

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

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## Research article

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# Abstract

## Background

Psoriasis is an inflammatory skin disease that is 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 have effect on both allergy and autoimmunity diseases in recent studies. Our objective was to identify differences in the faecal microbial composition of patients with psoriasis compared with healthy individuals in order to unravel the microbiota profiling in this autoimmune disease.

## Results

We collected fecal samples from 30 psoriasis patients and 30 healthy controls and sequenced them by 16S rRNA high-throughput sequencing and identified the differences in the gut microbial composition between two groups through data analysis. 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 correlation analysis based on microbiota and Inflammation-related indicators proved that microbiota dysbiosis might induce 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. Furthermore, it was reported intestinal flora alteration could activate an abnormal immune response that ultimately leads to the development of psoriasis (6).

There is a large and complex community of beneficial microbes that remain stable over long periods harbored in the human gut (7). The stability of beneficial microbes is closely related to human health (8). Studies have proven that the immune response was regulated by the microbiome in many physiological processes via interactions between innate immunity and acquired immunity (9, 10). 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 (11). 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 (12–15). 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 and several organisms are virtually absent in these two diseases (12). There was even evidence that manipulation of the composition of the gut microbiota affected phenotypes of psoriasis (16). However, current cross-sectional studies could not determine the change in the microbiome is a cause or a result. Thus, further evidence including consistency, specificity, timeliness, and biological plausibility are needed for understanding the relationship between the gut microbes and pathogenesis of psoriasis.

In the present study, we aimed to characterize the intestinal microbiota composition of patients with psoriasis and provide the evidence for the hypothesis that the intestinal microbiota dysbiosis may play a key role in the development of the psoriatic disease. In addition, 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

In order 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  $\pm$  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, and 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

	<b>Psoriasis</b>	<b>Healthy</b>
Male/Female	20 / 10	20 / 10
Age (years)	43.13 ± 13.79	43.7 ± 13.21
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. Through overlap relationship between reads, we spliced reads into Tags, then clustered Tags into OTU. 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 (Fig. 1A). Then the OTUs sequence and Greengenes database were annotated, and the result showed that predominant microbes were included. The top 5 taxa in relative abundance at family level include Bacteroidaceae, Lachnospiraceae, Prevotellaceae, Veillonellaceae, and Ruminococcaceae. The top 5 taxa in relative

abundance at the genus level include *Bacteroides*, *Prevotella*, *Roseburia*, *Faecalibacterium*, and *Lachnospira*. The top 5 taxa in relative abundance at order level include *Bacteroidales*, *Clostridiales*, *Enterobacteriales*, *Fusobacteriales*, and *Burkholderiales*. The top 5 taxa in relative abundance at the phylum level include *Bacteroidetes*, *Firmicutes*, *Proteobacteria*, *Fusobacteria*, and *Actinobacteria*. The top 5 taxa in relative abundance at species level include *Prevotella\_copri*, *Bacteroides\_plebeius*, *Faecalibacterium\_prausnitzii*, *Roseburia\_faecis*, and *Escherichia\_coli* (Fig. 1B).

The OUT Rank Abundance curves obtained for each sample tend to plateau, therefore 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) (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 (Fig. 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, whereas *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 compared with health control (all  $P \leq 0.05$ ) (Fig. 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 (Fig. 2E). The greatest difference in taxa from the phylum to the genus level was identified by an LDA score (Fig. 2F). The two taxa with the highest score in the psoriasis group were *Veillonellaceae* and *Megamonas*, which is consistent with the previous one.

### Correlation between gut microbiota and clinical indices

Correlation analyses were performed to further investigate identified potential associations of key microbial genera with clinical indices above (Fig. 3). Exact figures of these clinical indices were showed in Supplement 4 and 5. 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 PV and PP

To compare the microbiota communities of PV (24 cases) and PP (6 cases) were compared. Heat map based on the abundance ranks of the class level 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 them (Fig. 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 PP group than PV group and N group (all P-value  $\leq 0.05$ ) (Fig. 4B). LefSe analysis was performed to identify differentially abundant taxa in the PP group compared with the PV group (Fig. 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 was found 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 which are consist with Tan's research in 2018(13). Though the lower microbial diversity detected in other studies has been reported previously for other cohorts of patients with psoriasis (12, 15). As well, differences in sequencing methodologies and 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 psoriasis group (P) and 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 family level. At 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 (15, 16).

An early study proved the relative abundance of Veillonellaceae is increased in the intestinal mucosa of Crohn's disease patients (17). 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

(18). So we speculated Veillonellaceae played a role in abnormal immunity which is related to psoriasis arthritis 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 (19–21).

Previous studies showed the relative abundance of Faecalibacterium in gut microbiota was closely related to immune-regulation (22). It's also found that an increase in species belonging to this genus was associated with inflammatory diseases such as Crohn's disease (23). 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 may play a role in the disruption of barrier integrity and affection on the pro-inflammatory state in the gut (24, 25). Bacteroides, Proteobacteria, Actinobacteria, and Akkermansia did not show variability among groups that were detected abnormal in psoriasis patients in other studies (15, 16, 26). 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. As many studies have shown abnormal cytokine production in the T cells of psoriasis patients (27), we collected common biochemical indicators in patients with psoriasis, including cytokine test results, and found that IL-2R, IL-6 and IL-8 in patients with psoriasis were different from those in the general population. Through the correlation analysis of clinical phenotypes with microbes, we found a strong positive correlation between Phascolarctobacterium and IL-2R. 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 (28, 29). Microbiome dysbiosis has been proven to trigger several immune disorders through the activity of T cells and lead to an inflammatory process (30, 31). 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 (32). 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 (20, 26). Now our results supported that cytokines and gut microbes were related in the occurrence of psoriasis and immunoreaction might be the bridge which 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 (33) and the reduction of Bacteroides in psoriasis patients was also found by others (15). 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 if there are differences in the microbiota between pustular psoriasis and psoriasis vulgaris, the bacterial communities of patients with two types were compared. The microbial compositions at the species level are shown that *Faecalibacterium* and *Anaerorhabdus* were significantly high in patients with pustular psoriasis. The pustular psoriasis is a heterogeneous group of skin inflammatory diseases, which genetically distinct from psoriasis vulgaris (34). 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 there were no significant differences among the four psoriasis subgroups (16). Further studies are needed to find out the differences in the microbiota among the groups with different psoriasis severity levels or subgroups.

In summary, we indicated altered relative abundance for certain bacterial taxa and suggested alteration of the dysbiosis in the intestinal microbiota 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. Gut microbiota, as a hotspot of research in recent years, 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 a large number of 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 the composition of gut microbiota in patients with pustular psoriasis and psoriasis vulgaris has its characteristics. We predict that gut microbiota will play an important role in 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 a one-year period from July 2018 to July 2019, among them 24 were diagnosed with psoriasis vulgaris (PV), 6 with psoriasis pustulosa (PP), and 30 age and sex-matched healthy individuals were included in the present study.

Exclusion criteria were including antibiotic usage during one month before the study, infectious disease, other allergic and autoimmune diseases and cancer in both groups. 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.

### 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 30 ng 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 (35), 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(36), version 1.2.22q was used to perform the clustering. We selected a primer-specific version of the full GreenGenes 13.5 (37) 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 (38). 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

## 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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### 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.

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# Figures

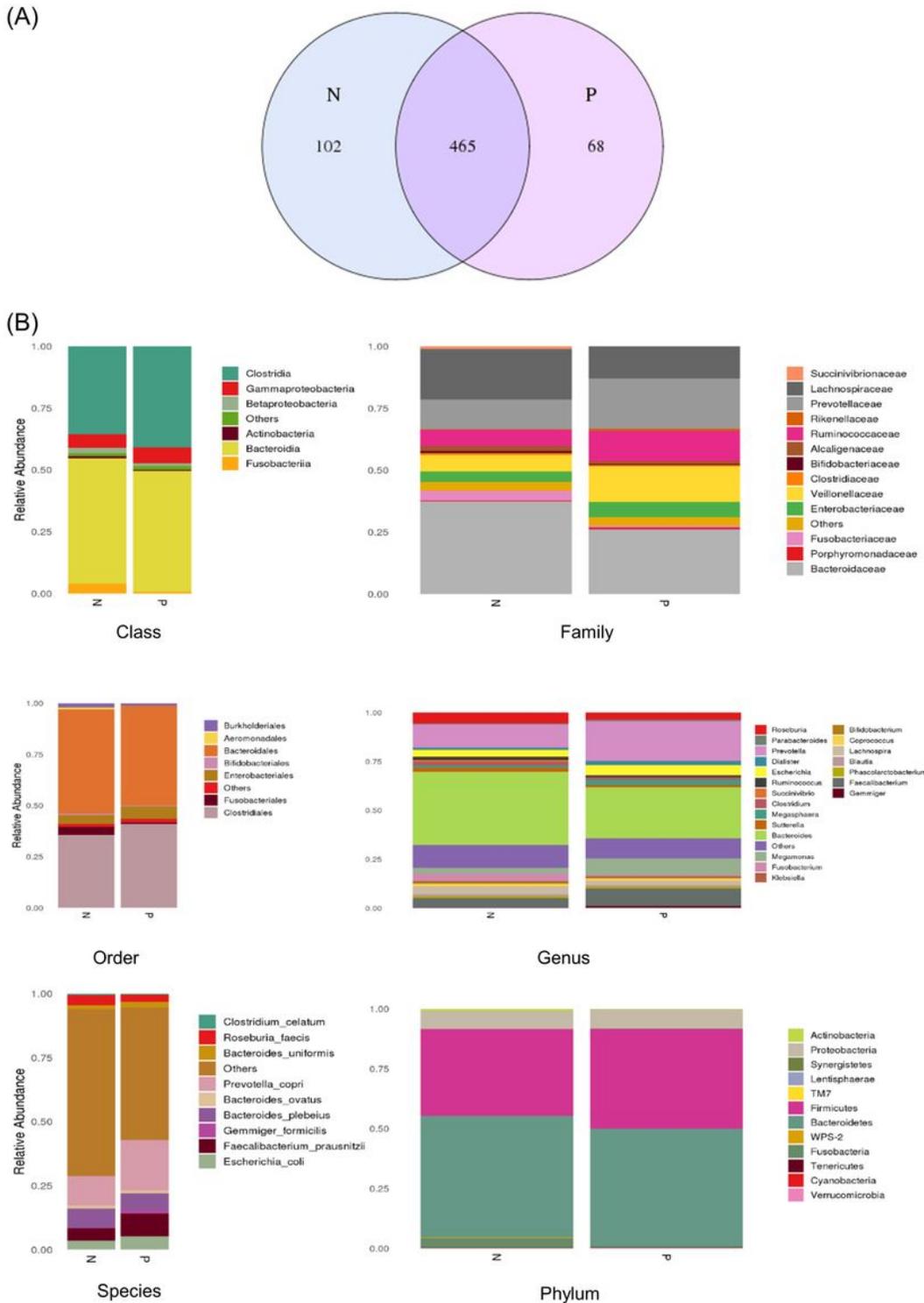
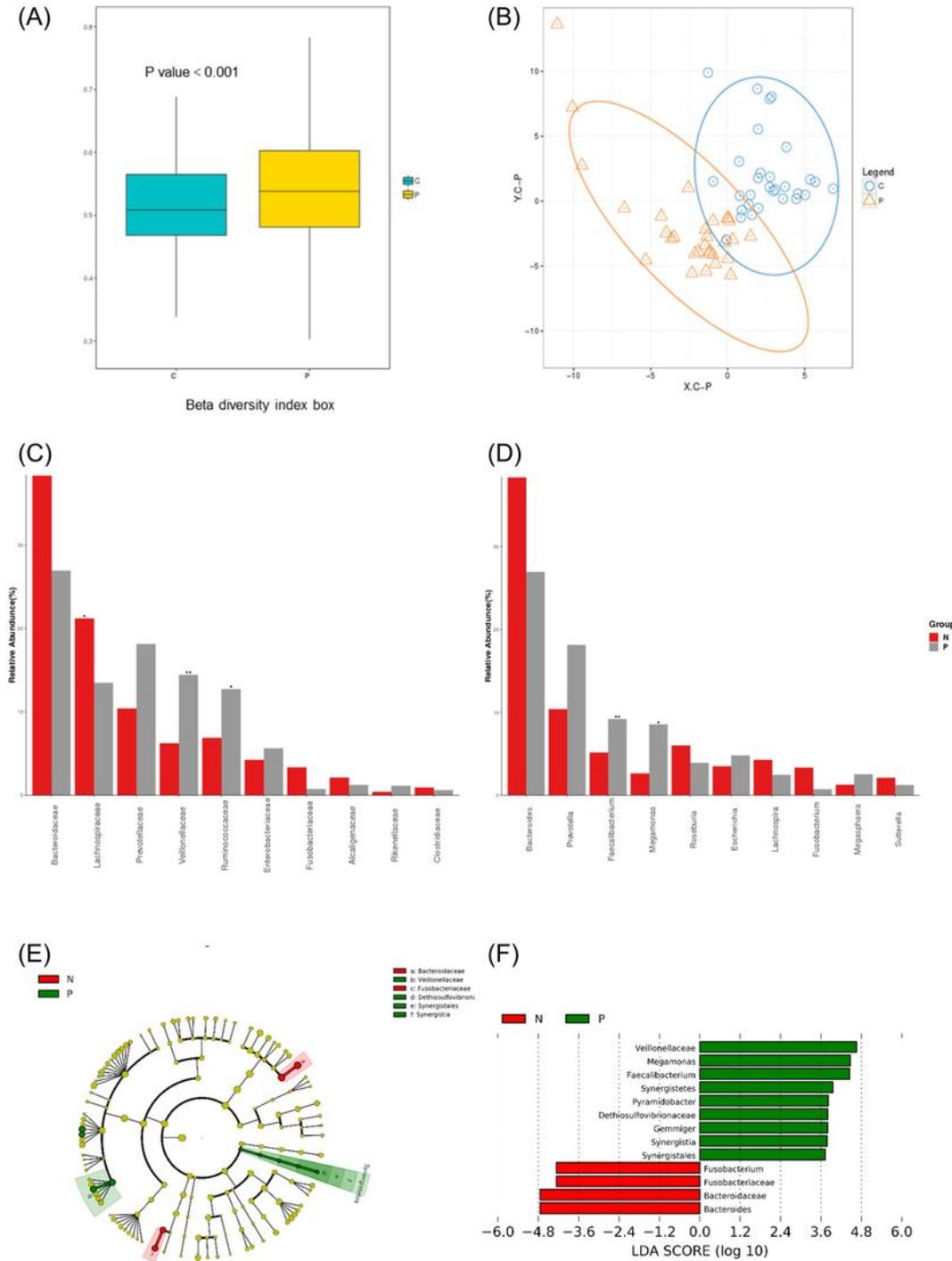


Figure 1

Figure 1A. Venn diagram showing the unique and shared operational taxonomic unit (OTU) in psoriasis (P) and healthy control group (N); Figure 1B. Comparison of fecal microbiota among psoriasis (P) and

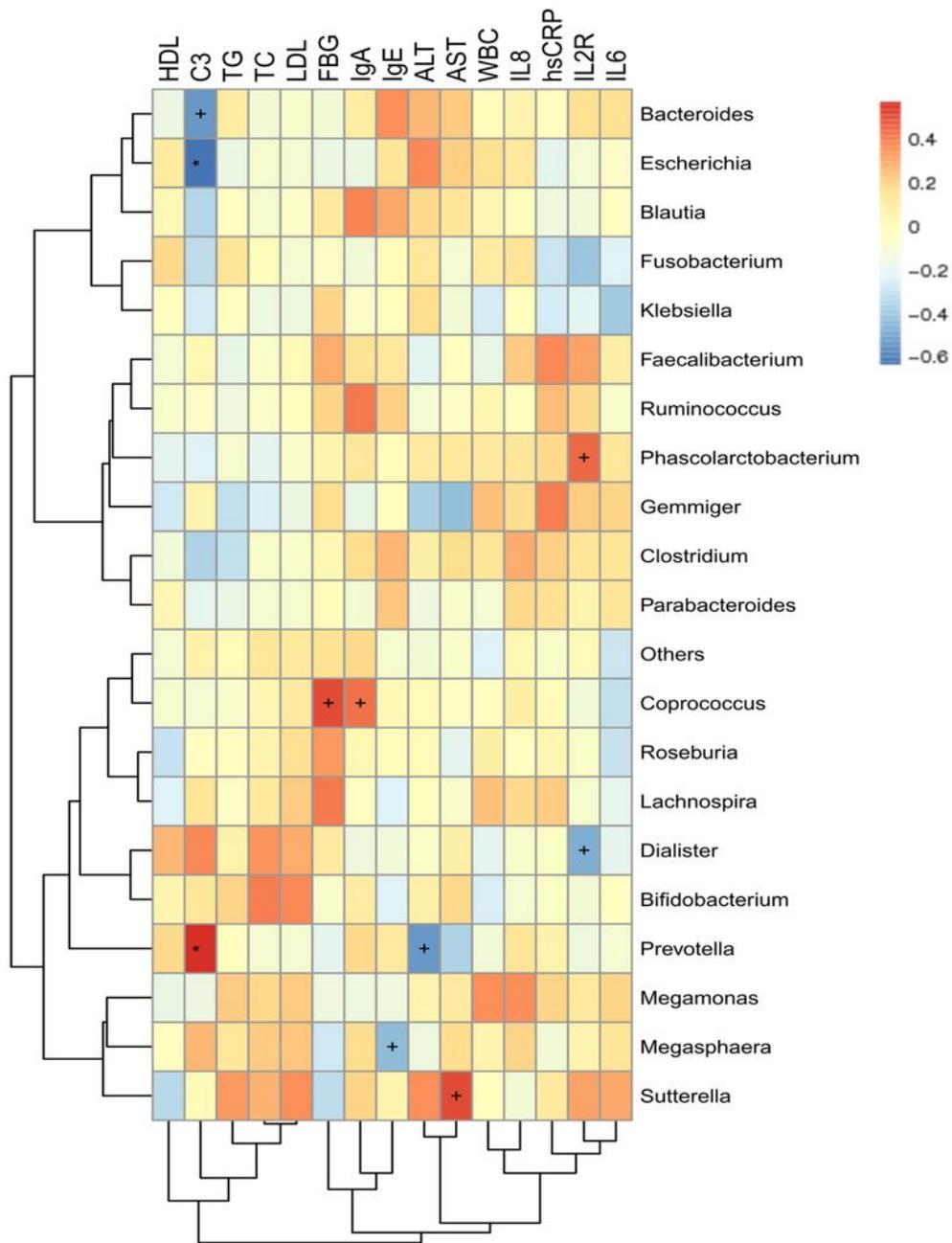
healthy control group (N). Relative abundance of the gut microbiota identified at class, family, order, genus, phylum and species level.



**Figure 2**

Figure 2A. Analysis of Beta diversity revealed significant differences between psoriasis group (P) and healthy control group (N) performed on the unweighted UniFrac ( $P \leq 0.001$ ). The results revealed a significant separation in the bacterial community composition between psoriasis patients and healthy

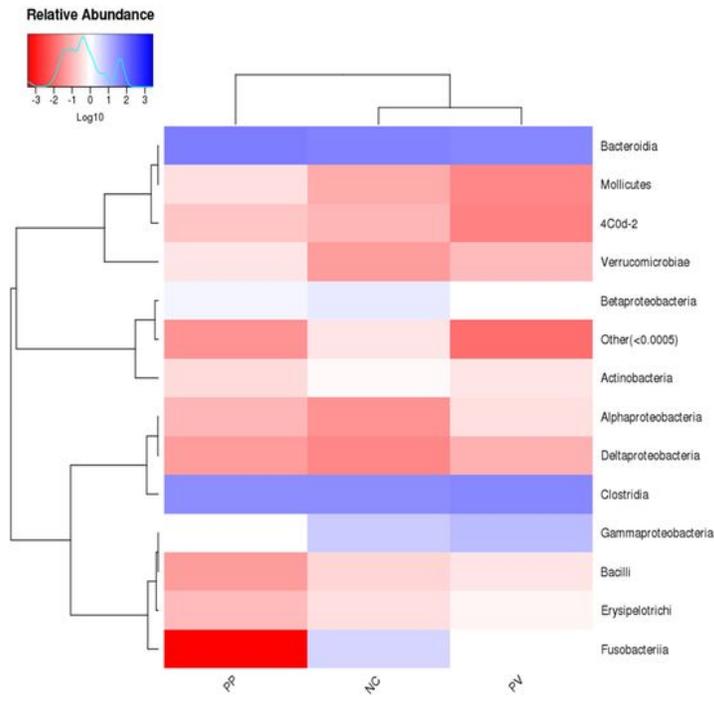
individual; Figure 2B. PLS-DA plot of OTU. The horizontal axis and the vertical axis indicate the top 2 components. Each dot represents one sample and yellow dots stand for psoriasis group (P) and blue dots stand for healthy control group (N). It revealed significant clustering of psoriasis group (P) and healthy control group (N); Figure 2C and 2D. The dominant Family and Genus in the psoriasis group (P) and healthy control group (N). Histogram representation of the relative abundance (%) of the main taxa and the significant differences (P-values) observed between two groups. \*  $0.01 < P\text{-value} \leq 0.05$  \*\*  $0.001 \leq P\text{-value} \leq 0.01$ ; Figure 2E and 2F. The enriched taxa in psoriasis group (P) and control (N) fecal microbiota were represented in Cladogram. The central point represents the root of the tree (Bacteria), and each ring represents the next lower taxonomic level (phylum to genus: p, phylum; c, class; o, order; f, family; g, genus). The diameter of each circle represents the relative abundance of the taxon. The taxa with no significant differences were colored yellow, the red nodes represented the microbiota that played an important role in the healthy control group (N). The green node represents the microbiome that plays an important role in the psoriasis group (P). And the most differentially abundant taxa between the psoriasis group (P) and healthy control group (N) which was generated from LEfSe analysis.



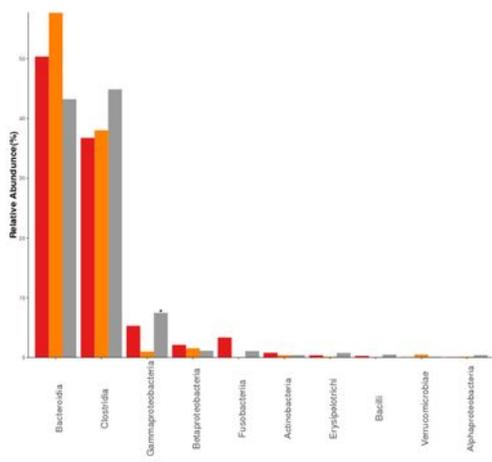
**Figure 3**

Pearson correlation analysis was performed to assess the correlation of clinical phenotypes with microbes at Genus level in the psoriasis group.\* P-value  $\leq 0.01$  + P-value  $\leq 0.001$

(A)



(B)



(C)

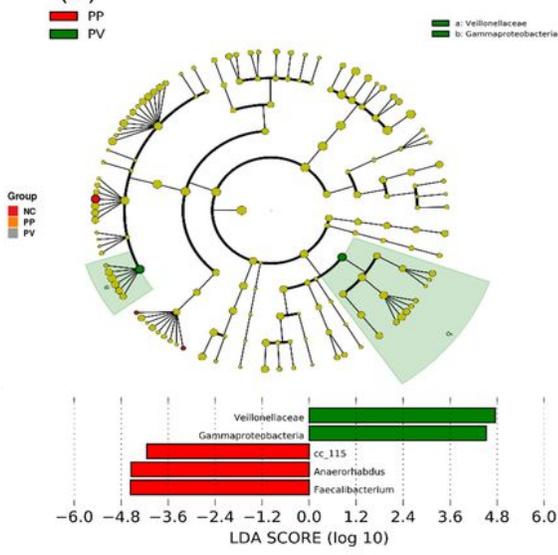


Figure 4

Figure 4A. 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); Figure 4B. 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. \*  $0.01 < P\text{-value} \leq 0.05$ ; Figure 4C. 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).

## Supplementary Files

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