)	Narro Interval
Akaike Information Criterion (AIC)	3479.381	3479.381	For Model Comparison
Bayesian Information Criterion (BIC)	3546.433	3546.433	For Model Comparison

(N = 180) skin biopsy observations derived from the NCBI GEO GSE13355 reference dataset. Bold numerical values indicate that the structural model metrics strictly surpass the standard established psychometric and genomic thresholds for acceptable or excellent overall model fit.

Figure 1. Structural equation model (SEM) diagram demonstrating the causal pathway between epigenetic dysregulation and the psoriatic transcriptomic phenotype.



Path diagram representing the structural and measurement relationships evaluated using the public NCBI GEO GSE13355 dataset (N = 180 skin biopsy profiles). Latent constructs are depicted in circles (Epigenetics and Psoriasis), whereas measured manifest gene indicators are shown in rectangles. Single-headed arrows represent directional pathways, with values indicating standardized factor loadings (λ) for the measurement model and the structural path coefficient (β) between the two latent variables.The structural path demonstrates a definitive coupling (1.00) from the latent Epigenetics construct to the Psoriasis phenotype. Dashed arrows indicate the reference indicators (DNMT1 and STAT3) fixed to a variance baseline during model specification. Double-headed curved arrows indicate significant covariance between residual variances, highlighting the highly significant correlation (0.32) between HDAC1 and EZH2 error terms. Small outer arrows with numerical values adjacent to the rectangles denote the standardized residual variances (uniqueness/error) for each manifest gene variable. All reported standardized loading and path estimates are statistically significant ($p < 0.001$).