Distinct patterns of gene expression in skin biopsies differentiate generalized pustular psoriasis from psoriasis vulgaris

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This comparison of gene expression in lesional and nonlesional skin from patients with GPP or PV showed distinct patterns of DEGs between the two conditions, supporting their classification as distinct diseases

PURPOSE

We aimed to better understand the differences between GPP and PV by comparing molecular profiles of lesional and nonlesional skin from patients with GPP or PV versus normal skin from healthy volunteers

INTRODUCTION

- GPP is a rare, severe, clinically heterogeneous disease characterized by acute life-threatening flares that present as widespread non-infectious pustules, and can occur with or without systemic inflammation[1,2]
- Historically, GPP has been considered a variant of PV; however, histopathological and clinical differences between GPP and PV indicate that these diseases are distinct, potentially requiring different treatment approaches[3–5]
- Genetic drivers of GPP and PV also differ. For example, GPP is frequently associated with mutations in *IL36RN*, which are not seen in PV; in contrast, PV follows a complex polygenic model, with a key genetic driver being HLA*C0602, which is not associated with GPP[6–8]

METHODS

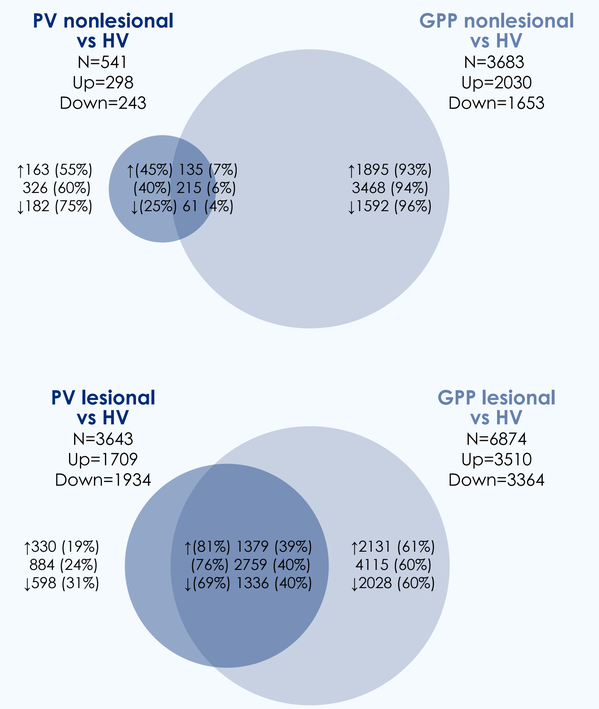
- Biopsies of lesional and nonlesional skin were obtained from patients with GPP (n=7) or PV (n=81), and biopsies of normal skin were obtained from healthy volunteers (n=10)
- Global transcriptome-wide RNA sequencing of the skin biopsies was performed using the Illumina Hi-Seq 4000 (Illumina)
- Read counts were derived and DEGs relative to normal skin (absolute fold change >1.5 and Benjamini–Hochberg FDR <0.05) were identified
- Statistical analysis was performed in the R *limma* package[9] framework using a mixed-effect model to estimate the least squared mean of each group and the between-group differences; GPP and PV changes were compared using a t-test for independent samples

CONCLUSIONS

- The comparatively high number of DEGs found in nonlesional skin from patients with GPP indicates that there is non-focal, widespread skin involvement in GPP but not PV
- Lesional and nonlesional skin from patients with GPP or PV have distinct profiles of DEGs, with the largest differences seen in genes involved in neutrophil-associated inflammation or connected with the Th1 axis
- These results add to a growing body of data supporting the classification of GPP as a disease separate to PV, based on genetics, transcription, and clinical features

RESULTS

Transcriptome analysis of skin biopsies from patients with PV or GPP compared with healthy volunteers



The circles in the Venn diagrams illustrate the numbers of DEGs (genes with altered expression in the indicated biopsy compared with the healthy volunteer biopsy). Upregulated genes are indicated by ↑, and downregulated genes by ↓. The numbers of DEGs identified in both GPP and PV are illustrated by the overlap between the circles.

- **Nonlesional and lesional skin from patients with GPP showed a higher number of DEGs compared with skin from patients with PV**
- **Although a core of DEGs were common in lesional skin from both diseases, only 6% of DEGs overlapped in nonlesional skin**

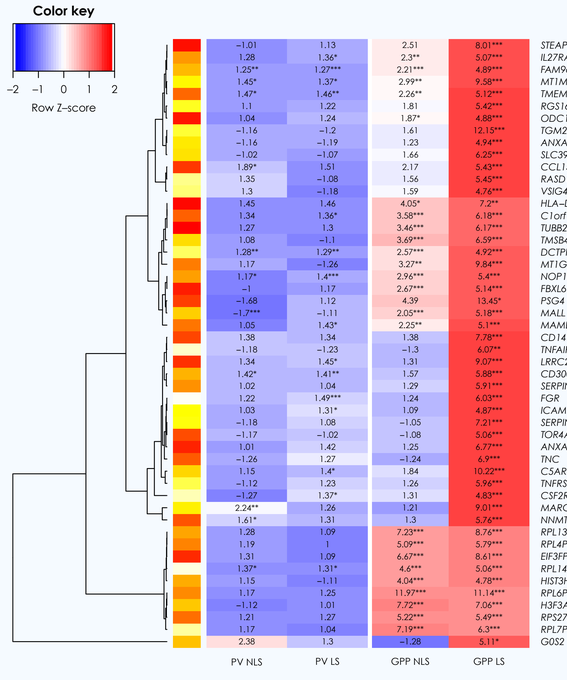
DEGs* relative to normal skin from healthy volunteers in lesional skin from patients with PV or GPP

Gene	Fold change PV LS vs HV	Fold change GPP LS vs HV	GPP LS vs HV / PV LS vs HV	p value†
IL1B	8.9	297.74	33.59	1.45E-07
IL19	102.85	3391.13	33.13	2.23E-06
CXCL8	66.69	1964.94	29.45	2.77E-06
SERPINB4	1424.13	36325.48	25.46	4.15E-06
FPR1	11.74	223.45	19.03	2.34E-07
CXCL1	31.43	565.9	18.00	8.01E-07
ADAMTS4	2.45	40.18	16.45	2.13E-08
HTR3A	13.73	210.21	15.35	4.68E-07
CCL20	32.24	475.69	14.72	1.10E-06
TGM2	-1.2	12.15	14.62	8.96E-09
S100A7A	2701.82	37106.53	13.74	8.00E-06
S100A8	559.31	7257.61	13.00	2.98E-06
MT1G	-1.26	9.84	12.38	8.26E-09
PSG4	1.12	13.45	12.04	1.05E-05
TRIM15	11.31	135.76	11.96	1.51E-07
IL36A	198.65	2338.56	11.79	5.17E-06
PPIAP22	1.58	18.64	11.79	6.00E-10
SAA1	6.62	74.27	11.16	3.84E-07
SERPINB3	63.92	707.11	11.08	7.49E-07

*Genes shown are those with a >10-fold difference in the extent of differential expression (relative to normal HV skin) between GPP lesional skin and PV lesional skin; †p value for the difference between GPP and PV (GPP LS vs HV / PV LS vs HV).

- **Among 1379 genes that were upregulated in both diseases, 789 (57%) showed higher dysregulation in GPP (p<0.05)**
- **The largest differences were seen in genes involved in neutrophil-associated inflammation (*CXCL1*, *CXCL8*, *CD177*, and *CCL20*) or connected with the Th1 axis (*IL1B* and *IL36A*)**

Heatmap of the 50 most upregulated DEGs in lesional skin from patients with GPP compared with normal skin from healthy volunteers (fold change >1.5 / FDR <0.05)



The numbers shown represent the fold change in expression level relative to normal skin from healthy volunteers. FDR-adjusted p value for the difference in expression level compared with normal skin from healthy volunteers: *<0.05, **<0.01, ***<0.001.

- **DEGs that were most strongly upregulated in lesional skin from patients with GPP were not upregulated in lesional skin from patients with PV**
- **24 of the 50 most strongly upregulated DEGs in lesional skin from patients with GPP were also upregulated in nonlesional skin**

Abbreviations

DEG, differentially expressed gene; FDR, false discovery rate; GPP, generalized pustular psoriasis; HV, healthy volunteer; LS, lesional skin; NLS, nonlesional skin; PV, psoriasis vulgaris; Th, T helper.

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