

# Dysbiosis of gut microbiota and its correlation with dysregulation of cytokines in psoriasis patients

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## Research article

**Keywords:** Psoriasis, Gut microbiome, 16S, Microbiota, Cytokines

**DOI:** <https://doi.org/10.21203/rs.3.rs-50642/v2>

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# Abstract

**Background:** Psoriasis is an inflammatory skin disease associated with multiple comorbidities and substantially diminishes patients' quality of life. The gut microbiome has become a hot topic in psoriasis as it has been shown to affect both allergy and autoimmunity diseases in recent studies. Our objective was to identify differences in the fecal microbial composition of patients with psoriasis compared with healthy individuals to unravel the microbiota profiling in this autoimmune disease.

**Results:** We collected fecal samples from 30 psoriasis patients and 30 healthy controls, sequenced them by 16S rRNA high-throughput sequencing, and identified the gut microbial composition using bioinformatic analyses including Quantitative Insights into Microbial Ecology (QIIME) and Phylogenetic Investigation of Communities by Reconstruction of Unobserved States (PICRUSt). Our results showed that different relative abundance of certain bacterial taxa between psoriasis patients and healthy individuals, including *Faecalibacterium* and *Megamonas*, were increased in patients with psoriasis. It's also implicated that many cytokines act as main effect molecules in the pathology of psoriasis. We selected the inflammation-related indicators that were abnormal in psoriasis patients and found the microbiome variations were associated with the level of them, especially interleukin-2 receptor showed a positive relationship with *Phascolarctobacterium* and a negative relationship with the dialister. The relative abundance of *Phascolarctobacterium* and dialister can be regard as predictors of psoriasis activity. The correlation analysis based on microbiota and Inflammation-related indicators showed that microbiota dysbiosis might induce an abnormal immune response in psoriasis.

**Conclusions:** We concluded that the gut microbiome composition in psoriasis patients has been altered markedly and provides evidence to understand the relationship between gut microbiota and psoriasis. More mechanistic experiments are needed to determine whether the differences observed in gut microbiota are the cause or consequences of psoriasis and whether the relationship between gut microbiota and cytokines was involved.

## Background

Psoriasis is an immune-mediated, genetic disease manifesting lesions with or without joint involvement. Due to the increasing prevalence and the complex pathogenesis, psoriasis has attracted worldwide attention in these years (1, 2). Infection, genetic factors, and exceptional immunity may be involved in the pathogenesis of psoriasis. The viewpoint that the immune system is involved in the pathogenesis of psoriasis also has been widely accepted (3), especially Th17 cells play a crucial role in the pathogenesis and development of psoriasis (4). Th17 cells, as well as Th1 cells and keratinocytes, secrete TNF- $\alpha$ , IFN- $\gamma$ , IL-1 $\beta$ , IL-6, IL-12, IL-17A, IL-22, IL-23 participating in pathophysiologic processes of psoriasis (5) and current biological therapies as T cell-directed agents have demonstrated excellent efficacy in psoriasis. Among them, serum IL-6 and IL-22 levels were considered to be positively correlated with the severity of psoriasis inpatients (6, 7). Furthermore, it was reported intestinal flora alteration could activate an abnormal immune response that ultimately leads to the development of psoriasis (8). However, it has not

been reported whether the gut microbiota is correlated with the level of inflammatory factors, or whether the microecology dysbiosis correlated with the severity of psoriasis.

A large and complex community of beneficial microbes remain stable over a long period harbored in the human gut (9). The stability of beneficial microbes is closely related to human health (10). Studies have proven that the microbiome regulated the immune response in many physiological processes via interactions between innate immunity and acquired immunity (11, 12). Recently, there has been growing interest in studies primarily focused on interactions between the gut microbiota and immune diseases, including psoriasis.

Several studies have identified gut microbiota dysbiosis as possible triggers or causes for recurrent episodes of psoriasis. Intestinal permeability was more frequently reported in plaque psoriasis patients, and the bacterial DNA from the gut can be detected in patients' blood (13). This result explained the possible conditions that gut microbiota became one of the pathogenic factors of psoriasis. Genome sequencing showed that the presence of gut microbiota had potential effects on psoriasis (14-17). They all showed that patients with psoriasis harbored the gut microbes were significantly different compared with healthy people. One of them pointed out that the microbiota dysbiosis in arthropathic psoriasis patients was similar to the patients with inflammatory bowel disease. Several organisms are virtually absent in these two diseases (14). There was even evidence that manipulating the composition of the gut microbiota affected phenotypes of psoriasis (18). However, current cross-sectional studies could not determine whether the microbiome's change is a cause or a result. Thus, further evidence, including consistency, specificity, timeliness, and biological plausibility, is needed to understand the relationship between gut microbes and the pathogenesis of psoriasis.

In the present study, we aimed to characterize the intestinal microbiota composition of patients with psoriasis and provide evidence for the hypothesis that the intestinal microbiota dysbiosis may play a vital role in the development of the psoriatic disease. Besides, we also collected laboratory indicators to analyze the correlation between clinical phenotypes and microbe species in the psoriasis group. An attempt was made to link the intestinal microbiota with the pathogenesis of psoriasis by immune-related inflammatory factors.

## Results

### The characteristics of participants

To explore the taxonomic composition of the gut microbiota from patients with psoriasis in comparison with healthy controls, 60 fecal samples were collected from 30 patients diagnosed with psoriasis and 30 healthy age-matched individuals for analysis. The healthy controls were composed of 20 males and 10 females, with a mean age of (43.7±13.21) years old and no history of psoriasis. The psoriasis patients were composed of 20 men and 10 women, with a mean age of (43.13±13.79) years old. The mean duration of the disease was (14.75±11.32) years. According to the medical history and physical

examinations, 18 of the 30 patients with psoriasis had the symptoms of pruritus. The skin lesions were found to be more than 50% in 18 of the 30 patients (Table 1).

Table 1. Characteristics of patients with psoriasis (n = 30) and healthy individuals (n = 30) included in this study

	Psoriasis	Healthy	P-value
Male/Female	20 / 10	20 / 10	1.000
Age (years)	43.13±13.79	43.7±13.21	0.871
Early-onset psoriasis (< 40 years)	25 / 30	-	-
Duration of the disease (years)	14.75±11.32	-	-
Pustular psoriasis	6 / 30	-	-
Pruritus	18 / 30	-	-
Psoriasis area ≥ 50%	18 / 30	-	-

The biochemical examination of blood in the psoriasis group found that the mean level of white blood cell (WBC) was  $7.55 \pm 0.52 \times 10^9 \text{ L}^{-1}$ , of alanine transaminase (ALT) was  $(21.95 \pm 3.87) \text{ U L}^{-1}$ , of aspartate aminotransferase (AST), was  $(20.18 \pm 1.90) \text{ U L}^{-1}$ , of total cholesterol (TC), was  $(3.99 \pm 0.18) \text{ mmol L}^{-1}$ , of triglyceride (TG), was  $(1.62 \pm 0.19) \text{ mmol L}^{-1}$ , of high-density lipoprotein (HDL) was  $(1.02 \pm 0.05) \text{ mmol L}^{-1}$ , of low-density lipoprotein (LDL) was  $(2.68 \pm 0.15) \text{ mmol L}^{-1}$ , of fasting blood glucose (FBS) was  $(4.88 \pm 0.16) \text{ mmol L}^{-1}$ , and of hypersensitive c-reactive protein (hsCRP) was  $(11.88 \pm 4.72) \text{ mg L}^{-1}$ , of Immunoglobulin A (Ig A) was  $2.54 \pm 0.26 \text{ g L}^{-1}$ , of Immunoglobulin E (Ig E) was  $2.54 \pm 0.26 \text{ IU mL}^{-1}$ , of complement 3 (C3) was  $1.09 \pm 0.03 \text{ g L}^{-1}$ , of interleukin-2R (IL-2R) was  $678.61 \pm 106.33 \text{ U mL}^{-1}$ , of interleukin-6 (IL-6) was  $10.91 \pm 4.59 \text{ pg mL}^{-1}$ , of interleukin-8 (IL-8) was  $45.07 \pm 31.57 \text{ pg mL}^{-1}$ .

#### Fecal microbiota analysis

Bacterial DNA extracted from fecal samples was used for 16S rRNA sequencing analyses. 60 Samples Clean Reads generated a total of 7656 518 single-end reads with an average of 127608 reads per sample. A total of 635 OTUs were obtained, using Venn diagrams to visually show the number of shared and unique OTUs in different groups. The results showed that there were about 465 OTUs shared in the two groups, 102 and 68 OTUs in the healthy control group (N) and the psoriasis group (P), respectively (Figure 1A). Then the OTUs sequence and Greengenes database were annotated, and the result showed that predominant microbes were included (Figure 1B).

The OTU Abundance curves obtained for each sample tend to plateau, indicating that sample biodiversity was adequately covered with the applied sequencing depth (Supplement 1). The Alpha diversity box showed that there was no significant difference based on the Wilcox Test in the microbial diversity of patients with psoriasis (P), compared with the healthy controls (N). The sobs index is  $140 \pm 50.824$  and  $150.1 \pm 45.883$ ,  $P=0.34$ ; Chao index is  $162.91 \pm 56.14$  and  $176.75 \pm 45.51$ ,  $P=0.21$ ; ace index is  $162.58 \pm 53.83$  and  $176.29 \pm 45.81$ ,  $P=0.27$ ; Shannon index is  $2.55 \pm 0.63$  and  $2.56 \pm 0.65$ ,  $P=0.92$ ; simpson index is  $0.18 \pm 0.11$  and  $0.20 \pm 0.15$ ,  $P=0.81$ ; coverage index is  $1.00 \pm 0.01$  and  $1.00 \pm 0.01$ ,  $P=0.34$  in healthy controls and psoriasis patients respectively (Supplement 2 and 3).

Moreover, the  $\beta$ -diversity analyses revealed significant clustering ( $P$ -value < 0.001) between healthy individuals and patients with psoriasis, supporting the theory that the gut microbiota composition differed between both groups (Figure 2A and 2B).

Next, bacterial communities from both healthy individuals and psoriasis patients were analyzed. At the family and genus level, the microbial composition differed between the psoriasis patients and healthy individuals. We identified the presence of top 10 taxa in relative abundance at the family level, and the Wilcoxon test showed that Veillonellaceae and Ruminococcaceae were relatively more abundant in psoriasis patients. In contrast, Lachnospiraceae were relatively less abundant in psoriasis patients (all  $P < 0.05$ ). Moreover, at the genus level, Faecalibacterium and Megamonas were relatively more abundant in psoriasis patients than health control (all  $P \leq 0.05$ ) (Figure 2C and 2D). We then conducted a LEfSe comparison of the gut microbiota between the control and psoriasis groups to explore the specific bacterial taxa associated with psoriasis development. The structure and predominant bacteria of the microbiota in the control and psoriasis groups were represented in a cladogram (Figure 2E). The greatest difference in taxa from the phylum to the genus level was identified by an LDA score (Figure 2F). The two taxa with the highest score in the psoriasis group were Veillonellaceae and Megamonas, consistent with the previous one.

### Correlation between gut microbiota and clinical indices in psoriasis patients

Correlation analyses were performed to investigate further identified potential associations of key microbial genera with clinical indices above (Figure 3). Exact figures of these clinical indices were showed in Supplement 4. Complement 3 (C3) showed a negative relationship with Bacteroides ( $P \leq 0.001$ ) and Escherichia ( $P \leq 0.01$ ), but it showed a positive relationship with the Prevotella group ( $P \leq 0.01$ ). Coprococcus had a great relationship with many clinical indices, and it showed a positive relationship with FBS ( $P \leq 0.001$ ) and IgA ( $P \leq 0.001$ ). Additionally, IL2R, which is abnormal in psoriasis patients, showed a positive relationship with Phascolarctobacterium ( $P \leq 0.001$ ) and a negative relationship with the Dialister group ( $P \leq 0.001$ ).

### Different microbiota analysis between psoriasis vulgaris (PV) and pustular psoriasis (PP)

To compare the microbiota communities of PV (24 cases) and PP (6 cases). Based on the abundance ranks of the class level, the heat map was demonstrated through R (v3.1.1) gplots. Hierarchical clustering (Euclidean distance, complete linkage) showed that the PV group and healthy control group (N) tended to cluster together, and the PP group is being singled out (Figure 4A). Then we identified the presence of the top 10 taxa in relative abundance at the class level, and the Kruskal test showed that Gammaproteobacteria was relatively less abundant in the PP group than PV group and N group (all  $P$ -value  $\leq 0.05$ ) (Figure 4B). LefSe analysis was performed to identify differentially abundant taxa in the PP group compared with the PV group (Figure 4C). Consistent with our previous analysis, Gammaproteobacteria and Veillonellaceae had the largest LDA score indicating that Gammaproteobacteria and Veillonellaceae were consistently different between the PP group and PV group. In addition, the genus level Faecalibacterium and Anaerorhabdus were the most significant taxa in the PP group, which could help us distinguish PP from PV.

## Discussion

The composition of the gut microbiota of the 30 patients with psoriasis was elucidated based on 16S rRNA gene profiling to evaluate the potential bacterial dysbiosis compared with a healthy control group of 30 individuals from the same geographic location.

There was no statistically significant difference between the psoriasis patients and normal healthy people in alpha diversity, demonstrating that the levels of community species diversity and richness were similar in these two groups, consisting of Tan's research in 2018(15). The lower microbial diversity detected in other studies has been reported previously for other cohorts of patients with psoriasis (14, 17). Also, differences in sequencing methodologies and the racial gap may account for some of the differences observed between studies. In contrast to alpha diversity used in diversity within a sample, beta diversity is used to describe diversity between different samples and indicate the similarity of two samples. We found that the beta diversity revealed significant differences between the psoriasis group (P) and the healthy control group (N), and two groups were able to be clustered independently, which is consistent with the next analysis of gut microbiota composition. More specifically, the patients with psoriasis enrolled in this study displayed a microbiota profile characterized by a reduction in Lachnospiraceae but increased proportions of Veillonellaceae and Ruminococcaceae at the family level. At the genus level, Faecalibacterium and Megamonas showed a general increase in microbial diversity in the psoriasis group. The increased proportion of Ruminococcaceae and Faecalibacterium was also detected in other researches (17, 18).

The depletion of Lachnospiraceae was also found in patients with primary Sjögren's syndrome and primary Sjögren's syndrome is a systemic inflammatory autoimmune disease that has similarities to psoriasis (19). It was suggested a protective effect of Lachnospiraceae in the inflammatory process as its decreased abundance in these two inflammatory disorders. Another study on amnesic mild cognitive impairment (aMCI) found that Lachnospiraceae was increased in aMCI subjects and their results represented Lachnospiraceae had beneficial effects on hosts (20). An early study proved the relative abundance of Veillonellaceae is increased in Crohn's disease patients (21). Crohn's disease is related to host pathways that indicated an underlying role for aberrant immune responses to the intestinal microbiota. The research on psoriatic arthritis pointed gut microbiota profile detected in psoriatic arthritis was similar to inflammatory bowel disease (22). So we speculated that Veillonellaceae played a role in abnormal immunity related to psoriasis arthritis and even other psoriasis subgroups. We also found Megamonas was significantly higher in the psoriasis group. Megamonas was significantly correlated with systemic inflammatory cytokines and detected increased significantly in many other pathological processes, including HIV-1 Infection and obesity (23-25).

Previous studies showed the relative abundance of Faecalibacterium in gut microbiota was closely related to immune-regulation (26). It's also found that an increase in species belonging to this genus was associated with inflammatory diseases such as Crohn's disease (27). As for skin Diseases, Faecalibacterium subspecies have been shown to have a high relative abundance in infant eczema and atopic dermatitis, and these results indicated that Faecalibacterium might play a role in the disruption of barrier integrity and affection on the pro-inflammatory state in the gut (28, 29). Bacteroides,

Proteobacteria, Actinobacteria, and Akkermansia did not show variability among groups detected abnormal in psoriasis patients in other studies (17, 18, 30). As well, sample selection and sequencing analysis may account for some differences observed between studies. Indeed, more research is needed to identify the differences and their significances.

One of the unique aspects of this study is correlation analysis between gut microbiota and inflammation-related indicators. The remarkable abnormality in relative abundance including Lachnospiraceae, Veillonellaceae, and Ruminococcaceae from our results. These families are involved in butanoate metabolism and butyrate production (31, 32). Butyrate, as a bacterial product, have been implicated in regulation of various inflammatory factors including IL-10, IL-6 and IL-18 (33). Including butyrate-induced process, the mechanism of interaction between gut microbiota and inflammatory response still needs further study. It's feasible to analyze the correlation between the serum level of inflammatory factors and intestinal microbial composition in psoriasis as abnormal cytokine production and enteric dysbacteriosis both involved in it (34).

We collected common biochemical indicators in patients with psoriasis, including cytokine test results representing the level of inflammation. IL-2R, IL-6, and IL-8 serum concentration in patients with psoriasis could be the predictor of disease severity and the marker of response to therapy (35-37). Through the correlation analysis of clinical phenotypes with microbes, we found a strong positive correlation between *Phascolarctobacterium* and IL-2R. It's indicated the increased abundance of *Phascolarctobacterium* could be regard as a pathogenic factor involved in the inflammatory response and a predictor of disease activity. Psoriasis is a chronic inflammatory skin disease in which effector T cells are increased in peripheral blood, and IL-2R as an activation marker of T cells is significantly elevated in psoriasis patients (35-37). Microbiome dysbiosis has been proven to trigger several immune disorders through the activity of T cells and lead to an inflammatory process (40, 41). The study showed that that treatment with broad-spectrum antibiotics in an imiquimod-induced inflammation psoriatic model in mice reduced the percentage of phenotypic skin thickness and active T cells (42). Their results supported the relationship between microbiome dysbiosis and T cell-mediated inflammatory immune response. It's indicated that *Phascolarctobacterium* was correlated significantly with the systemic inflammatory cytokines and psoriasis patients showed an increased presence of *Faecalibacterium* (24, 30). Our results supported that cytokines and gut microbes were related in the occurrence of psoriasis and immunoreaction might be the bridge that connected them. We have found another interesting aspect that the level of C3 was in a negative correlation with *Bacteroides* in our research. It's reported C3, and C4 levels were significantly higher in patients with psoriasis than in healthy controls (43), and the reduction of *Bacteroides* in psoriasis patients was also found by others (17). The results suggest that an immune response associated with gut microbes may also activate complement involvement. The correlation between gut microbes and Inflammation-related indicators confirmed the involvement of gut microbes in the pathogenesis of psoriasis from one aspect and suggested the possible mechanism of the involvement of gut microbes in the pathogenesis of psoriasis.

To determine whether the gut microbiota in pustular psoriasis patients and psoriasis vulgaris patients is different, the bacterial communities of patients with two types were compared. The microbial compositions at the species level show that *Faecalibacterium* and *Anaerorhabdus* were significantly high in patients with pustular psoriasis. Pustular psoriasis is a heterogeneous group of inflammatory skin diseases genetically distinct from psoriasis vulgaris (44). Our results indicated that pustular psoriasis was distinct from psoriasis vulgaris in gut bacterial communities and provided evidence for the differences in pathogenesis between pustular psoriasis and psoriasis vulgaris. However, other studies have found no significant differences between the four psoriasis subgroups (18). Further studies are needed to determine the differences in the microbiota among the groups with different psoriasis severity levels or subgroups.

In summary, we indicated altered relative abundance for specific bacterial taxa and suggested alteration of the dysbiosis in the intestinal microbiota that existed in psoriasis patients. The correlation analysis with inflammatory cytokines and microbiota was further evidence that gut microbiota induced immunologic pathogenesis of psoriasis. Our results were consistent with previous research focused on psoriasis, even more autoimmune diseases. In a follow-up experiment, the pathogenic mechanism and effect of gut microbes on psoriasis still needed to be done. This entire endeavor is ultimately to achieve a microbiota-based therapeutic approach.

## Conclusion

Psoriasis is a chronic, immune-mediated skin disease that there is an increased incidence rate in recent years. Most advancements in psoriasis have been in its pathogenesis. It's well accepted that abnormal immune responses mediated by cytokines are involved in the development of psoriasis, including TNF- $\alpha$ , IL-17, IL-6, etc. As a hotspot of research in recent years, the gut microbiota is related to both psoriasis and cytokines. However, whether the gut microbiota can be involved in the development of psoriasis, accompanied by the overproduction of inflammatory cytokines, still needs to be confirmed by many studies. Our manuscript shows that the gut microbiota profile of patients is associated with abnormal cytokine levels, based on the result that patients displayed a dysbiosis compared with normal controls. We also find that gut microbiota composition in patients with pustular psoriasis and psoriasis vulgaris has its characteristics. We predict that gut microbiota will play an essential role in the clinical diagnosis and treatment of psoriasis as therapeutic targets or biomarkers of psoriasis.

## Methods

### Study population

A total of 30 patients with a clinical diagnosis of psoriasis who were attending a dermatology outpatient clinic in the Second Affiliated Hospital of Xi'an Jiaotong University during one year from July 2018 to July 2019, among them 24 were diagnosed with psoriasis vulgaris (PV), 6 with pustular psoriasis (PP), and 30 age and sex-matched healthy individuals were included in the present study. Exclusion criteria

included antibiotic usage during one month before the study, infectious disease, other allergic and autoimmune diseases, and cancer in both groups. This study's protocol was approved by the local Ethical Committee of the Second Affiliated Hospital of Xi 'an Jiaotong University. We informed all the volunteers about their participation in the study and received their signed informed consent.

### Fecal sample collection and DNA extraction

Fecal samples were collected and immediately stored at – 80 °C. Bacterial DNA was extracted from fecal samples with the QIAamp DNA Stool Mini Kit following product specification. Isolated DNA was stored at -20 °C until sequencing.

### Sequencing

The PCR reaction system was composed of 30ng genomic DNA samples and corresponding fusion primers, and PCR reaction parameters were set for PCR amplification. PCR amplification products were purified by Agencourt AMPure XP magnetic beads and dissolved in Elution Buffer. We used the Agilent 2100 Bioanalyzer to detect the fragment range and concentration of the library. The HiSeq platform was best suited to the size of the inserted fragment, so it was used for sequencing. Hyper-variable region V3 to V4 was selected using forward primer F515 (GTGCCAGCMGCCGCGG) and reverse primer: “E.coli 907-924” (CCGTCAATTCMTTTRAGT) to examine the bacterial composition. The QIIME (45), v1.7.0, the software was used to process the raw data files from the sequencer.

### Microbial profiling analysis and Statistical analysis

The operational taxonomic unit (OTU) formation was performed using the QIIME reference optimal picking, and UPARSE(46), version 1.2.22q was used to perform the clustering. We selected a primer-specific version of the full GreenGenes 13.5 (47) as the reference database. The Mothur (version: 1.31.2) software was used to calculate the alpha diversity indices. The corresponding rarefaction curve and box/bar plots were drawn by software R. We used QIIME pipeline to calculate the beta distance between samples. Since the number of sequences could influence the beta diversity, samples were downsampled to the same sequencing depth, the minimum of sample size. LDA Effective Size (LEfSe) is a biomarker discovery and explanation tool which could be used for high-dimensional data. The statistical significance with biological consistency and effect size estimation were coupled by LEfSe (48). The software used the non-parametric factorial Kruskal-Wallis (KW) sum-rank test to detect features with significant differential abundance with respect to the class of interest, then used LDA to estimate the effect size of each differentially abundant feature.

## Abbreviations

OTU: Operational taxonomic units; LEfSe: Linear discriminant analysis effect size; LDA: Linear discriminant analysis; FBS□Fasting blood sugar; PV: psoriasis vulgaris; PP: Pustular psoriasis.

# Declarations

## Acknowledgements

We are indebted to all study participants involved in the study. We are grateful to the support provided by the Xi'an Jiaotong University and The Second Hospital Affiliated to Xi'an Jiaotong University.

## Authors' contributions

To qualify for authorship, we hereby declare that the authors have made substantial contributions to the intellectual content of the paper. Each author's specific contribution is as following: XZ analyzed the data and wrote the paper; LS wrote the paper; TS contributed essential reagents or tools; SG designed the research study; KG designed the research study and performed the research. We indicate that all authors have read and approved the manuscript.

## Funding

This work was supported by a grant to KG from the National Natural Science Foundation of China (No.51707149) □Basic scientific research fund of Xi'an Jiaotong University (No.xjj2017071) and the State Key Laboratory of Intense Pulsed Radiation Simulation and Effect (Grant No. SKLIPR.1609).

## Availability of data and materials

The datasets generated for this study can be found in the SRA accession database: ID PRJNA646468. <http://www.ncbi.nlm.nih.gov/bioproject/646468>

## Ethics approval and consent to participate

The protocol of this study was approved by the local Ethical Committee of the Second Affiliated Hospital of Xi 'an Jiaotong University. We informed all the volunteers about their participation in the study and received their signed informed consent.

## Consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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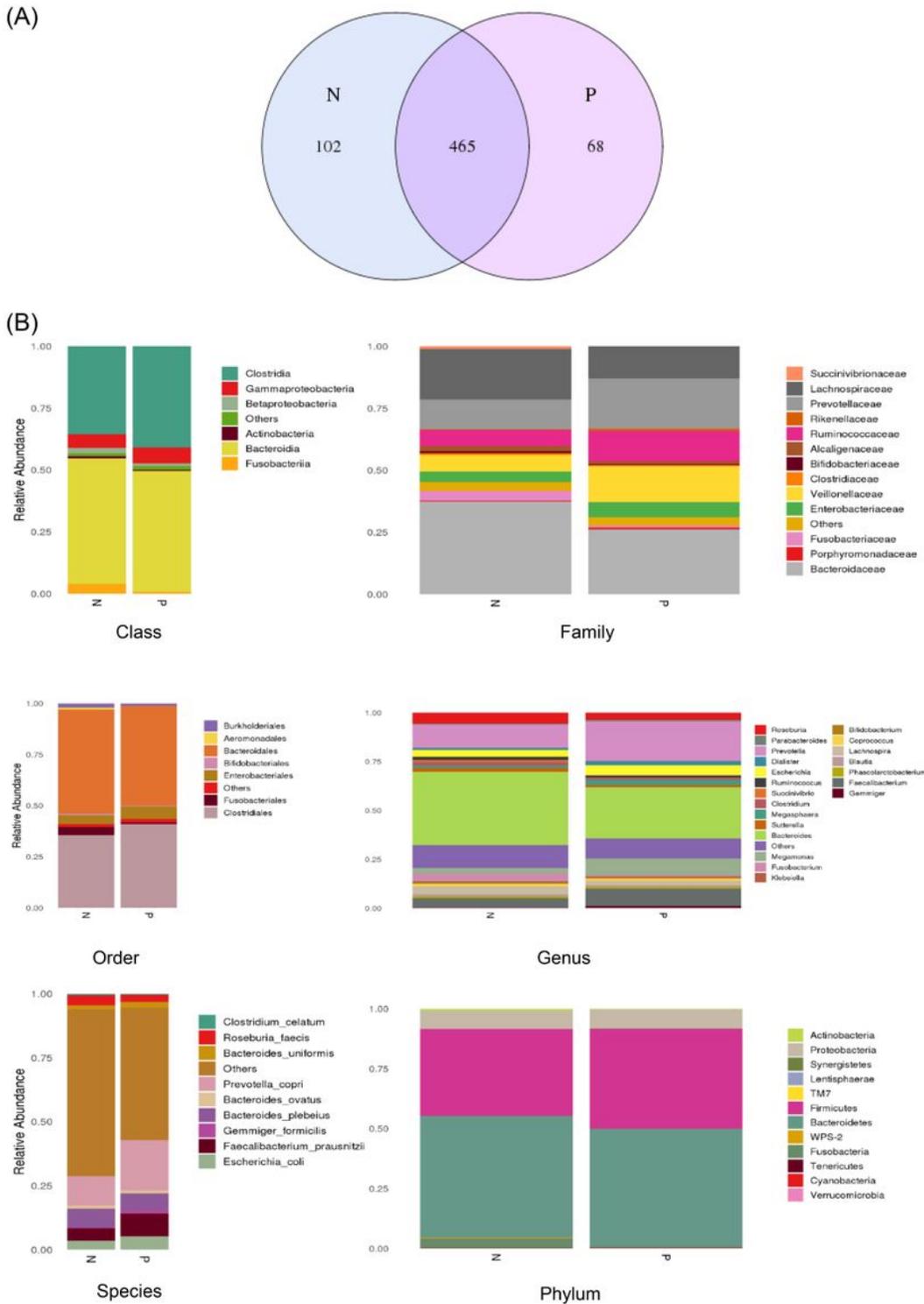
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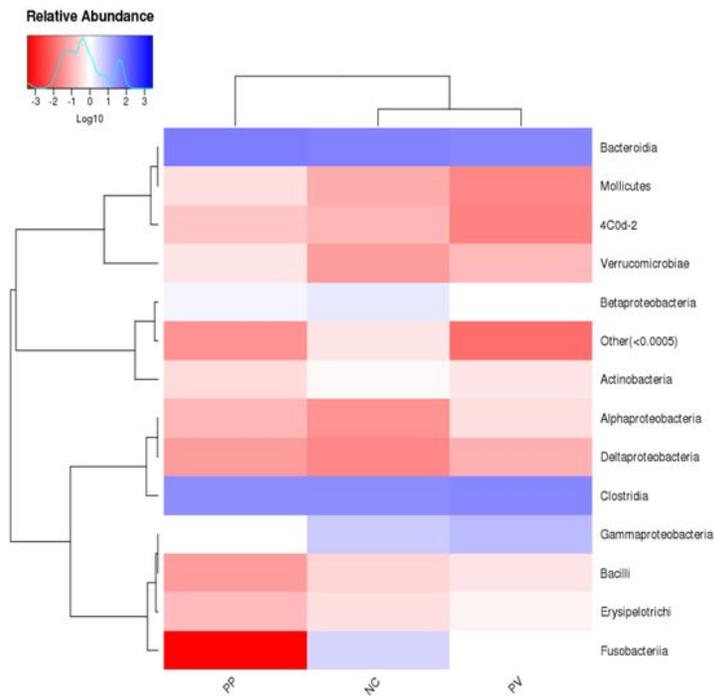
## Figures



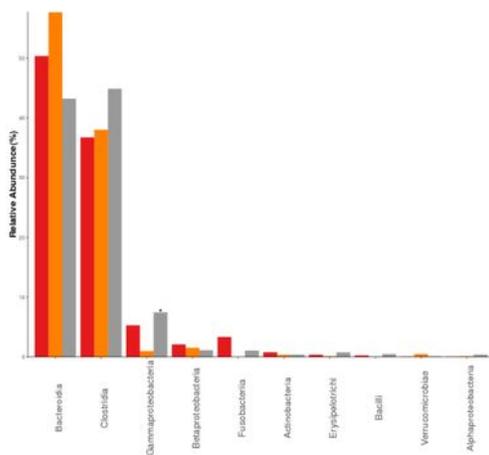
**Figure 1**

A. Venn diagram showing the unique and shared operational taxonomic unit (OUT) in psoriasis (P) and healthy control group (N); B. Comparison of fecal microbiota among psoriasis (P) and healthy control group (N). Relative abundance of the gut microbiota identified at class, family, order, genus, phylum and species level.

(A)



(B)



(C)

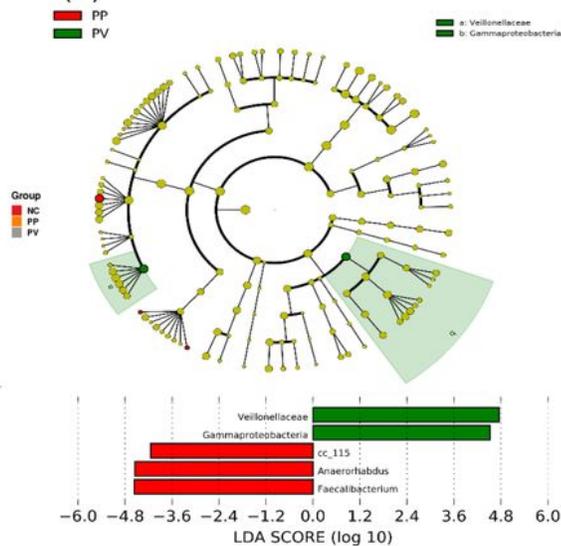


Figure 4

A. Heat map based on the abundance ranks of the class level. Red and blue indicate high and low abundance, respectively. Hierarchical clustering (Euclidean distance, complete linkage) shows that psoriasis pustulosa group (PP) tends to be singled out against psoriasis vulgaris group (PV) and healthy control group (NC); B. The dominant Class in the psoriasis pustulosa group (PP), psoriasis vulgaris group (PV) and healthy control group (NC). Histogram representation of the relative abundance (%) of the main

taxa and the significant differences (P-values) observed between two groups. \*  $0.01 < P\text{-value} \leq 0.05$ ; C. LefSe analysis was performed to identify differentially abundant taxa, which are highlighted on the phylogenetic tree in cladogram format and for which the LDA scores are shown. Red and green colors indicate an increase or decrease in taxa, respectively, in the psoriasis pustulosa group (PP) and psoriasis vulgaris group (PV).

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