Investigation of the molecular pathogenesis of Generalized Pustular Psoriasis (GPP) and its overlap with Psoriasis Vulgaris (Ps).

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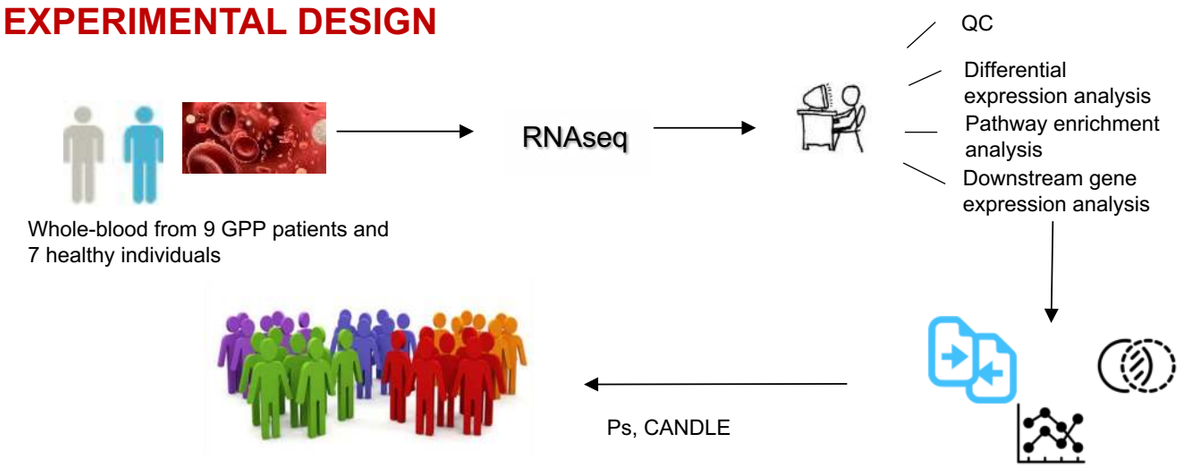
INTRODUCTION

Psoriasis is a complex, immune-mediated skin disorder that can be classified into several forms. While Psoriasis Vulgaris (Ps) has been widely studied, Generalized Pustular Psoriasis (GPP) remains poorly understood, so that treatment is challenging.

Genetic studies have identified mutations in *AP1S3*, *CARD14* and *IL36RN*, indicating an involvement of innate, autoinflammatory pathways appearing to be distinct from those causing Ps. **The aim of this study is to investigate the molecular pathogenesis of GPP and its overlap with Ps and autoinflammatory diseases.**

EXPERIMENTAL DESIGN



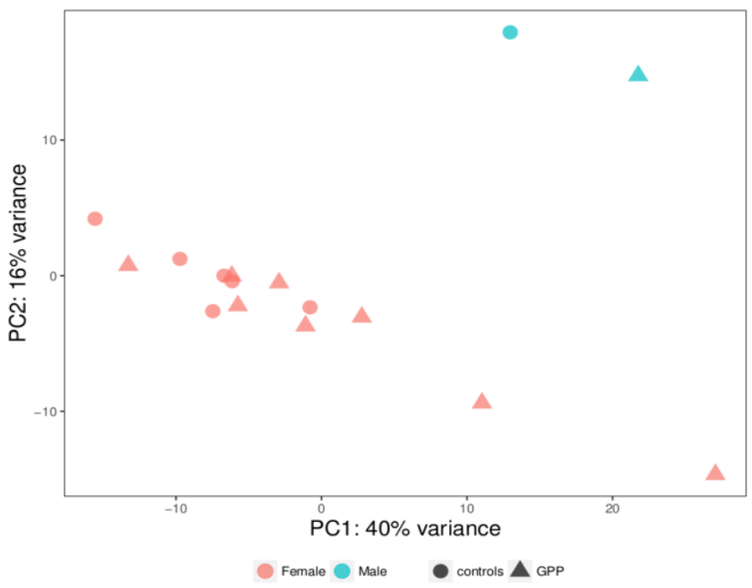
RESULTS

1. Overview of patient cohort.

Sample	Gender	Ethnicity	Age of onset	Mutation status	Systemic upset*	Ps concurrence
GPP1	F	European	10	*AP1S3*-R33W	Yes	No
GPP2	F	European	42	*IL36RN*-S113L	Yes	Yes
GPP3	M	European	5	*IL36RN*-S113L/S113L	Yes	No
GPP4	F	European	7	*IL36RN*-S113L/R48W	Yes	No
GPP5	F	European	5	Neg	Yes	No
GPP6	F	European	45	Neg	No	No
GPP7	F	European	51	*IL36RN*-S13L/S113L	Yes	No
GPP8	F	Indian	31	Neg	No	Yes
GPP9	F	European	29	Neg	Yes	No

*Systemic upset was defined as the concurrence of two of the following: fever > 38C, neutrophil count > $15x10^9$/L, CRP> 100mg/L.

2. Principal component analysis (PCA) of the RNAseq gene expression values reveals sample heterogeneity.

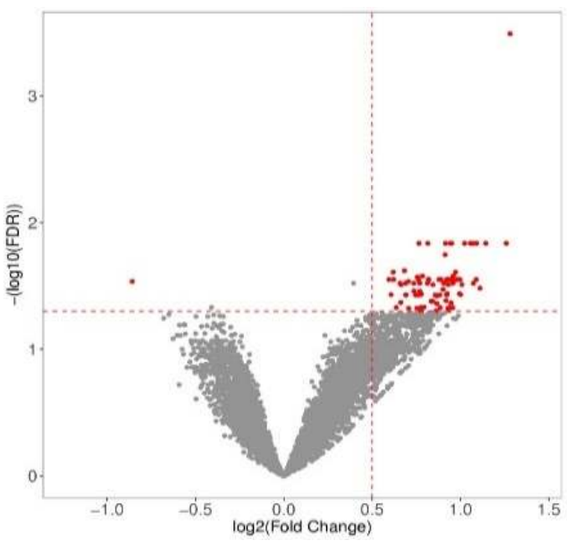


RNA isolated from whole-blood samples was analysed by RNA-seq. PCA shows that GPP cases are an heterogeneous group of samples. Notably, the males cluster apart from the females. In order to deal with this confounding effect, the data were corrected for sex.

3. Identification of 86 differentially expressed genes (DEGs).

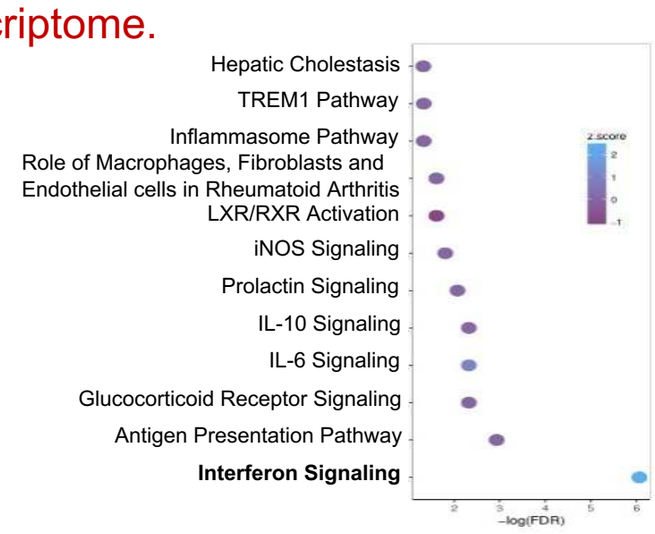
Top up-regulated genes:

- *SERPING1*
- *TNFAIP6*
- *BTNL8*
- *IFITM3*
- *PLSCR1*
- *FCGR1B*
- *IL1R2*
- *CEBPD*
- *DUSP1*
- *OASL*



The volcano plot shows the results of the differential expression analysis, with up-regulated genes (False Discovery Rate (FDR) <5%, Fold change (FC) >1.5) highlighted by red dots.

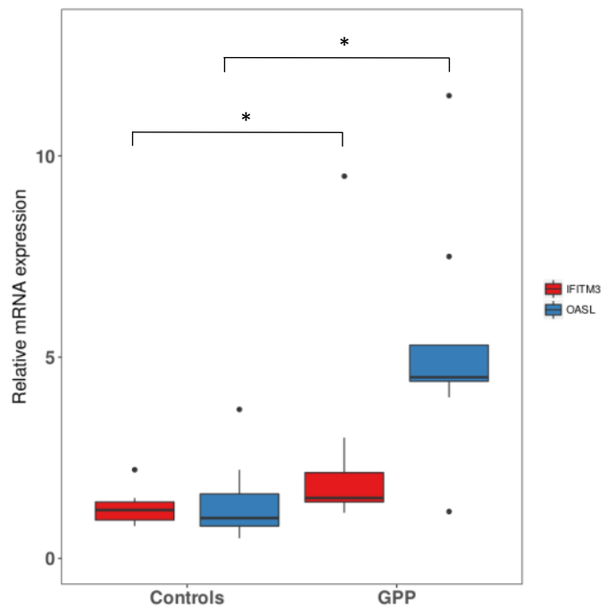
4. Genes contributing to IFN signalling are enriched within the GPP transcriptome.



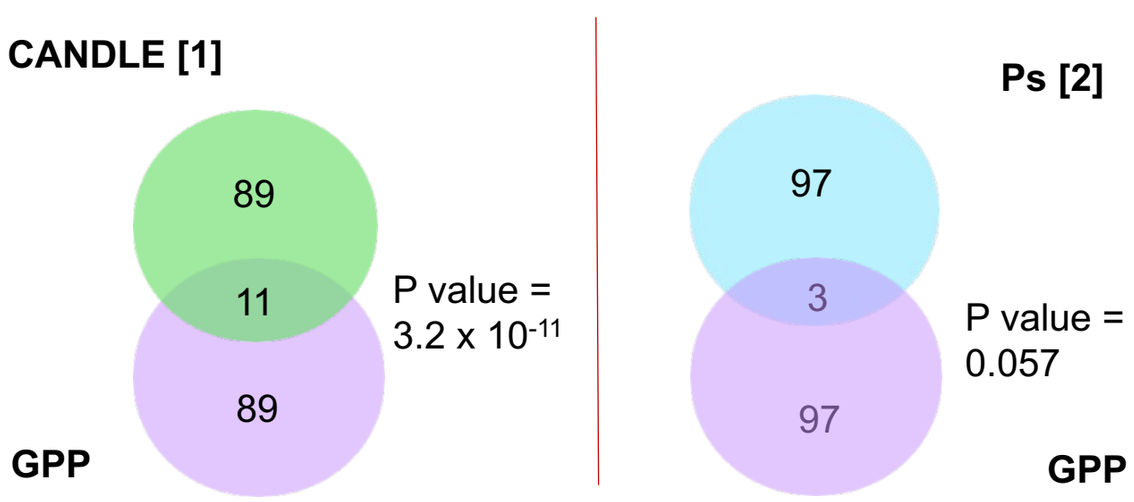
5. Interferon signature genes (ISGs) are up-regulated in GPP patients.

The up-regulation of two representative interferon-signature genes (*OASL* and *IFIT3*) was validated by real-time PCR.

Boxplots show median gene expression values with interquartile ranges.
*P < 0.05



6. Substantial overlap between the genes up-regulated in GPP and in the IFN-mediated disease known as CANDLE.



Method: comparison of the top 100 differentially expressed genes.

CONCLUSIONS

Although Ps and GPP are described as part of the psoriasis-spectrum, the analysis of their transcriptomes highlighted important differences. At the systemic level, GPP is more similar to type-I-IFN mediated disease than to Ps. Consequentially, investigating the role of type-I-IFN in GPP might lead to a deeper understanding of disease pathogenesis.

References
[1] Brehm A. et al.; Additive loss-of-function proteasome subunit mutations in CANDLE/PRAAS patients promote type I IFN induction. J Clin Invest. 2015. [2] Johnston A. et al.; IL-1 and IL-36 are dominant cytokines in generalized pustular psoriasis. J Allergy Clin Immunology 2016 (GSE79704).