The diagnostic value and therapeutic predictive value of immune genes in psoriasis

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Abstract

Background: We already know that abnormal immune cell infiltration is related to the pathogenesis of psoriasis (PSO), but the role of immune cell infiltration in the pathogenesis and treatment of psoriasis is unknown.The purpose of this study was to determine the diagnostic and predictive value of immune-related genes in psoriasis.

Methods: Six gene expression datasets were downloaded from GEO database to analyze gene expression in psoriasis tissues. Single-sample gene set enrichment analysis (ssGSEA) was used to assess immune cell infiltration in psoriatic tissue. Immune-related genes were screened by overlapping immune-related genes with differentially expressed genes (DEGs). Protein interaction (PPI) networks are used to identify key DEGs. We analyzed the diagnostic value of key genes in psoriasis and the predictive value of key genes in three types of biological therapy. Immunohistochemistry (IHC) was used to detect gene expression in psoriasis tissues.

Results: There were significant differences in immune cell infiltration between psoriatic tissue and normal skin tissue. PRC1, GATA3, IL1RN and CCL20 are the key genes of four subclusters in PPI network. PRC1, GATA3, IL1RN and CCL20 have diagnostic value in psoriasis, among which PRC1 and CCL20 have better diagnostic value than GATA3 and IL1RN. After treatment with effective biologic agents, the expression of PRC1, GATA3, IL1RN and CCL20 decreased in skin tissues of patients. GATA3 and IL1RN did not change significantly in patients with non-response to Ustekinumab, and the expression of GATA3 did not change significantly in patients with non-response to Etanercept, that showed good predictive value. Immunohistochemical analysis confirmed that the expression of PRC1, GATA3, IL1RN and CCL20 in PSO tissue was significantly different from that in normal skin tissue, and immune-related genes PRC1, GATA3, IL1RN and CCL20 could be used as auxiliary diagnostic indicators of psoriasis. GATA3 and IL1RN may serve as promising predictors of tumor necrosis factor inhibitors and IL-12/23 inhibitors therapy in patients.

Conclusion: This study reveals the significance of immune genes in the pathogenesis and treatment of psoriasis. These key genes may provide new ideas for future treatments.

Introduction

Psoriasis is a chronic, recurrent immune-inflammatory skin disease with an overall prevalence of 10% in the global general population[1]. Psoriasis comorbidity has also gradually attracted the attention of researchers, and it has been found that patients with psoriasis are at increased risk of arthritis, obesity, diabetes, depression, hypertension and cardiovascular diseases[2]. However, the pathogenesis of psoriasis is not completely clear, and may be related to genetics, infection and other factors[3]. Multiple studies have shown that there is a complex interaction between keratinocytes, immune cells and inflammatory mediators in psoriasis, and innate immunity and adaptive immunity complement each other in the occurrence and development of psoriasis, and occur simultaneously in psoriasis comorbidities[4, 5]. It has

been reported that there are significant differences in the expression of a variety of innate immune cells in psoriatic lesions. Immune cells can release a variety of inflammatory mediators, such as IL12, IL23, etc. stimulated by a variety of pathogenic factors. IFN-g secreted by Th1 cells can induce Th17 cells through IL-1 and IL-23, and Th17cells can secrete IL-17, etc. These inflammatory mediators can be made using keratinocytes to amplify skin inflammation[6–9]. Therefore, the interaction between immune cells and cytokines is a key target in the treatment of psoriasis. Genomic databases can quantify the relationship between immune cell infiltration and disease in diseases. Therefore, in this study, we used single-sample gene set enrichment analysis (ssGSEA)[10] to estimate immune cell infiltration in PSO and evaluate the role of immune-related cytokines in PSO, which will highlight the relationship between immunity and permeate at the molecular level and provide patients with potential therapeutic targets for PSO.

Materials And Methods

Data processing and analysis

Download data from the GEO database, including GSE13355 (58 psoriasis tissues, 58 psoriasis tissues without inflammation involved, and 64 normal skin tissues), GSE109428 (7 PSO tissues and 6 normal skin tissues), GSE78097 (27 PSO tissues and 6 normal skin tissues),GSE153007(28 PSO tissues and 5 normal skin tissues), GSE98820 (14 psoriatic tissues treated at week 12 with Secukinumab), GSE117239(42 psoriatic tissues treated at week 12 with Ustekinumab, including 11 non-responders, Etanercept, and 29 PSO tissues treated at week 12, including 10 non-responders). Raw data were preprocessed by adjustment, quantile normalization, summary, and log2 transformation.

Immune infiltration analysis

The degree of immune invasion was calculated according to the expression level of immune cell-specific marker genes. By defining the immune cell-associated gene set, the enrichment score of the gene set represents the density of tumor-infiltrating immune cells. The marker genes of 28 kinds of immune cells were derived from previous studies[11], including 28 common immune cells and 782 genes. ssGSEA analysis is performed using the R language (version 4.1.2).

Identification of immune-related differentially expressed genes (DEGs)

When multiple probes were mapped to the same gene symbol, the probes in each data set were first converted to gene symbol. We chose their mean values for gene expression. The DEGs between PSO and non-inflammatory psoriatic tissues were analyzed using "limma packs" in R language, or the difference between PSO and normal skin tissue. DEGs with a p value less than 0.05 were considered significant. DEGs and DEGs that overlapped with immune cell-specific marker genes were defined as immune-related DEGs.

Gene ontology, Disease ontology, Kyoto Encyclopedia of Genes and Genomes of immune-associated proteins

Gene ontology (GO), Disease ontology (DO) and KEGG were used to analyze the function of immune-related genes. GO analysis of biological processes (BP). Associated diseases were identified by DO analysis. Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis was used to identify important pathways of gene enrichment. "Cluster Profiler" software package was used for GO analysis and DO analysis, and a p value < 0.05 was considered to be statistically significant enrichment.

Protein-protein interaction (PPI) network analysis of immune-associated DEGs

PPI network of immune-related DEGs was constructed based on the data of STRING database. The STRING database is an online tool for protein and protein interaction analysis that indicates the interaction between two proteins with a composite score. In this study, only interaction pairs with a PPI composite score of > .7 were selected as significant. In addition, Cytoscape plug-in, Molecular Complex Detection (MCODE) was used to identify subclusters of PPI networks. According to the gene score in each sub population (MCODE score > 4; Number of nodes > 5).

Immunohistochemistry (IHC) was performed

Skin tissue of 20 PSO patients diagnosed in the Second Affiliated Hospital of Harbin Medical University from December 2020 to 2021; The plastic surgery department obtained 20 cases of normal skin tissue. This study was approved by the Ethics Committee of Harbin Medical University. The primary antibodies used are as follows: rabbit antibody -prc1 (Affinity Biosciences Cat# DF2955, RRID: AB_2840939; 1:100 dilution); Rabbit anti-gatA3 (Affinity Biosciences Cat# AF6233, RRID: AB_2834800; 1:100 dilution E); Rabbit anti-IL1RN (Affinity Biosciences Cat# DF6812, RRID: AB_2838773; 1:0 dilution); Rabbit anti-ccl20 (Affinity Biosciences Cat# DF2238, RRID: AB_2839469; 1:100 dilution). Immunohistochemical tests were performed in a conventional manner. Immunohistochemical results of PRC1, GATA3, IL1RN and CCL20 were evaluated by intensity score combined with staining intensity and area. The intensity score ranged from 0 to 9, with 0 indicating no expression and 9 indicating high expression.

Statistical analysis

Continuous variables in clinical characteristics were compared between the two groups using the student T test. Variance analysis was used to compare the continuous variables between the three groups. Pearson analysis was used to analyze the correlation between gene expression and immune cell component. The diagnostic value and predictive value of gene expression in PSO patients were analyzed by using the receiver operating characteristic curve, and the area under the curve (AUC) was used to estimate the diagnostic or predictive value. All statistical analyses were performed using R software (version 4.1.2) and SPSS19.0 software (SPSS, Inc., Chicago, IL, USA). A two-tailed P value < 0.05 was considered statistically significant.

Results

1. The immune infiltration is obviously abnormal in psoriasis

By using GSE13355 data set, we revealed the immune infiltration of 28 immune cell subsets in patients with psoriasis. The proportion of immune cells was significantly different among the three groups (FIGURE 1). Using ANOVA, we found significant differences in the 26/28 immune cell ratio among the three tissues (Fig. 2). The proportion of immune cells was the highest in psoriatic tissue compared with non-inflammatory psoriatic tissue and normal skin tissue.

2. Functional analysis of immune-related genes in psoriasis

We screened DEGs between psoriatic and normal skin tissues using the GSE13355 data set. Logfc > 1 and P < 0.05 were DEGs, and 546 DEGs were identified. A total of 68 immune-related DEGs were identified after overlapping with immune-related genes (Supplemental table). By analyzing the GO function of these immune-related DEGs (Fig. 3a). We found that they are mainly involved in the active regulation of cellular activation and adhesion processes and responses to external stimuli, cytokines - mediated signaling pathways, and chemotactic translation; By analyzing the DO analysis of these immune-related DEGs (Fig. 3b), psoriatic arthritis, demyelinating disease, multiple sclerosis, type 2 diabetes, arteriosclerosis. KEGG analysis (Fig. 3c) showed that the cytokines-cytokines receptor interaction, chemokine signaling pathway, IL-17 signaling pathway, and TNF signaling pathway were the most abundant.

3. Protein interactions

We constructed 68 networks of immune-related DEG using the PPI network and identified four significant sub populations with scores of 9, 6, 4.5, and 4.5, respectively. PRC1, GATA3, IL1RN and CCL20 were the key genes of the four subclusters (FIGURE 4).

4.**Correlation of PRC1, GATA3, IL1RN and CCL20 with immune cells.**

We found that PRC1, GATA3, IL1RN and CCL20 are markers of activated $CD4^+$T cell, type 2 T helper cell, and central memory $CD8^+$T cell. Using the GSE13355 dataset, we calculated the correlation between 28 immune cells and PRC1, GATA3, IL1RN and CCL20 in PSO.As shown in Fig. 5, PRC1 and activated $CD4^+$T cell, type 2 T helper cell, memory B cell, monocyte, immature B cell, natural killer cell was significantly correlated (P < 0.05);GATA3 was significantly correlated with type 17 T helper cell, activated dendritic cell, effector memory $CD4^+$T cell (P < 0.05).IL1RN and neutrophil, macrophage, mast cell, type 17 T helper cell, the value of activated dendritic cell was significantly correlated (P < 0.05).CCL20 and neutrophil, mast cell, type 2 T helper cell, type 17 T helper cell, natural killer cell, the central memory $CD4^+$T cells were significantly correlated (P < 0.05).

5.**Diagnostic value of PRC1, GATA3, IL1RN and CCL20 in psoriasis**

Firstly, the diagnostic value of PRC1, GATA3, IL1RN and CCL20 in psoriasis was determined by using GSE13355 as the training data set. The results showed that in normal skin tissue is used as the control, the AUC value of the gene was 0.9841, 0.9916, 0.9491,0.9960, explain the key genes has a good diagnosis value (FIGURE6a). Next, three data sets GSE109428, GSE1530072 and GSE78097 were used to verify the results. The diagnostic value of the four genes was similar to the results of GSE13355 data set, showing good diagnostic ability (FIGURE 6b-d).

6.**Predictive value of PRC1, GATA3, IL1RN and CCL20 in the treatment of PSO**

GSE98820 was a data set describing the difference before and after treatment with Secukinumab. GSE117239 included the data before and after the treatment of Ustekinumab and Etanercept, also including the data with and without treatment response. The results showed that PRC1, IL1RN and CCL20 expression decreased after treatment and GATA3 expression increased in all three kinds of treatments (Fig. 7a-c). Notably, the expression of GATA3 and IL1RN did not change significantly in non-response to Ustekinumab (P = 0.072; FIGURE 7d), the expression of GATA3 did not change significantly in non-response to Etanercept (FIGURE 7e). Next, we determined the predictive value of PRC1, GATA3, IL1RN and CCL20 in the three kinds of treatments of PSO.As Fig. 8; PRC1, GATA3, IL1RN and CCL20 have strong predictive value in treated patients. These results indicate that these four indicators have better monitoring and prediction of the therapeutic effect of psoriasis.

7.**Expression of PRC1, GATA3, IL1RN and CCL20 in PSO tissues**

The expression of PRC1, GATA3, IL1RN and CCL20 in PSO tissues of our hospital was detected by immunohistochemistry (FIGURE 9). The results showed that compared with the corresponding normal skin tissues, the expression of PRC1, IL1RN and CCL20 in PSO tissues was significantly increased, while the expression of GATA3 was significantly decreased ($P < 0.05$). This is consistent with the results of GSE13355 data set. In conclusion, our results suggest that PRC1, GATA3, IL1RN and CCL20 are involved in the pathogenesis of PSO.

Discussion

Studies show that psoriasis is a chronic inflammatory skin disease. Infiltration of immune cells in the skin and excessive proliferation of keratinocytes were the main pathological manifestations. A series of basic and clinical studies in psoriasis have shown that psoriasis is mediated by components of the innate and adaptive immune system, and there is significant immune infiltration in tissues. In the course of PSO, immune cells release a variety of inflammatory mediators, which act on keratinocytes and magnifies skin inflammation[12].Therefore, immune cells and inflammatory factors are the focus of research. At present, many effective biological agents are used to reduce inflammatory factors in patients to alleviate symptoms, such as tumor necrosis factor inhibitors, IL-17A antagonists, IL12-IL23 antagonists, etc.[13, 14, 15].In this study, bioinformatics methods and Bioconductor package in R language were used to analyze the expression matrix of psoriasis tissues with inflammation involvement, normal skin and normal skin

tissue of psoriasis patients without inflammation involvement, and to summarize the degree of immune infiltration in psoriasis patients' skin lesions. The infiltration degree of 23 immune cells was significantly different from that of normal tissues, which confirmed that the abnormal infiltration of immune cells plays an indispensable role in the pathogenesis and progression of psoriasis, and further explained the relationship between immune micro-environment and psoriasis. The intersection of marker genes of immune cells and DEGs was used to obtain immune-related genes in psoriasis tissues. Four key genes, PRC1, GATA3, IL1RN and CCL20, were screened out through PPI network subcluster analysis. These four genes were significantly correlated with multiple immune cells and were related to psoriasis. PRC1 has been shown to be a substrate for a variety of cyclin-dependent kinases (CDK)[16], which are present at high levels during the S and G2 / M phases of mitosis and exist in the nucleus during interphase. Finally, it accumulates in the intermediate region of the spindle in the mitotic postponement at the later stage[17]. Previous experiments have confirmed that PRC1 is over-expressed in a variety of cancers, such as breast cancer, gastric cancer, liver cancer, non-small cell lung cancer, etc., and is associated with various invasive clinical pathological features and poor prognosis[18, 19]. PRC1 expression can be regulated and elevated through a variety of signaling pathways, such as non-estrogen receptor (ER), p53 and Wnt signaling pathways, which are frequently altered or mutated in several cancers[20–22].

In simple terms, PRC1 is associated with cell proliferation and is a marker gene for $CD4^+$T cells. Accordingly, in psoriasis, keratinocytes proliferate excessively, the cell cycle is accelerated, and $CD4^+$T cells infiltrate. Our experimental results showed that PRC1 was significantly correlated with Activated $CD4^+$T cell and Type 2 T Helper cell in psoriasis. The relationship between Activated $CD4^+$T cell and Activated $CD4^+$T cell was significantly positive. We also found that PRC1 has high diagnostic value for psoriasis, but has no special performance in the treatment effect of biological agents. Immunohistochemical results also confirmed that PRC1 was significantly elevated in psoriatic tissues.

GATA3 has been shown to be critical for the proliferation and differentiation of human and mouse keratinocytes, regulating the expression of a variety of proliferation and differentiation markers, including Ki67 and filaggrin (FLG)[23]. Studies have shown that GATA3, the main regulator of T helper cells subgroup, may be a potential therapeutic target in the treatment of cancer, metabolic diseases, inflammation, tissue regeneration and repair[24]. GATA3 determines the fate of plastic Treg by controlling whether it will convert in to either th1-treg or APC-T-reg[25]. Wudh et al. interpret that Psori-CM02 impairs IMQ-induced psoriasis by promoting Th2 cell response targeting of GATA3[26].

IL1RN encodes a protein that binds to the IL-1 receptor and inhibits the binding of IL-1α and IL-1β, the first member of the IL-1 family to be described as having antagonistic functions[27]. IL1RN is a susceptibility gene for psoriasis[28]. In patients with psoriasis, the expression of CXCL2 and IL1RN in Treg cells and the expression of CCL3 in Treg and T helper cells were increased, while the NFKB1 binding modens in the enriched regions of psoriasis were accessible[29]. SU et al. found that IL1RN is highly expressed in both psoriasis and atherosclerosis, and is related to inflammation[30].

CCL20 is the only known high affinity homologue of CCR6. In various subpopulations of $CD4^+$T cells, CCR6 is highly expressed on Treg and Th17 cells and drives these cells to migrate to CCl20-rich inflammatory tissues[31]. In addition, CCL20 inhibits Treg differentiation and promotes the pathogenic Th17 cells in intestinal associated lymphoid tissue galt, and high concentrations of CCL20 promote the pathogenic phenotype of $CD4^+$T cells under inflammatory conditions. $CD4^+$T cells expressing CCL20 and CCR6 are abundant in psoriatic lesions[32], and the serum level of CCL20 in patients with psoriasis is elevated[33]. The TNF -α inhibitor infliximab significantly reduces local induction of CCL20 and shows great promise in psoriasis[34]. Getschman et al. invented a group of CCL20 variants that competitively bind CCR6 with CCL20 to prevent psoriatic inflammation and up-regulation of IL-17A and IL-22[35].

Taken together, these four genes play an important role in immunizing inflammatory diseases. We tested the diagnostic value of these four genes by using the subject curve, and all of them have strong diagnostic significance. As we already know, GATA3 and CCL20 are highly expressed in psoriasis, while PRC1 has not been reported in the literature, but it also has strong diagnostic value. However, IL1RN is controversial. Some previous studies believed that IL1RN is an anti-inflammatory factor and its expression is reduced in psoriasis. However, in this study, we analyzed several data sets and immunohistochemical results of tissues, which showed that IL1RN expression was increased in psoriatic tissues. In addition to their diagnostic value, we analyzed the specificity of these four genes in treatment. Using several data sets, we analyzed three clinically common biological agent, tumor necrosis factor alpha inhibitors, IL-17A antagonists, and IL-12/23 inhibitors. The metrics we selected showed significant differences between pre-treatment and post-treatment. It is worth noting that the data results of non-response to Ustekinumab and Etanercept showed that the expression of GATA3 and IL1RN was not significant. In the treatment of psoriasis, patients are not sensitive to the selection of biological agents, which wastes the treatment time and cost.

Based on our experimental results, GATA3 and IL1RN may be associated with non-response to treatment. GATA3 expression of type 17 T Helper cell and activated dendritic cell showed negative correlation. The expression of IL1RN was positively correlated with neutrophil, type 1 T helper cell, and type 17 T helper cell. From the perspective of related immune cells, these immune cells do play an important role in the pathogenesis of psoriasis. So, what is the mechanism that influences the therapeutic effect in the non-response to treatment is still unknown. Our results can only prove that GATA3 and IL1RN have high specificity in non-response and can be used as indicators of therapeutic effect, but a large number of experimental data are still needed to support.

Conclusion

This study provides insight into the underlying immune cells of PSO and identifies PRC1, GATA3, IL1RN and CCL20 as diagnostic indicators of PSO. We also identify promising therapy predictors of GATA3 and IL1RN in patients receiving biological agents. However, there are still many limitations in this study, and more clinical samples are needed for verification and further evaluation in the future.

Declarations

Acknowledgments

Not applicable.

Authors' contributions

All authors have participated in the work to take public responsibility for appropriate portions of the content; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

The research was obtained by the Second Affiliated Hospital of Harbin Medical University Medical Ethics Committee approved. All patients provided written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interest

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Figures

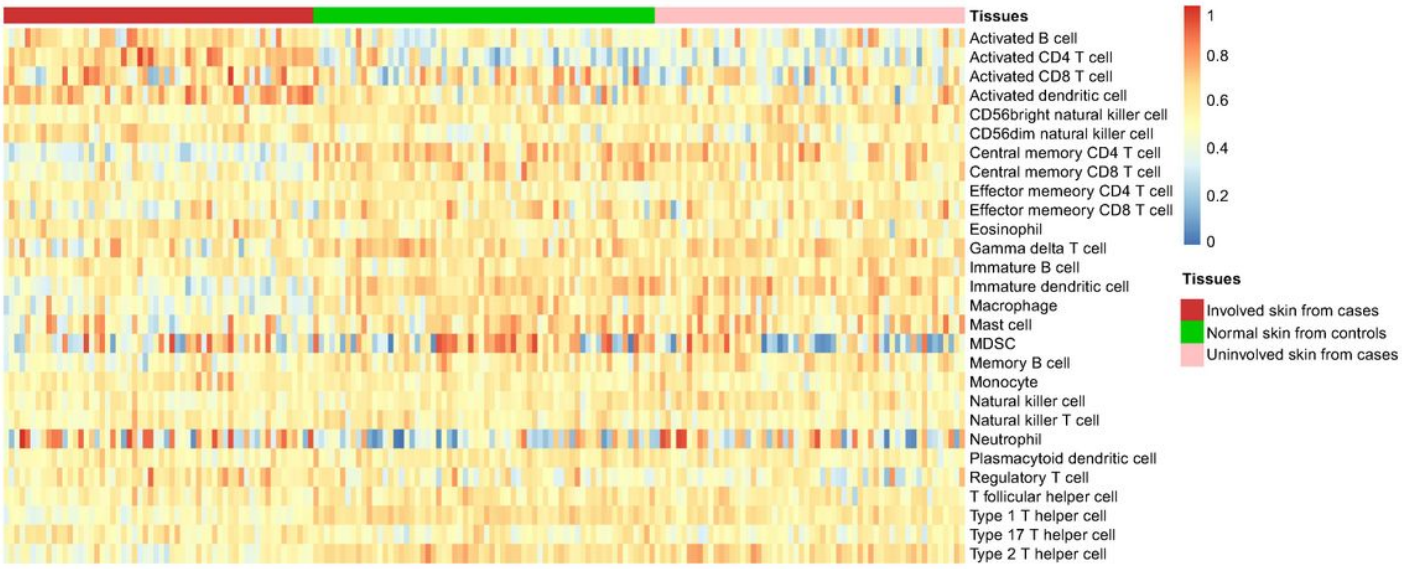

Figure 1

Heat map of infiltration of 28 immune cell subsets (n=180 tissues).

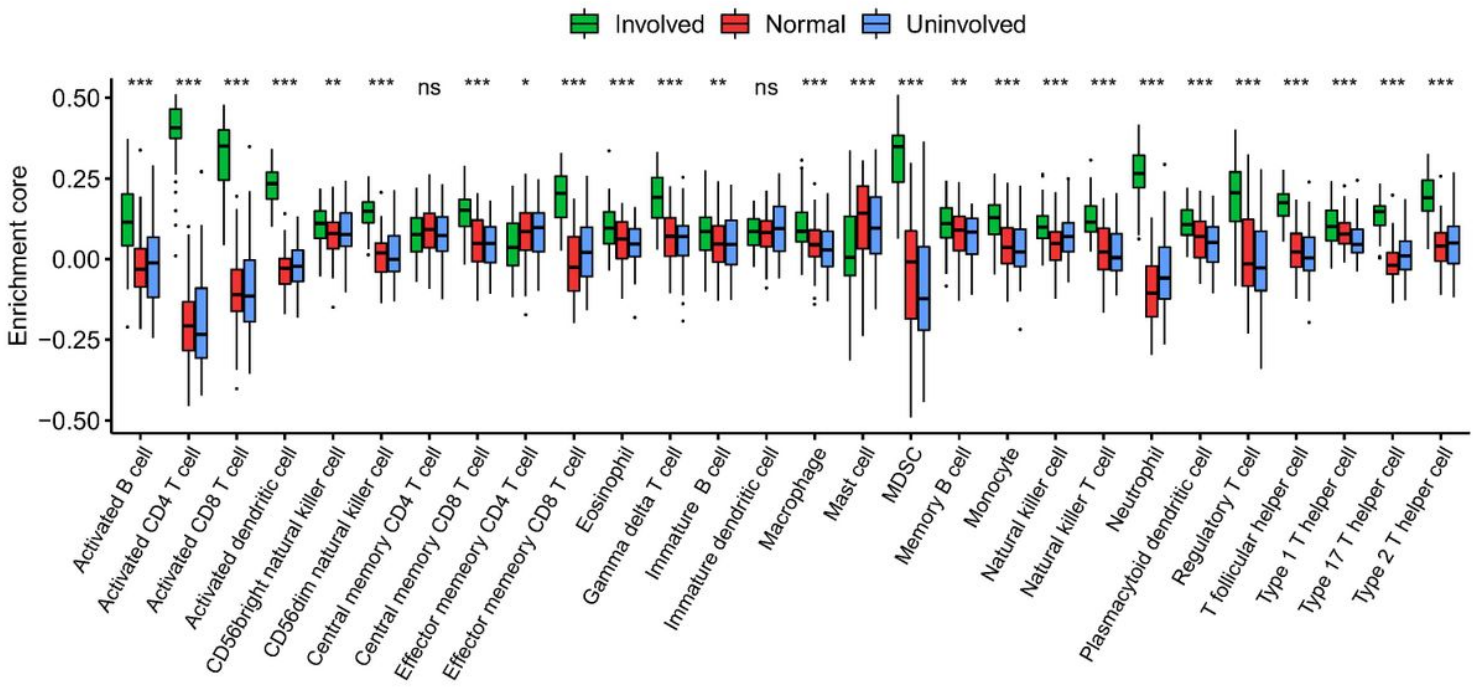

Figure 2

The immune infiltration landscape in psoriasis.

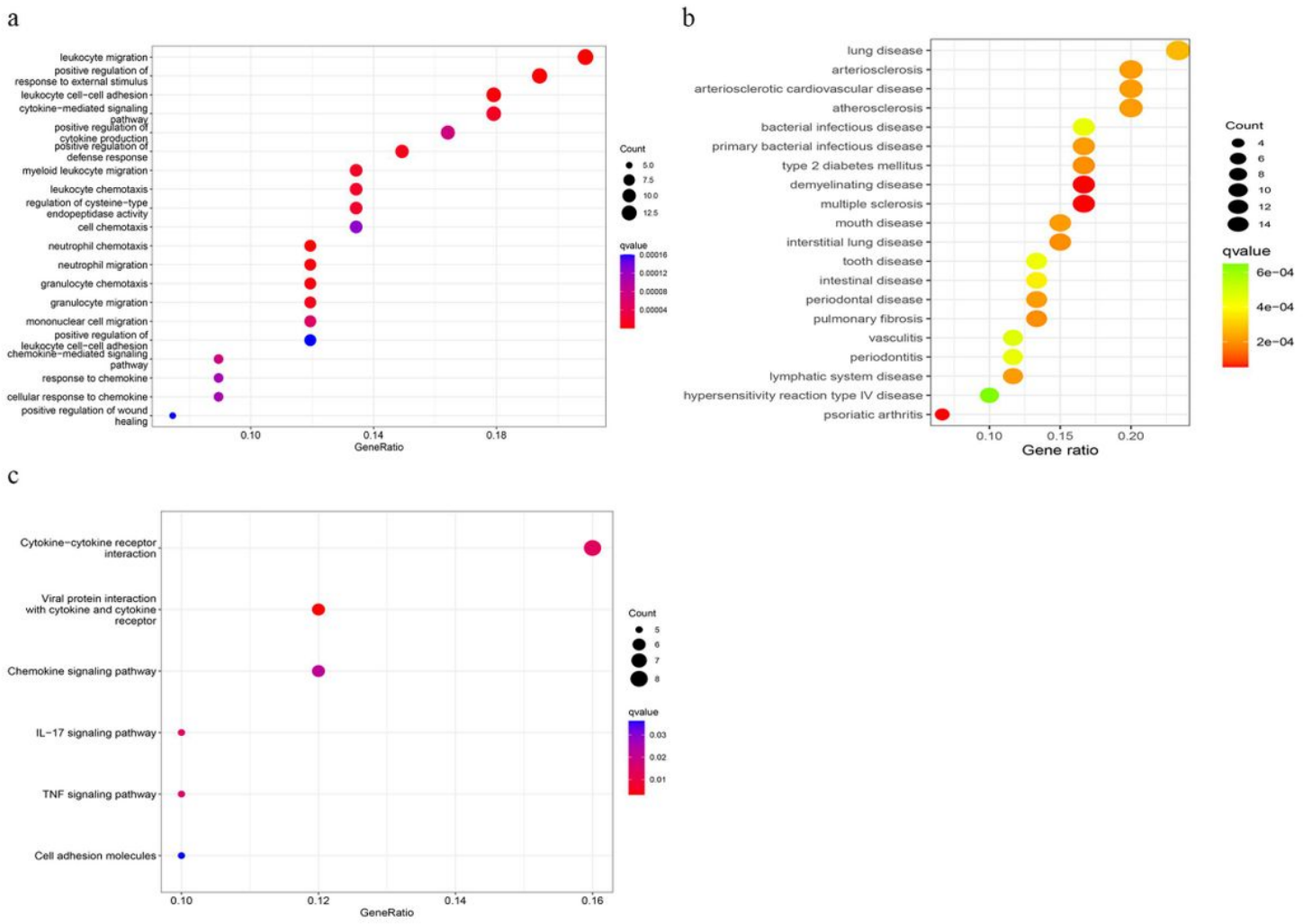

Figure 3

Functional enrichment analysis of immune-related genes in psoriasis. (a) GO analysis (b) DO analysis (c) KEGG analysis

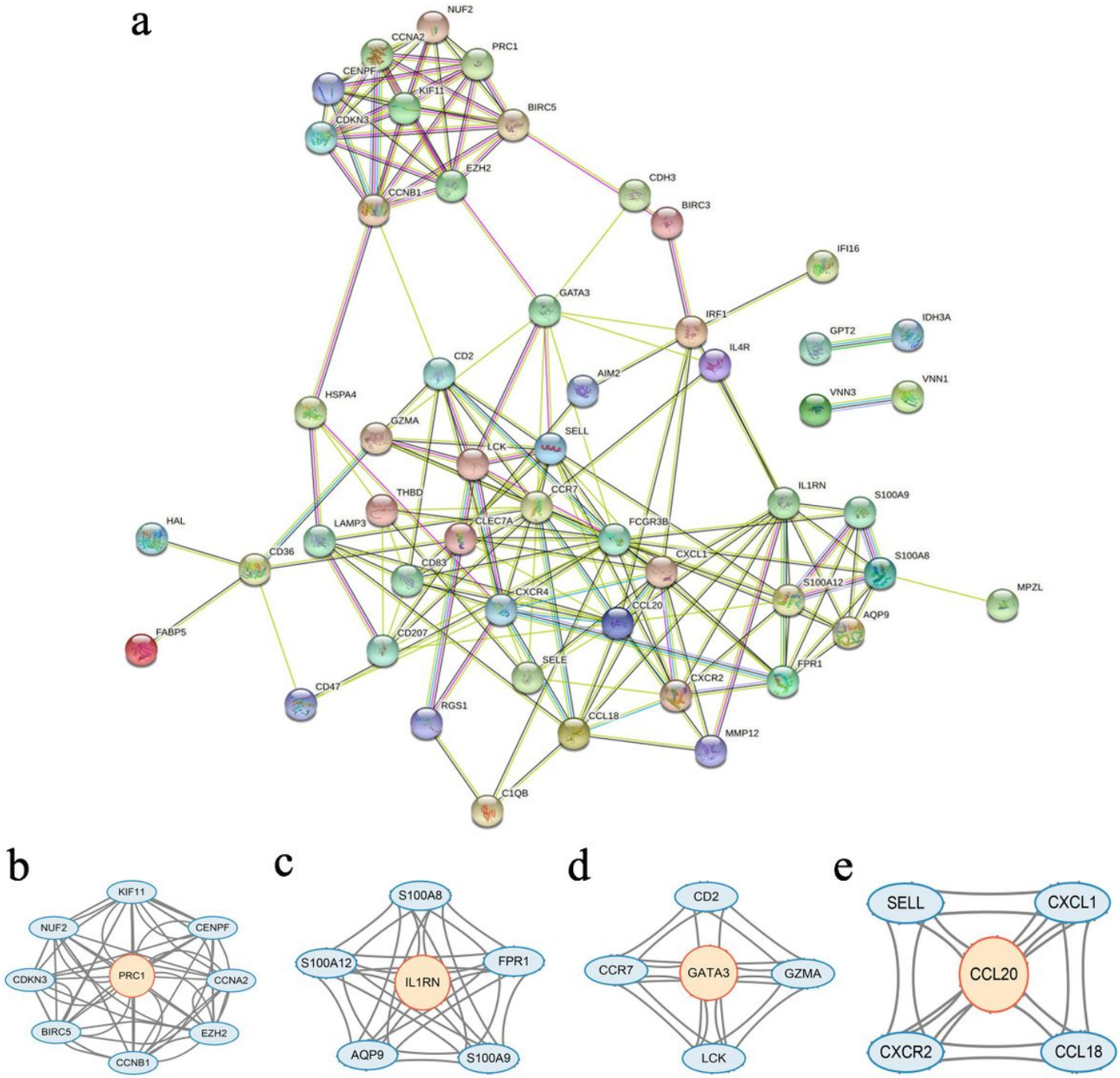

Figure 4

Protein-protein interaction (PPI) network of DEGs;

(a) Detecting 68 immune-related PPI networks, each circle node represents a gene; (b-e) Subclustering of PPI networks, with the center of the network as the key gene.

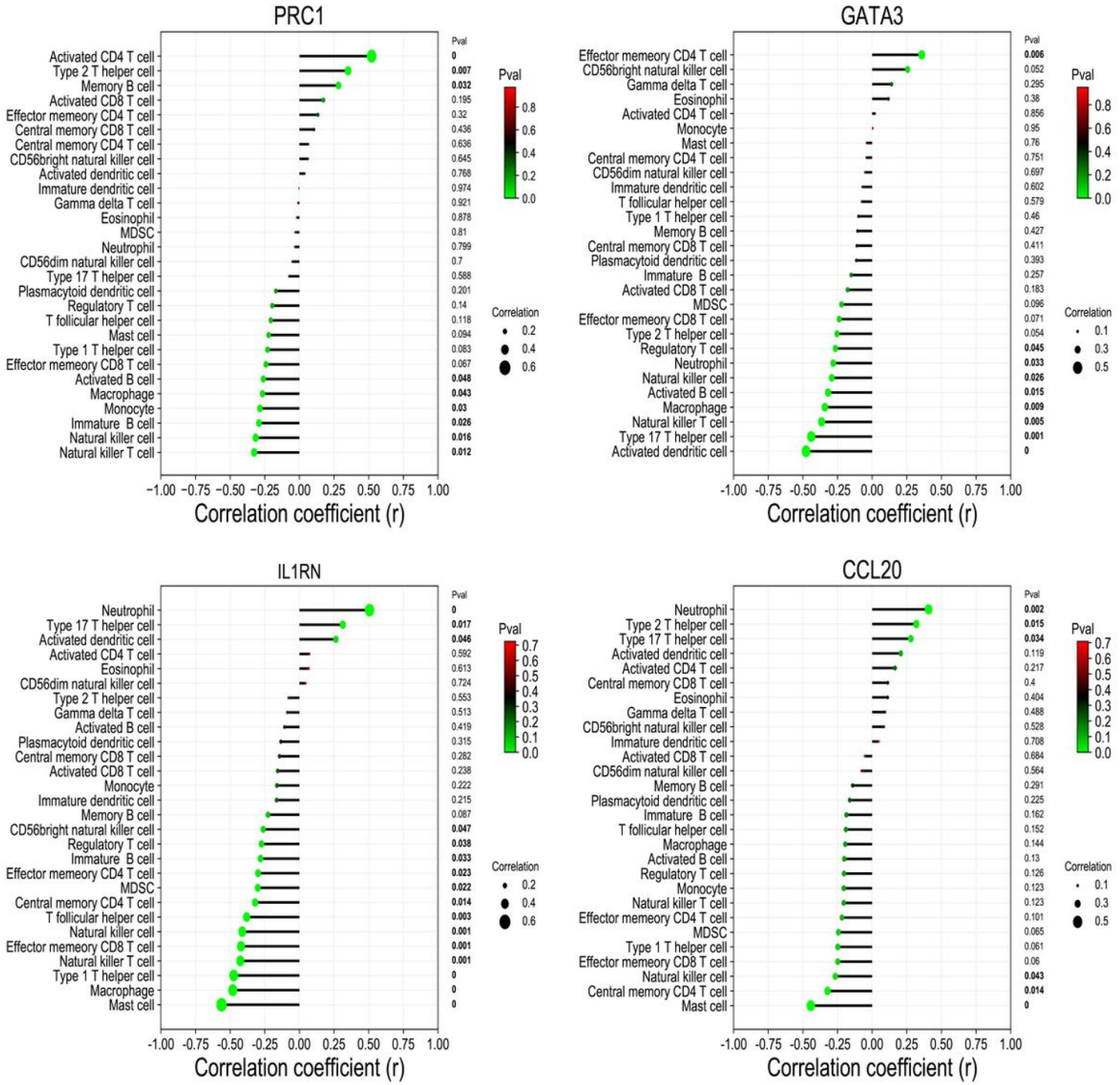

Figure 5

The correlation of PRC1, GATA3, IL1RN and CCL20 with immune cells

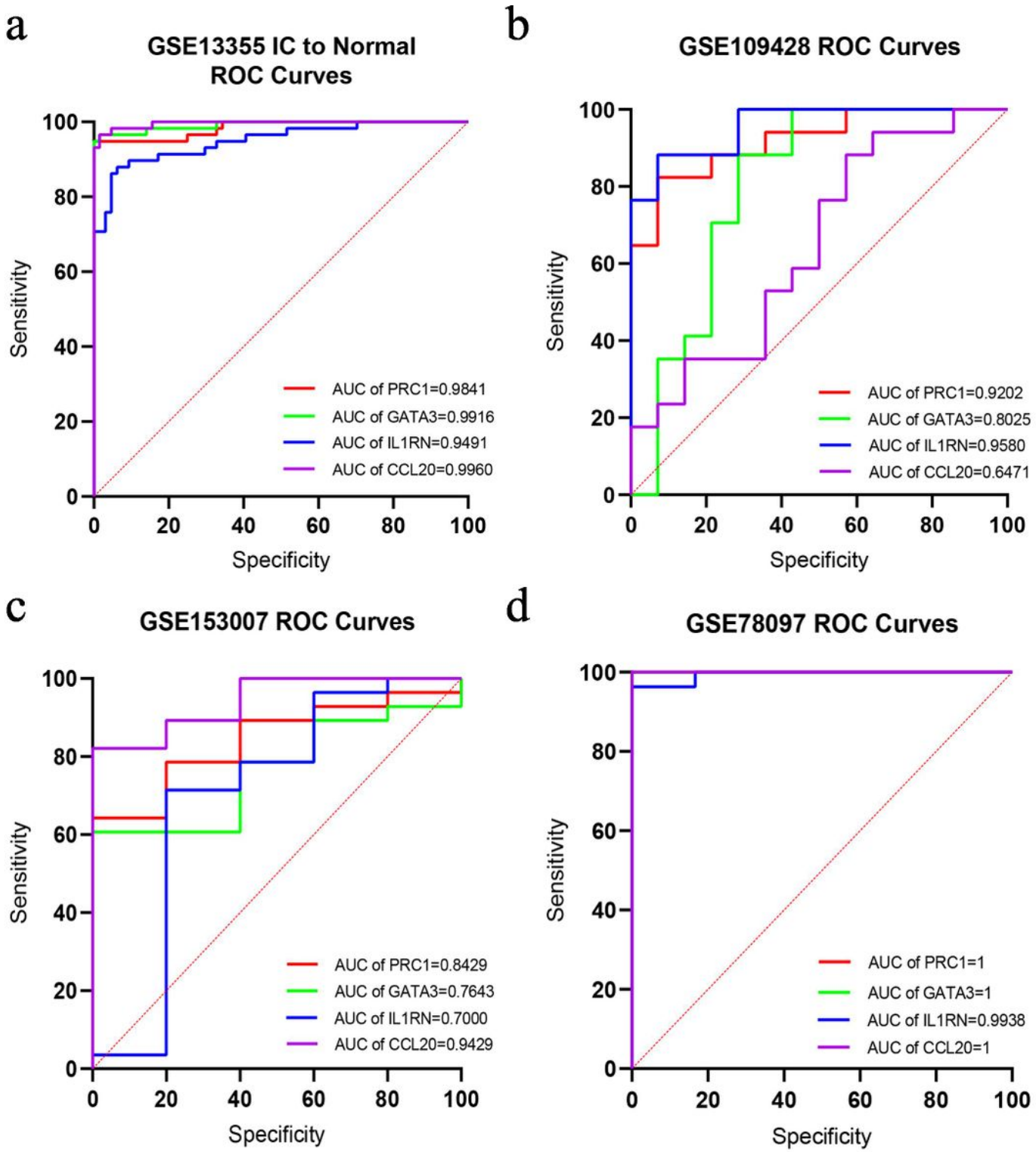

Figure 6

Diagnostic values of PRC1, GATA3, IL1RN and CCL20 in psoriasis;

(a) Diagnostic values of PRC1, GATA3, IL1RN and CCL20 in PSO (GSE13355 data set);

(b) Diagnostic values of PRC1, GATA3, IL1RN and CCL20 in PSO (GSE109428 data set);

(c) Diagnostic values of PRC1, GATA3, IL1RN and CCL20 in PSO (GSE153007 data set);

(d) Diagnostic values of PRC1, GATA3, IL1RN and CCL20 in PSO (GSE78097 data set)

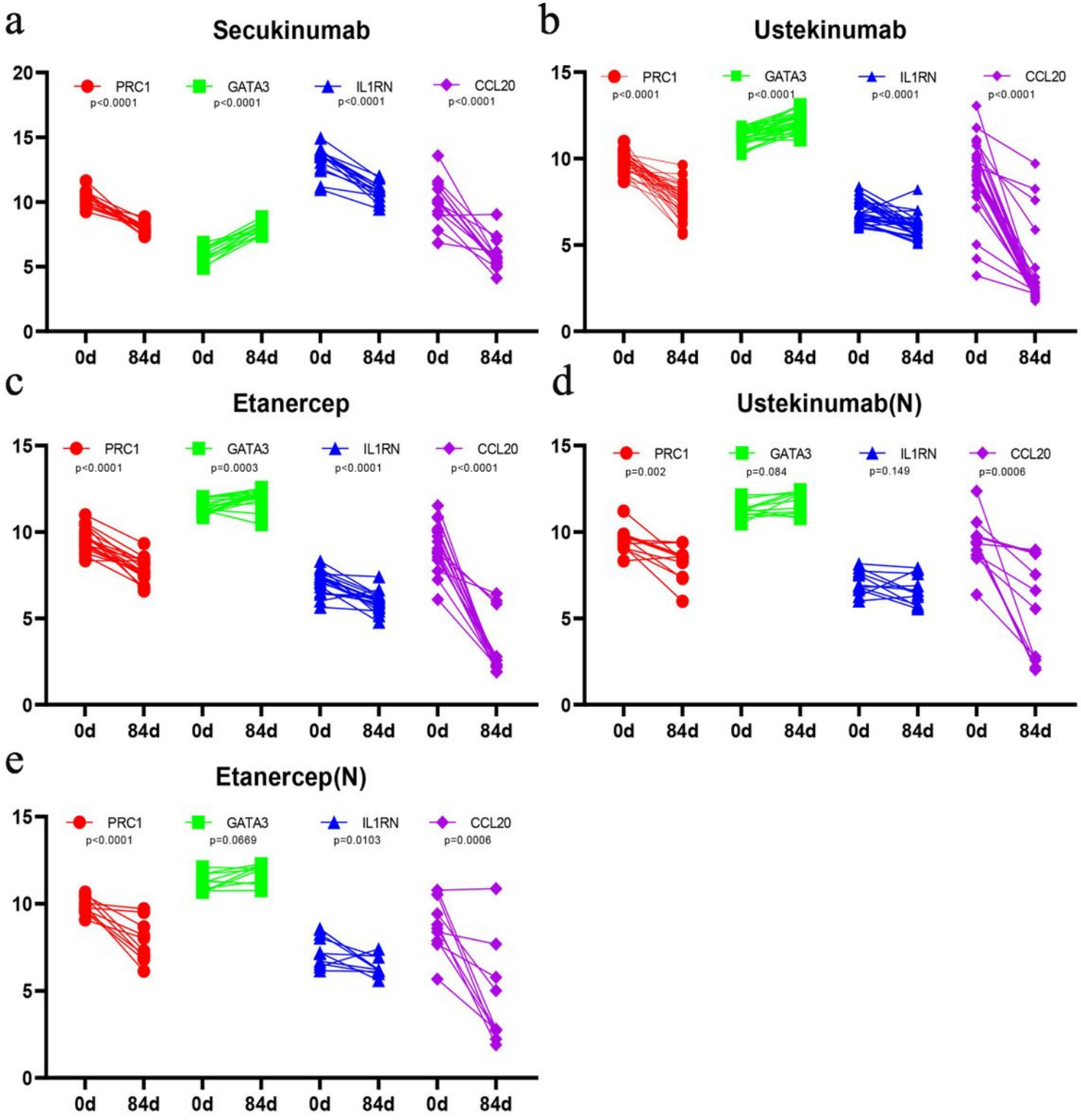

Figure 7

Expression of PRC1, GATA3, IL1RN and CCL20 before and after biological agent treatment;

(a) Expression of PRC1, GATA3, IL1RN and CCL20 before and after effective treatment with Secukinumab

(b) PRC1, GATA3, IL1RN and CCL20 at Expressions of PRC1, GATA3, IL1RN and CCL20 before and after effective treatment with Ustekinumab

(c) Expressions of PRC1, GATA3, IL1RN and CCL20 before and after effective treatment with Etanercept Expression;

(d) Expression of PRC1, GATA3, IL1RN and CCL20 before and after Ustekinumab-ineffective treatment;

(e)Expression of PRC1, GATA3, IL1RN and CCL20 before and after Etanercept-ineffective treatment

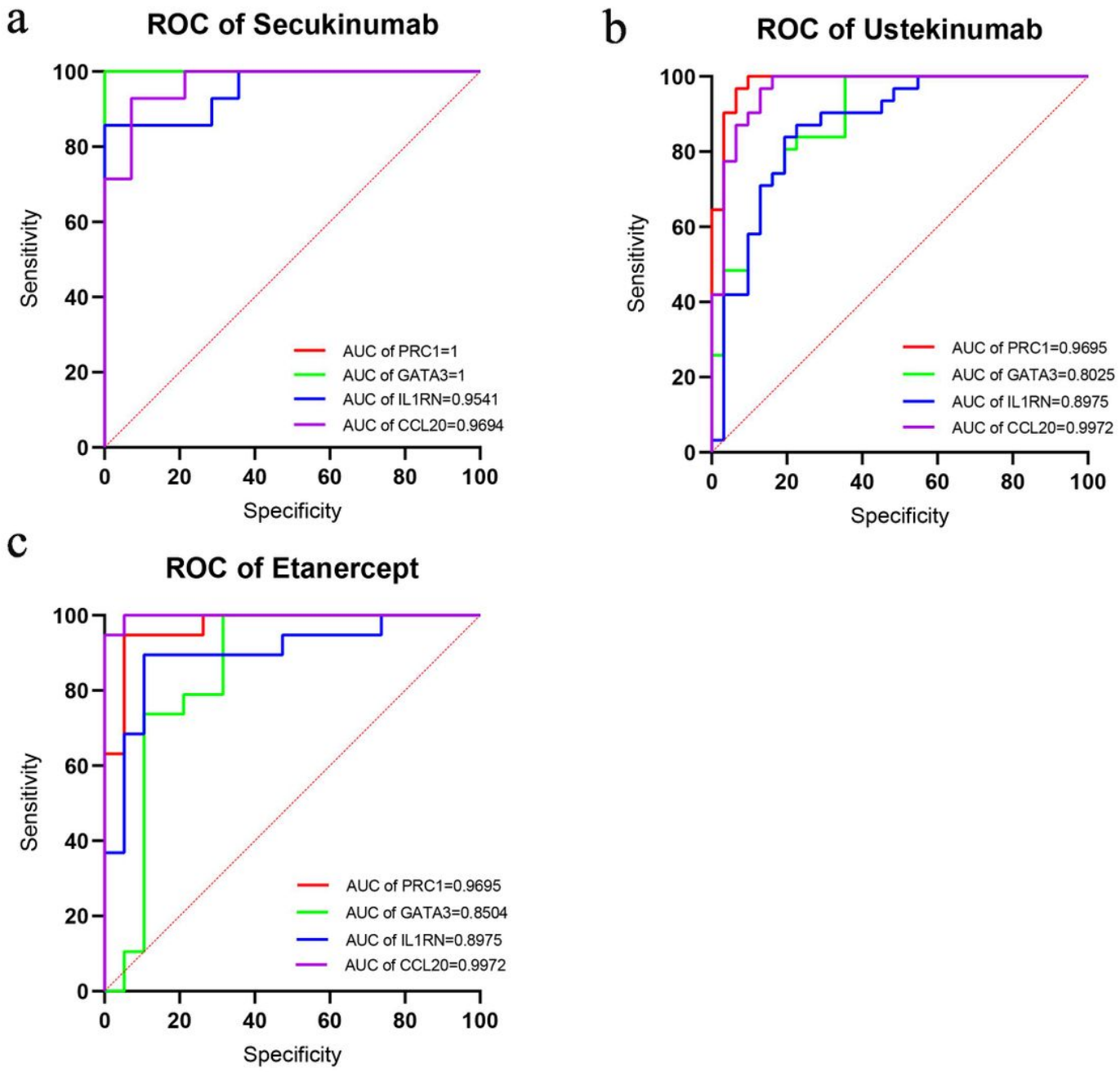

Figure 8

Predictive values of PRC1, GATA3, IL1RN and CCL20 for effective treatment with three kinds of biological agents

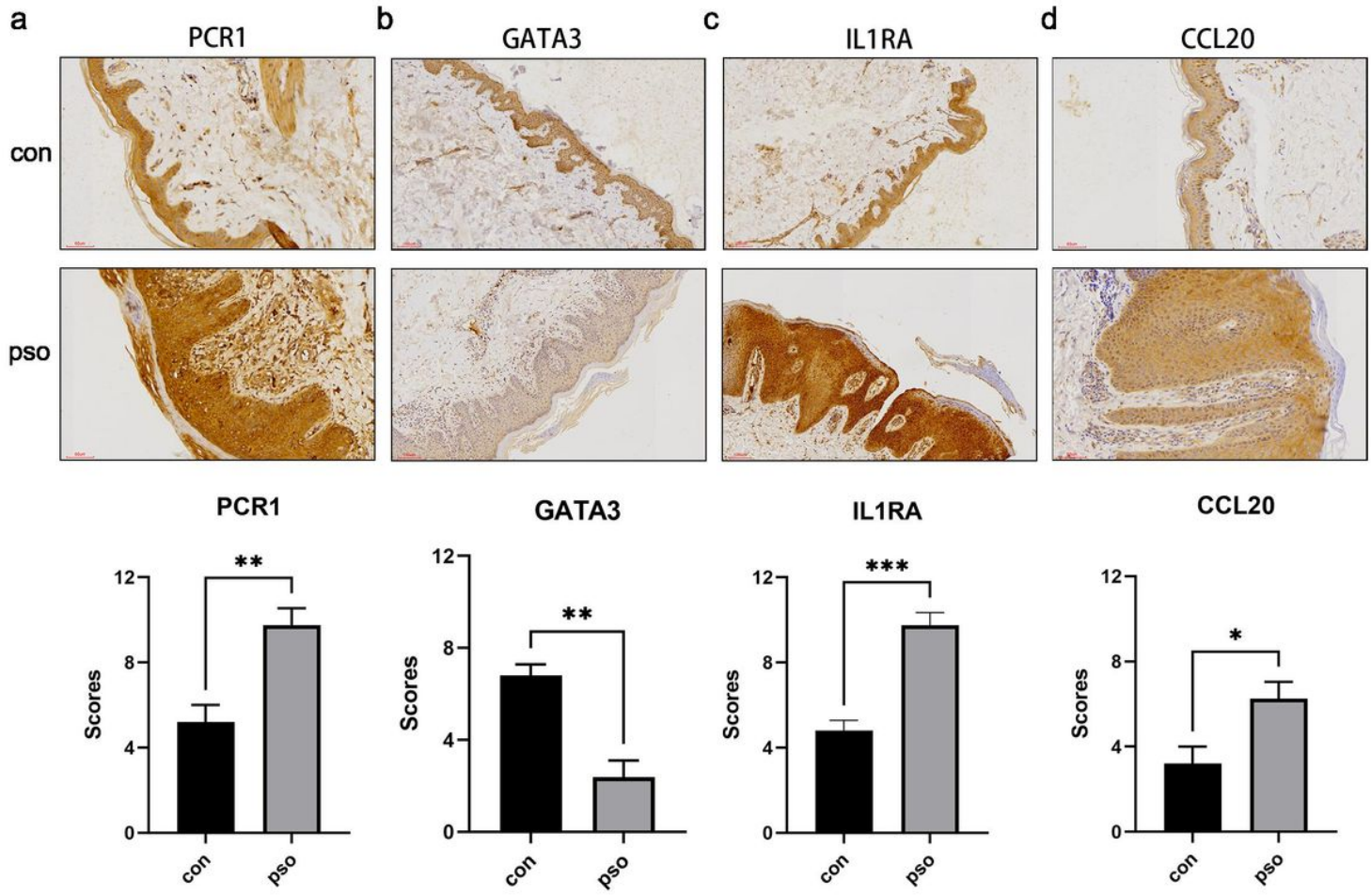

Figure 9

Expression of PRC1(a), GATA3(b), IL1RN(c) and CCL20(d) in psoriasis and normal tissues

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplement.xlsx