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

DeCorey Bolton Jr., Michael Gage, Taylor Pralle & Julianna Vargo

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Introduction

- High-throughput paired-end RNA sequences from NCBI database
- Reanalysis of study with a Psoriasis vs. Psoriatic Arthritis lens
- Hypothesized finding a difference between gene expression levels between PsO and PsA that might explain PsA development from regular PsO

Background

- Psoriasis (PsO) is a chronic genetically linked autoimmune disease that affects the skin through the creation of dry, irritable patches.
- Special genetic variation: **psoriatic arthritis (PsA)**
  - Can emerge and develop among normal PsO patients

Psoriasis (PsO)	Shared Traits	Psoriatic Arthritis (PsA)
• Effect remains to the skin • Diagnosed via skin biopsy • Typically precedes PsA if PsA develops at all	• Skin lesions (red, scaly, patchy skin) • Autoimmune response • About 30% of PsO patients also are diagnosed with PsA	• Effect progresses to joints • Joint pain, swelling, and limited mobility • Diagnosed via MRI, blood sample, and/or synovial fluid sample

Significance

- There is currently a lack of understanding surrounding the development and mechanisms of PsA.
    - PsA is challenging to diagnose:
        - Requires blood or synovial fluid sampling from fully symptomatic patients
- Diagnostic procedure is invasive & painful.
- Furthering our knowledge of PsA will allow for the discovery of possible methods of detecting PsA before the development of symptoms.

Current Knowledge

- Immune response to psoriasis :
  - Proliferation and build up of skin cells (keratinocytes)
    - Formation of plaques and scaly patches

- T helper 17 (Th17) releasing cytokine cells (IL-22) stimulates and progresses the keratinization of the skin cells.
  - The process of keratinization:
    - Dependent on the recognition of type of differentiation marker:
      1. Early differentiation markers
      2. Late differentiation markers

- PsO has polygenetic attributes, allowing it to be expressed through several different genes.

Experimental Design

(Deng et. al., 2022)

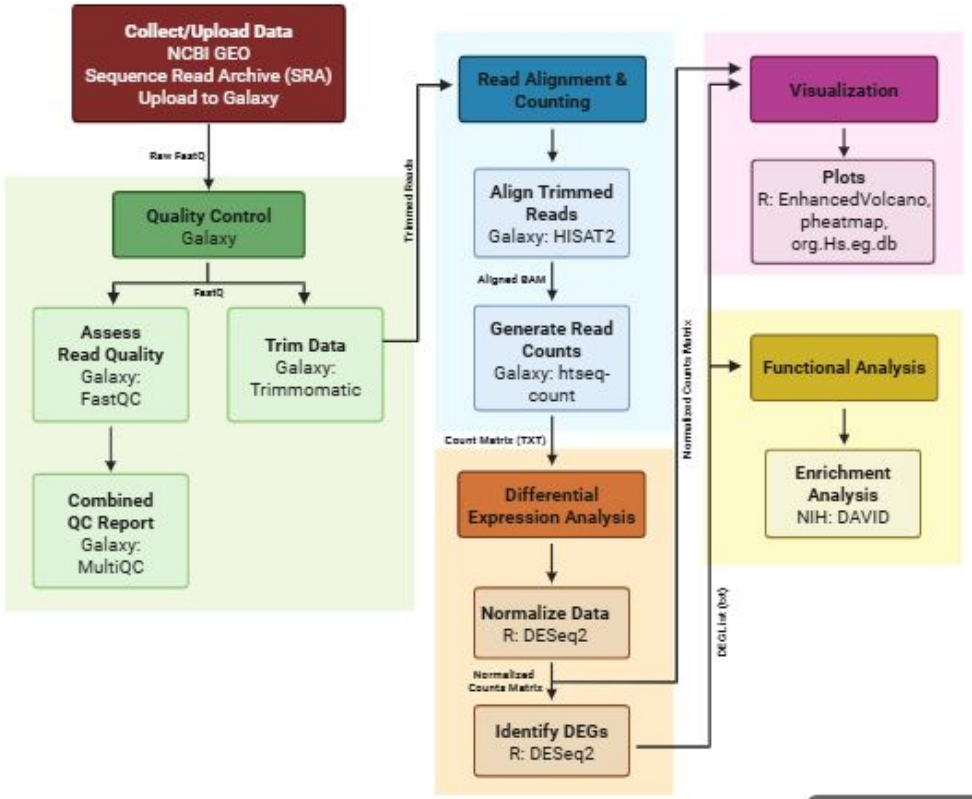
Dataset Source: GSE186063

Samples include high-throughput paired-end sequence reads taken via skin biopsies.

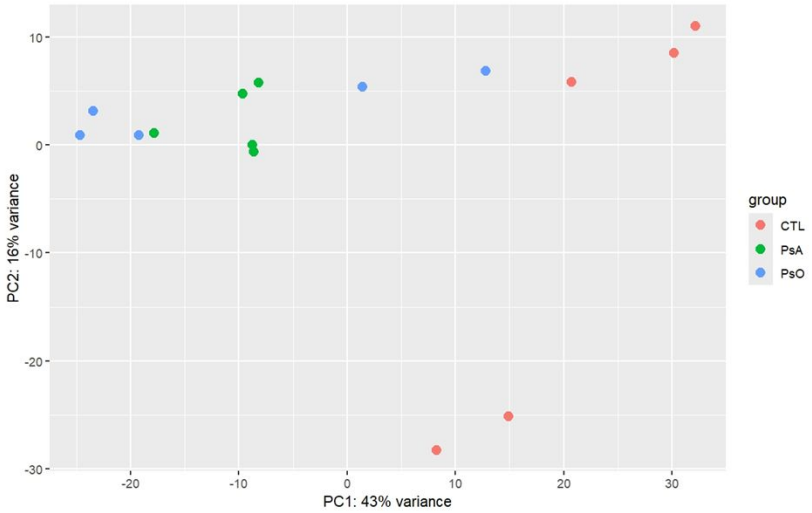
- 5 from subjects with dermatologist-confirmed PsO with no concurrent diagnosis of PsA as sample group 1
- 5 from subjects with diagnosed PsA as sample group 2
- 5 from subjects with Ankylosing Spondylitis and no history of PsO or skin lesion as controls

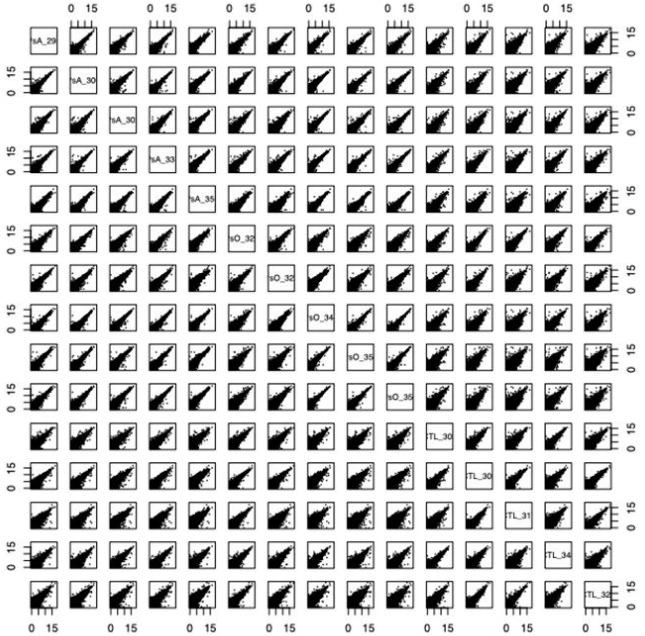
Sample	GEO Accession	Condition	Characteristic	TissueType
male, 47 years	GSM5629992	lesional	PsA	skin
male, 52 years	GSM5629994	lesional	PsA	skin
male, 29 years	GSM5629989	lesional	PsA	skin
male. 54 years	GSM5630002	lesional	PsA	skin
male, 48 years	GSM5630026	lesional	PsA	skin
male, 48 years	GSM5630010	lesional	PsO	skin
male, 26 years	GSM5630020	lesional	PsO	skin
male, 50 years	GSM5630008	lesional	PsO	skin
male, 26 years	GSM5630031	lesional	PsO	skin
male, 33 years	GSM5630018	lesional	PsO	skin
male, 32 years	GSM5629988	non-lesional (control)	AS (non-psoriatic)	skin
male, 49 years	GSM5629985	non-lesional (control)	AS (non-psoriatic)	skin
male, 26 years	GSM5629974	non-lesional (control)	AS (non-psoriatic)	skin
male, 46 years	GSM5629973	non-lesional (control)	AS (non-psoriatic)	skin
male, 47 years	GSM5630030	non-lesional (control)	AS (non-psoriatic)	skin

Methods – Workflow



Diagnostic Analysis





Results

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

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

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

DESeq2 Results

- PsO vs CTL: 1490 (664 up, 826 down)
- PsA vs CTL: 1250 (621 up, 629 down)
- PsO vs PsA: 0

Notable Genes

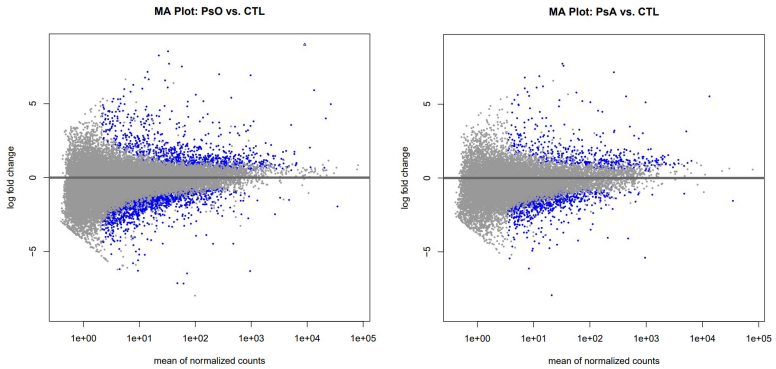
Upregulated

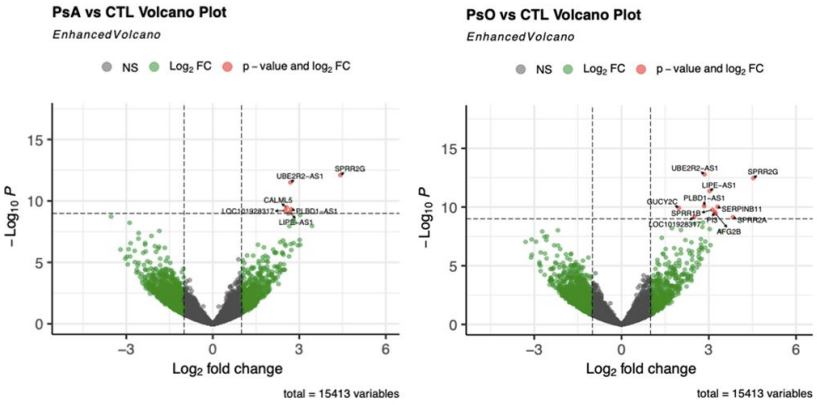
- PI3
- S100A9, S100A7A
- SPRR2A, SPRR2B, SPRR2G

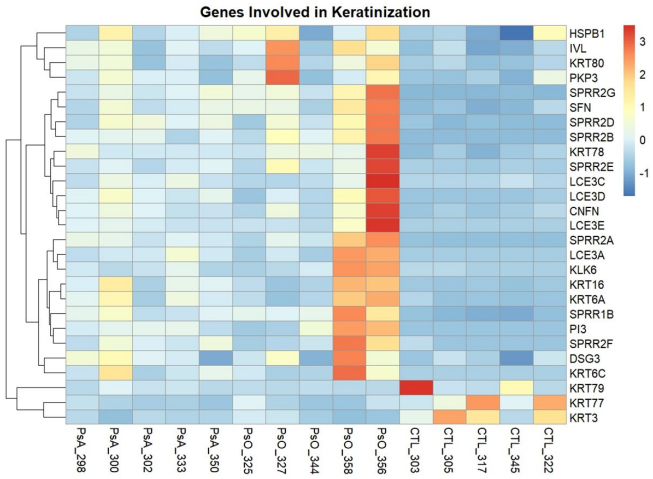
Downregulated

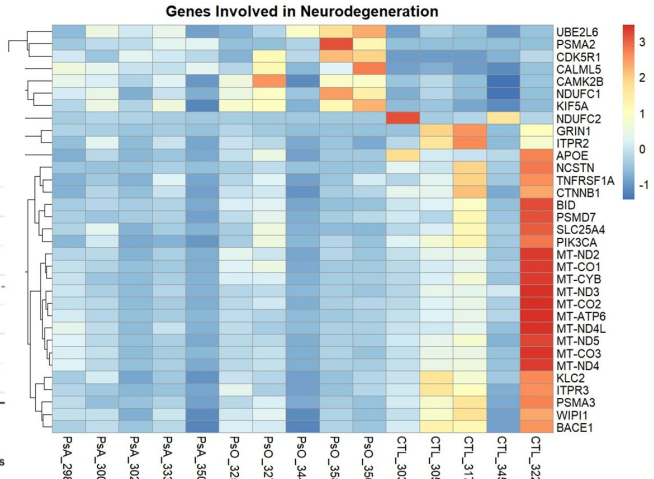
- NDUFC2
- FADS1
- FOXA1

Results cont.









DAVID Results

- Top shared pathways were "*keratinization*" and "*cornified envelope*".
- Highly anticipated
- Involvement in known psoriatic pathology

Unique Findings

- PsO group showed correlation with neurodegenerative disease pathways
  - Alzheimer's
  - Parkinson's
  - Prion Disease

- CALML5
- CDK5R1
- CAMK2B

Discussion

- Results comparison to original study
  - No DEGs identified between PsO and PsA lesion groups
    - Aligns with original study
  - Compared PsO and PsA lesions samples vs. healthy control skin separately
- DAVID Analysis
  - Top terms verify sample characteristics
    - Keratinization
    - Keratinocyte differentiation
    - Epidermal cell differentiation
  - PsO group had enrichment of neurodegenerative disease pathways (AD and PD)
    - CALML5: encodes CLSP; neuroprotective
    - CAMK2B: Learning and synaptic function
    - CDK5R1: Dual role in neurodegeneration and neural repair pathways

Conclusions

- Original hypothesis was not supported
  - PsA-specific pathways not identified over PsO samples
- Potential link to neurodegeneration either in pathogenesis or therapeutic applications

Proposal for Experimental Validation

- Re-analysis of all samples from original study
  - Are the genes of interest in non-lesional skin?
  - Are the genes of interest more high up-regulated in PsO non-lesional skin vs PsA non-lesional skin?
- Longitudinal cohort study
  - PsO and PsA patients
  - Development of AD or PD over time
- Port-mortem brain tissue samples
  - Spinal fluid samples

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