Successful treatment of psoriasis with secukinumab constructed a new homeostasis of gut microbiome

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Research Article

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Abstract

Background: Secukinumab (an interleukin (IL)-17 inhibitor) has been reported to be able to alter gut microbiome composition in psoriatic patients. However, it still remains unclear the gut microbiota alteration and related functional changes caused by successful secukinumab therapy in psoriatic patients. In this study, fecal samples from healthy people as comtrol (H; n=35), psoriatic patients without therapy (BT; n=32) and patients after 5-month successful secukinumab treatment (AT; n=11) were collected., Then gut microbiomes were investigated using next-generation sequencing targeting 16S ribosomal RNA.

Results: Successful secukinumab therapy caused a significantly elevated microbiota richness and biodiversity, as well as an alteration in the gut microbiota composition than psoriasis without therapy and healthy control. The psoriatic patients after secukinumab successful therapy showed a microbiota profile characterized by increased proportions of the phylum *Firmicute,* families *Comamonadaceae* and *Erwiniaceae*, and a reduction in the phylum *Bacteroidota*, compared to the other two groups. Besides, we discovered that secukinumab treatment group exhibited more significant abundance in contains mobile elements phenotype, form biofilms phenotype, gram positive phenotype, and less abundance in gram negative phenotype and potentially pathogenic phenotype by BugBase. Functional analysis showed the different COG pathways and KEGG pathways such as downregulated cardiovascular diseases pathway and upregulated infectious diseases between secukinumab therapy group and the other two groups.

Conclusions: Secukinumab therapy enhanced the diversity of gut microbiota and altered the composition of the gut microbiome, which actually may construct a more stable homeostasis of gut microbiome with less potentially pathogenicity.

Background

Microbiome, sometimes called the second genome, refers to a large and diverse community of microorganisms and their genes[1]. The human microbiome can be defined as the set of micro-organisms which lives on or inside our body, including the oral cavity, nostrils, skin, gastrointestinal and genitourinary tract[2, 3]. Intestinal microbiome has been given a lot emphasize for the hypothesis on the link between the brain–gut–skin proposed by dermatologists John H. Stokes and Donald M. Pillsbury firstly[4]. Thanks to recent advances in next-generation sequencing, researchers have been able to analyze the biological characteristics of the microbiome and host in diseases, which makes a better understanding of the relationship between microbiome and the host's health or disease[5].

Strikingly, several studies have emphasized a vital influence of the gut microbiota on the host immune homeostasis, dysbiosis of which is related to the development of several autoimmune diseases[6, 7]. The gut microbiome is confirmed to play an important role in modulating both innate and acquired immune responses, the alterations of which may lead to an inflammatory process and immune disorders[8-10].

Although, composition of human gut microbiome is relatively stable around the age of two, it can be influenced by numerous factors, including lifestyle, comorbidities, antibiotic courses and other factors.

Psoriasis, an immune-mediated inflammatory chronic skin disease, affects 2–3% of the population worldwide[11]. IL-23/ Th17 axis-related inflammatory activation has been reported responsible for this pathogeny[1]. In the context of genetic predisposition, psoriasis can be triggered by various endogenous and exogenous factors, including bacterial infection, antibiotic treatment or profound dietary modification[12, 13]. Recent studies have demonstrated that gut microbiome is involved in the underlying pathogenesis of psoriasis, since certain gut microbiota played a significant impact on the function of various tissues, including skin[14, 15]. Actually, many researchers have observed a peculiar composition of gut microbiota in psoriatic patients. The increase in the number of *Firmicutes* and decrease of *Bacteroidetes* phyla have been discovered, which induce a disorder in inflammatory cascade[16].

To date, the traditional treatment for psoriatic patients, including topical and/or systemic therapy, is not adequate all the time. Recently, the advent of immunomodulating biologic drugs leads to a substantial improvement of disease control. Secukinumab, a kind of biological drug targeting interleukin (IL)-17, has a promising efficacy in psoriasis treatment. Besides, IL-17 inhibitor was reported to be able to alter gut microbiome composition in psoriatic patients[17] , which menifested as higher level of phylum *Proteobacteria* and lower levels of *Bacteroidetes* and *Firmicutes*[17]. What's more, researchers found the baseline gut microbiota was significantly different between responders and non-responders to secukinumab treatment, which suggested that the gut microbiota may serve as a potential response to treatment biomarker in psoriasis of secukinumab therapy[17]. However, it still remains unclear the gut microbiota alteration and related functional changes caused by successful secukinumab therapy in psoriatic patients.

Addressing the questions, we collected the feces from psoriatic patients after 5-month secukinumab treatment or without treatment, and feces from healthy people as control. And then, we detected gut microbiota composition in above groups using the 16S rRNA

method, and to investigate the influence of secukinumab successful therapy on gut microbiome.

Materials And Methods

Study subjects

Moderate-to-severe (PASI > 10 or BSA > 10) psoriatic patients successfully treated by 5-month secukinumab treatment (n=11), which was defined by achieving a PASI 90 response, were selected, and age-, sex-, and disease severity-matched (1:3) psoriatic patient without therapy were identified. The control group compromised age- and sex-matched (1:3 or 1:4) healthy donors (**Table S1**). All participants with 18-25 BMI were selected from the Second Affiliated Hospital of Xi'an Jiaotong University, and they did not receive antibiotics, probiotics, glucocorticoids, or immunosuppression during the 6 previous months. Besides, they have not suffered from diseases of the digestive system, immune system and

other severe illnesses. Finally, we collected 11 samples from secukinumab group, 32 samples from psoriasis without treatment group (one patient lost) and 35 samples from healthy control group. The study was approved by the Ethical Committee of the Second Affiliated Hospital of Xi'an Jiaotong University. All study subjects signed informed consent forms.

Samples collection and DNA extraction.

Fresh fecal samples were collected in a specimen collection kit and stored at -80 °C before further manipulation in the laboratory. All fecal samples were transferred to the laboratory in an ice box.

DNA from stool samples was extracted using the DNA Isolation Kit (MoBio, Carlsbad, CA, UnitedStates) according to the manufacturer's instructions. Using NanoDrop 2000 (Thermo Fisher Scientific, Waltham, USA), the concentration and purity of bacterial genomic DNA were tested. Total DNA quality was deteced by electrophoresis using a 1% agarose gel. All the genomic DNA was stored at -20 °C and at -80°C for short-term and long-term use respectively.

PCR amplification and sequencing

The V3 + V4 region of the 16S rDNA genes were amplified with the universal primers (F: 5'-ACTCCTACGGGAGGCAGCA-3', R: 5'- GGACTACHVGGGTWTCTAAT-3') by PCR. Next, the 16S rDNA gene sequencing was performed on fecal samples from our 78 samples on the Illumina Hiseq 2500 sequencing platform (Biomarker Technologies Corporation, Beijing, China) in PE250 mode (2 × 250 bp paired ends). The analysis of microbiota was carried out on BMK Cloud platform (www.biocloud.net).

Particularly, the paired-end reads were assembled using FLASH software to produce Raw Tags. To get the clean tags, Trimmomatic (version 0.33) was used to perform quality filter. Using UCHIME (version 8.1), we screen for and remove putative chimeric sequences. Operational taxonomic units (OTUs) were clustered with more than 97% identity by USEARCH (version 10.0), while the OTUs whose proportions were less than 0.005% of the total OTUs were removed.

Bioinformatics and statistical analysis

Using Mothur software, alpha diversity based on OTU level, including indices to measure evenness (Simpson) and richness (ACE), Good's coverage, and species accumulation curves were investigated. The difference in alpha diversity between groups was examined by Student's t-test. The Non-MetricMulti-Dimensional Scaling (NMDS) analysis based on binary_jaccard was performed to assess the beta diversity of the bacterial community using QIIME software. To test whether beta diversity is statistical different among different samples, permutational analysis of variance (PERMANOVA) was performed using R software. Linear discriminant analysis (LDA) effect size (LEfSe) was used to further determine the specific significantly different bacterial taxa among cohorts. LDA values > 2.0 with a P value < 0.05 were considered significantly enriched. The functional abundance spectrum of the Kyoto Encyclopedia of Genes and Genomes (KEGG) ortholog functional profile was predicted by PICRUSt procedure from the

16S rRNA gene data. Besides, the phenotype prediction of the gut microbiota was analyzed by BugBase using Pairwise Mann-Whitney-Wilcoxon tests.

Results

Characteristics of study participants and sequence of gut microbiome

We enrolled 78 participants including 11 psoriatic patients after 5-month secukinumab treatment, 32 psoriatic patients without treatment, and 35 healthy people as control. There were no significant differences in demographic information between AT, BT, and H group. A summary of related characteristics of above three groups are presented in **Table 1**, and detailed related information of participants is shown in **Table S1**.

Table 1 Charasitics of each group

	AT	BT	H
Male/female	10/1	29/3	31/4
Age (years)*	37.82	38.38	37.31
Types of patients			
Psoriasis vulgaris	11	32	
Psoriasis arthritis	0	0	
Pustular psoriasis	0	0	
Erythrodermic psoriasis	0	0	

*Median

AT psoriatic patients after receiving 5-month secukinumab treatment, *BT* psoriatic patients without therapy, *H* healthy people.

Then, 78 fecal samples were collected, containing 5,841,838 raw sequences with a mean length of 456 base by 16S rDNA sequencing and analysis. After quality trimming and chimera checking, we obtained 5,585,894 high-quality sequences in total for further analysis. 424 OTUs in all samples were identified, and 382, 412, and 420 OTUs were confirmed in AT, BT, H respectively. The data summary is shown in **Table 2**. All sequences in three groups were verified high coverage values over 99%. The species accumulation curves of genus level had reached a plateau in all three groups (**Fig. 1A**). Above results illustrate that most fecal microbiota species were detected, which provided good sequencing depth for fecal microbiota exploration in follow-up analysis.

Table 2 Fecal microbiota community indices

Group	OTUs	Good's	Richness index (M ± SD)	Diversity index (M ± SD)
			ACE	Simpson
AT	382	0.9994	280.9624 ± 6.0319	0.9200 ± 0.0105
BT	412	0.9994	235.4373 ± 10.7863	0.8019 ± 0.0287
H	420	0.9994	246.2601 ± 12.2193	0.8452 ± 0.017

AT psoriatic patients after receiving 5-month secukinumab treatment, *BT* psoriatic patients without therapy, *H* healthy people.

Secukinumab treatment leads to significant change in gut microbial diversity

We set out to investigate the richness of fecal microbiota and structural difference among these three groups, the α-diversity (ACE index and Simpson index) of gut microbiota was calculated (**Table 2**). By ACE indices, we discovered that secukinumab therapy induced significantly increased microbiota richness compared to that of the other two groups (**Fig. 1B**). Also, secukinumab therapy had an elevated biodiversity than the other two groups by Simpson indices (**Fig. 1C**). However, there were no significant differences of α-diversity of gut microbiota between psoriatic patients without therapy and healthy people as indicated by both ACE and Simpson indices.

Further, in order to assess the similarity of gut microbial communities among these three groups, beta diversity was analyzed. NMDS based on binary_jaccard was performed, which suggested that the fecal microbiota of secukinumab treatment group was different from the other two groups (stress=0.1480<0.2) (**Fig. 1D**). The separation trend of secukinumab treatment and psoriasis without treatment is more obvious, and beta diversity of secukinumab treatment is lower, which is validated significantly (p =0.002, PERMANOVA) (**Figs. 1D, E**).

Secukinumab treatment altered gut microbiota composition

The taxonomy of fecal microbiota was evaluated using the RDP classifier. Two dominant phyla, *Firmicutes* and *Bacteroidetes*, based on different relative abundances among three groups were identified. *Firmicutes* (70.12%) increased and *Bacteroidetes* (19.38%) decreased in secukinumab treatment group, when compared to psoriasis without therapy group (*Firmicutes* 51.24%, *Bacteroidetes* 40.15%) and healthy people (*Firmicutes* 56.94%, *Bacteroidetes* 33.95%) (**Figs. 2A, B**). In family level, higher proportions of *Lachnospiraceae* (29.32%) and *Ruminococcaceae* (22.75%) and lower proportions of *Bacteroidaceae* (14.91%), *Prevotellaceae* (1.78%) and *Veillonellaceae* (4.97%) in secukinumab treatment group were verified (**Figs. 2C, D**). In genus level, the abundance of *Faecalibacterium* (15.31%) was higher and the abundance of *Bacteroides* (14.91%) and *Prevotella_9* (0.03%) was lower in secukinumab treatment group than the other two groups (**Figs. 2E, F**).

To further evaluate the differences in the gut microbiota composition between each two groups, Metastats analysis was performed. In phylum level, there was a significant increase in *Firmicutes* and a decrease in *Bacteroidota* in secukinumab treatment group than the other two groups. Although the level of *Firmicutes* seemed lower and *Bacteroidota* seemed higher in psoriasis without therapy group than healthy control group, there was no statistical significance (**Table 3A, placed at the end of the text**). Significant decreases in the orders *Rhizobiales* and *Bacteroidales* were observed in secukinumab treatment group compared the other two groups, and a significant decrease in *unclassified_Firmicutes* was confirmed only when compared to healthy control group (**Table 3B**). In secukinumab treatment group, two families *Comamonadaceae* and *Erwiniaceae* were significantly more abundant and one family *Xanthobacteraceae* was massively less abundant than the other two groups, and three families *unclassified_Firmicutes*, *uncultured_Clostridiales_bacterium* and *Porphyromonadaceae* were less abundant when compared to healthy control group (**Table 3C**). In genus level, when compared to healthy control group, secukinumab treatment group presented obviously decreased genera *Bradyrhizobium*, *unclassified_Firmicutes* and *uncultured_Clostridiales_bacterium*, but increased genera *Hydrogenophaga*, *Pantoea* and *unclassified_Comamonadaceae*. What's more, when compared to psoriasis without therapy group, secukinumab treatment group showed statistically decreased genera *Bradyrhizobium*, *Hydrogenophaga* and *Lactococcus*, but increased genera *Pantoea* and *unclassified_Comamonadaceae*. Stikingly, lower levels of genera *uncultured_Clostridiales_bacterium*, *Alloprevotella* and *Butyrivibrio*, and higher level of *genus Prevotella_7* were identified in psoriasis without therapy compared to healthy control, while there was no profound significance between these two groups in phylum, order and family levels.

Consequently, we investigated the specific significantly different bacterial taxa among these three groups by using LEfSe analysis at genus level (LDA score > 2, $p < 0.05$). Several genera, including *Faecalibacterium*, *Agathobacter*, *Subdoligrnulum*, *Bifidobacterium* and *Dialister*, were significantly enriched in the secukinumab treatment group, while genera *Succinivibrio* and *Paraprevotella* were obviously enriched in psoriasis without treatment group (**Fig. 3A**). Besides, we detected the gut microbiota composition's alteration between the secukinumab treatment group and the healthy control group. We identified that genera such as *Faecalibacterium*, *Subdoligrnulum* and *Ruminococcus* were significantly increased in secukinumab treatment group, whereas *Limosilactobacillus*, *Desulfovibrio* and *Paraprevotella* were significantly enriched in healthy control group (**Fig. 3B**). Finally, in **Fig. S1**, we discovered that genera *Prevotella_7*, *Weissella* and *Lactococcus* were increased in psoriasis without therapy, while *Megasphaera*, *Dialister*, *Romboutsia* and other genera were enriched in healthy control.

Secukinumab treatment altered phenotypic functions of gut microbiota in psoriatic patients

The potential prediction for phenotypic functions in complex communities among these three groups was analyzed by BugBase. 5 predicted phenotypic functions (contains mobile elements, forms biofilms, gram-negative, gram-positive and potentially pathogenic) exhibited significant differences in abundance (**Fig. 4**). Secukinumab treatment group showed obvious increased abundance in contains mobile elements phenotype than the other two groups, which manifested as increased *Lachnospiraceae* and

Ruminococcaceae but decreased *Veillonellaceae* abundance (**Fig. 4A**). Besides, the gut microbiota of secukinumab treatment group demonstrated more significant abundance in form biofilms phenotype, having elevated abundance of *Bifidobacteriaceae*, *Coriobacteriaceae* and *Verrucomicrobiaceae*, and reduced abundance of *Enterobacteriaceae* and *Alcaligenaceae* than psoriasis without therapy group (**Fig. 4B**). What's more, we observed that the abundance of gut microbiota in secukinumab treatment group was significantly lower in gram negative phenotype (*Veillonellaceae*, *Prevotellaceae*, *Enterobacteriaceae* and *Bacteroidaceae*) (**Fig. 4C**), while statistically higher abundance of gut microbiota in gram positive phenotype (*Lachnospiraceae* and *Ruminococcaceae*) was confirmed than the other two groups (**Fig. 4D**). Finally, potentially pathogenic phenotype was evaluated. Interestingly, the gut microbiota abundance of secukinumab treatment group and healthy people group were both obviously reduced in this phenotype than the psoriasis without therapy group. Secukinumab treatment group suggested massively decreased *Veillonellaceae*, *Prevotellaceae* and *Bacteroidaceae*, while healthy control group demonstrated obviously reduced *Prevotellaceae* and *Bacteroidaceae* (**Fig. 4E**).

Secukinumab therapy influenced biological function of gut microbiota in psoriatic patients.

To better understand how biological functions in secukinumab treatment may be affected, we used PICRUSt2 to evaluate the composition of functional gene in fecal microbiota of our samples. As a result, a total of 5 significantly different functional COGs between secukinumab treatment group and healthy control group were found, as well as 7 COGs between secukinumab treatment group and psoriasis without therapy group were predicted (**Fig. S2**).

Moreover, further analyzation in the context of the KEGG database was performed to better clarify metabolic function changes of the community samples. In secukinumab treatment group, the functional genes for metabolism of terpenoids and polyketides, membrane transport, substance dependence and infectious diseases: viral were high enriched, whereas metabolism of cofactors and vitamins, glycan biosynthesis and metabolism, transport and catabolism and circulatory system were significantly reduced in comparison with healthy people group (**Fig. 5A**). Detailed information was shown in **Table S2.** Additionally, compared to psoriasis without therapy group, eight KEGG pathways (including infectious diseases: viral, infectious diseases: parasitic, substance dependence and others) were significantly enriched and 5 KEGG pathways (cardiovascular diseases, circulatory system, glycan biosynthesis and metabolism, amino acid metabolism and metabolism of cofactors and vitamins) were statistically reduced in the secukinumab treatment group (**Fig. 5B** and **Table S2**).

Discussion

In this research, we investigated the composition of gut microbiota in psoriatic patients after secukinumab successful therapy by 16S rRNA gene sequencing. Our results indicated that successful secukinumab therapy caused significantly elevated microbiota richness and biodiversity, as well as an alteration in the composition of the gut microbiota, which may modulate inflammatory reaction in psoriasis[18]. When compared to psoriasis without therapy, the psoriatic patients after secukinumab

successful therapy showed a microbiota profile characterized by increased proportions of the phylum *Firmicute*, families *Comamonadaceae* and *Erwiniaceae* and genera *Pantoea* and *unclassified_Comamonadaceae*, and a reduction in the phylum *Bacteroidota*, orders *Rhizobiales* and *Bacteroidales*, family *Xanthobacteraceae* and genera *Bradyrhizobium*, *Hydrogenophaga* and *Lactococcus*.

It has been confirmed that the pathogenesis of psoriasis is associated with systemic immune and inflammatory response, which could alter gut mucosa and thereby induce gut inflammation[19]. The *Firmicutes/Bacteroidetes* (F/B) ratio has been explored a lot before, which has been found elevated in gut microbiota of psoriatic patients in most studies based on previous data[20–22]. Both *Firmicutes* and *Bacteroidetes* are well-known short-chain fatty acids (SCFAs) producers, including acetate, propionate and butyrate[23]. Acetate and propionate are mainly produced by phylum *Bacteroidetes*, while butyrate is produced by phylum *Firmicutes*[23]. Butyrate is a vital factor to help to maintain the epithelial barrier, leading to anti-inflammatory effects. Also, it could suppress the oxidative stress and regulates the balance between Th17/Treg lymphocytes[6, 16, 24]. Although F/B ratio is higher in gut microbiota of psoriasis, the microbiome diversity and richness reduce which causes the imbalance between particular SCFAs: acetate synthesis increases while butyrate synthesis decreases[25, 26].

We speculated that secukinumab therapy enriched gut microbiome in psoriatic patients, which may modulate gut dysbiosis in psoriasis by SCFAs and play evident anti-inflammatory effects.

What's more, we found higher proportions of *Ruminococcaceae* in family level by using the RDP classifier. *Ruminococcaceae* has been confirmed to be correlated with the number of medium-chain fatty acids (MCFAs), which support Th1 and Th17 cell differentiation[27, 28]. Th17 cells, producing an essential proinflammatory cytokine interleukin-17, act as a central role of the psoriasis, while Th1 cells participate in the occurrence of disease. The interaction between Th1/Th17 cells and dendritic, mast cells, macrophages and neutrophils promotes the inflammatory response via IL-17, IL-19, IL-22, IL-23, TNF-α and other inflammatory cytokines, which results in the formation of psoriatic plaques[5, 16]. As the MCFAs modulate Th1/Th17 differentiation, the upregulated concentration of MCFAs related to increased abundance of family *Ruminococcaceae* should help improve the course of psoriasis.

Is the gut microbiome of psoriatic patients after secukinumab successful therapy the similar to that of healthy people? Strikingly, we found the richness and diversity of gut microbiota are higher after secukinumab therapy compared to healthy people. Moreover, secukinumab group showed enriched abundance of gut microbiota in phylum *Firmicutes*, families *Comamonadaceae* and *Erwiniaceae*, genera *Hydrogenophaga*, *Pantoea* and *unclassified_Comamonadaceae* and a reduced abundance of that in phylum *Bacteroidota*, orders *Rhizobiales*, *Bacteroidales* and *unclassified_Firmicutes*, families *Xanthobacteraceae, unclassified_Firmicutes*, *uncultured_Clostridiales_bacterium* and *Porphyromonadaceae*, genera *Bradyrhizobium*, *unclassified_Firmicutes* and *uncultured_Clostridiales_bacterium.* Hence, despite secukinumab successful treatment, the gut microbiota composition of psoriasis was still statistically different from that of healthy people. We

suggested that successful treatment of psoriasis with secukinumab actually constructed a new homeostasis of gut microbiome.

Further, we explored the gut microbiota related functional change after secukinumab therapy. By BugBase analysis, we discovered that secukinumab treatment group exhibited more significant abundance in contains mobile elements phenotype, form biofilms phenotype, gram positive phenotype, and less abundance in gram negative phenotype and potentially pathogenic phenotype. Biofilms are described as a complex structure of microbiome that can grow on many different surfaces, the formation of which can promote pathogenicity as well as the stability of bacterial communities leading to stronger stress tolerance[29]. Mobile genetic elements (MGEs) contribute to bacterial adaptation and evolution which make a better resistance to environment change[30]. And therefore, we speculated that secukinumab therapy constructed a more stable gut microbiome. Also, the potentially pathogenic phenotype of gut microbiota was reduced after secukinumab therapy in psoriasis.

Besides, functional analysis by COGs and KEGG pathways were shown in Fig. 5, **Fig S2** and Table 2. 3 KEGG pathways including metabolism of cofactors and vitamins, glycan biosynthesis and metabolism and circulatory system were significantly reduced in secukinumab therapy group the other two groups. What's more, KEGG pathway of cardiovascular diseases was also decreased in secukinumab therapy group than psoriasis without therapy. Researchers have found that psoriasis is related to increasing risk of developing metabolic syndrome, diabetes and cardiovascular diseases[31]. However, the incidence of related cardiovascular diseases has not been detected in psoriasis after secukinumab treatment. On the contrary, KEGG pathways of infectious diseases: parasitic and viral were significantly increased after secukinumab therapy in psoriasis. Actually, infection is the most reported side effect of secukinumab therapy, which is in accordance with our data in gut microbiota[32]. And it should be given more attention when using secukinumab treatment.

The limitations of the study are as follows: (1) 78 samples were involved in our study and more samples need testing for further evaluation. (2) 16S rRNA gene sequencing has limitations, further study should combine the analysis methods of metagenome and metabolism. (3) The dietary habits have not been screened, which may have an impact on the gut microbiota.

Conclusion

In summary, our research uncovers that secukinumab enhanced the diversity of gut microbiota and altered gut microbiome composition, which actually constructed a new homeostasis of gut microbiome. Besides, secukinumab treatment causes a more stable gut microbiome with less potentially pathogenicity, and functional alteration need more exploration. Also, more information on gut microbiota investigation during biologic drug therapy deserves to be added, which will become a vital mean of predicting the efficacy and risks of drug treatment and the course of disease.

Table 3
Taxonomic differences among three groups at the phylum (A), family (B) and genus (C) levels.

	AT	H	BT
(A)			
p: Firmicutes	7.00E-01 ± 3.27E-02	5.37E-01 ± 3.52E-02*	4.98E-01 ± 4.14E-02**
p: Bacteroidota	1.96E-01 ± 2.99E-02	3.67E-01 ± 3.49E-02*	4.16E-01 ± 4.33E-02**
(B)			
o: Rhizobiales	2.01E-04 ± 2.42E-05	4.96-05 ± 1.35E-05*	5.56E-05 ± 2.74E-05*
o: Bacteroidales	1.96E-01 ± 2.99E-02	3.67E-01 ± 3.49E-02*	4.16E-01 ± 4.33E-02*
o: unclassified_Firmicutes	0	3.60E-05 ± 3.60E-05*	
(C)			
f: Comamonadaceae	9.57E-04 ± 1.18E-04	4.28E-05 ± 3.67E-05*	7.32E-05 ± 3.56E-05*
f: Erwiniaceae	8.44E-04 ± 7.63E-05	3.17E-04 ± 7.39E-05*	3.01E-04 ± 7.84E-05*
f: Xanthobacteraceae	2.01E-04 ± 2.42E-05	4.96E-05 ± 1.35E-05*	5.56E-05 ± 2.74E-05*
f: unclassified_Firmicutes	0	3.60E-05 ± 3.60E-05*	
f: uncultured_Clostridiales_bacterium	0	3.04E-04 ± 3.04E-04*	
f: Porphyromonadaceae	0	2.24E-04 ± 2.23E-04*	
(D)			
g: Bradyrhizobium	2.01E-04 ± 2.42E-05	4.96E-05 ± 1.35E-05*	5.56E-05 ± 2.74E-05*
g: Hydrogenophaga	3.21E-04 ± 3.74E-05	1.47E-05 ± 1.38E-05*	3.57E-05 ± 1.81E-05*

Note: Values are expressed as means ± SD.

	AT	H	BT
g: Lactococcus	0		2.16E-04 ± 2.10E-04*
g: Pantoea	8.44E-04 ± 7.63E-05	3.17E-04 ± 7.39E-05*	3.01E-04 ± 7.84E-05*
g: unclassified_Comamonadaceae	6.36E-04 ± 1.08E-04	2.81E-05 ± 2.29E-05*	3.75E-05 ± 1.83E-05*
g: unclassified_Firmicutes	0	3.60E-05 ± 3.60E-05*	
g: uncultured_Clostridiales_bacterium	0	3.04E-04 ± 3.04E-04*	0#
g: Alloprevotella		4.14E-04 ± 4.04E-04	0#
g: Butyrivibrio		2.33E-03 ± 2.33E-03	0#
g: Prevotella_7		1.20E-06 ± 8.88E-07	9.62E-04 ± 8.75E-04#
Note: Values are expressed as means ± SD.			

P.adj indicates the *P* values corrected by multiple testing. $^{*}p.adj < 0.05$ versus AT, $^{**}p.adj < 0.01$ versus AT, $^{\#}p.adj < 0.05$ versus H.

AT psoriatic patients after receiving 5-month secukinumab treatment, *BT* psoriatic patients without therapy, *H* healthy people.

Declarations

Ethics approval and consent to participate

The protocol was approved by the Ethics Committee at Xi'an Jiaotong University, Xi'an, China (Permit Number: XJTU 2022-1035).

Consent for publication

Not applicable.

Availability of data and material

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

XSD, KG, SMG and CY provided conceptual framework; XSD and DLC provided the study design; SZK and BP assembled the data; CY performed analyses with contributions from SZK, BP, LFZ and DLC; XSD, SMG and CY provided data visualizations; XSD and KG wrote the manuscript. All authors read and approved the final manuscript.

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Figures

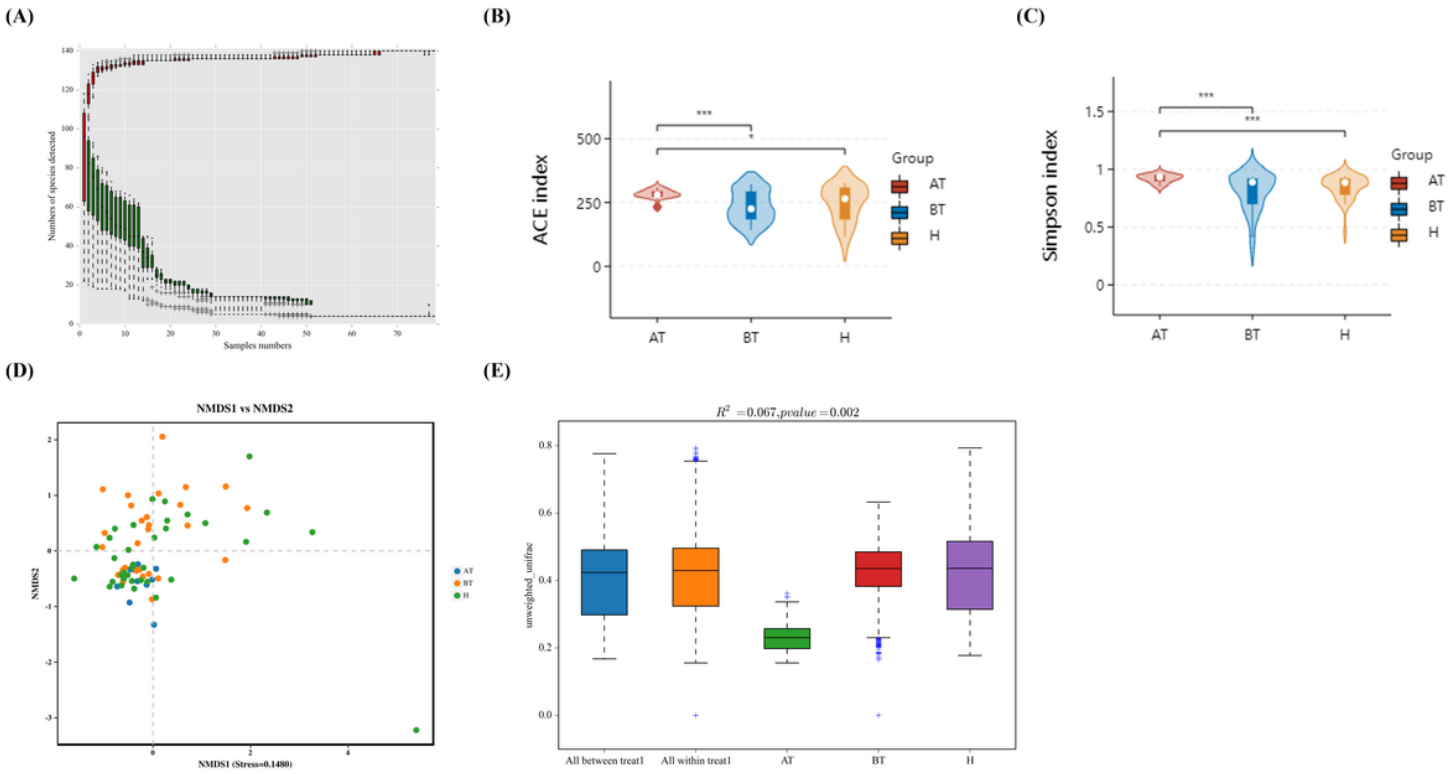

Figure 1

Secukinumab therapy altered gut microbial diversity. (**A**) Species accumulation curves of genus level had reached a plateau. (**B, C**) The richness of fecal microbiota and structural difference were analyzed by ACE indices (**B**) and Simpson indices (**C**) respectively. (**D**) The difference of gut microbial communities was investigated using NMDS based on binary_jaccard (Stress < 0.2). (**E**) Permanova anaylasis based on unweighted_unifrac was used to confirm the significant difference of beta diversity. *AT* psoriatic patients

after receiving 5-month secukinumab treatment, *BT* psoriatic patients without therapy, *H* healthy people. $^{*}p < 0.05$ versus AT, $^{**}p < 0.01$, $^{***}p < 0.001$.

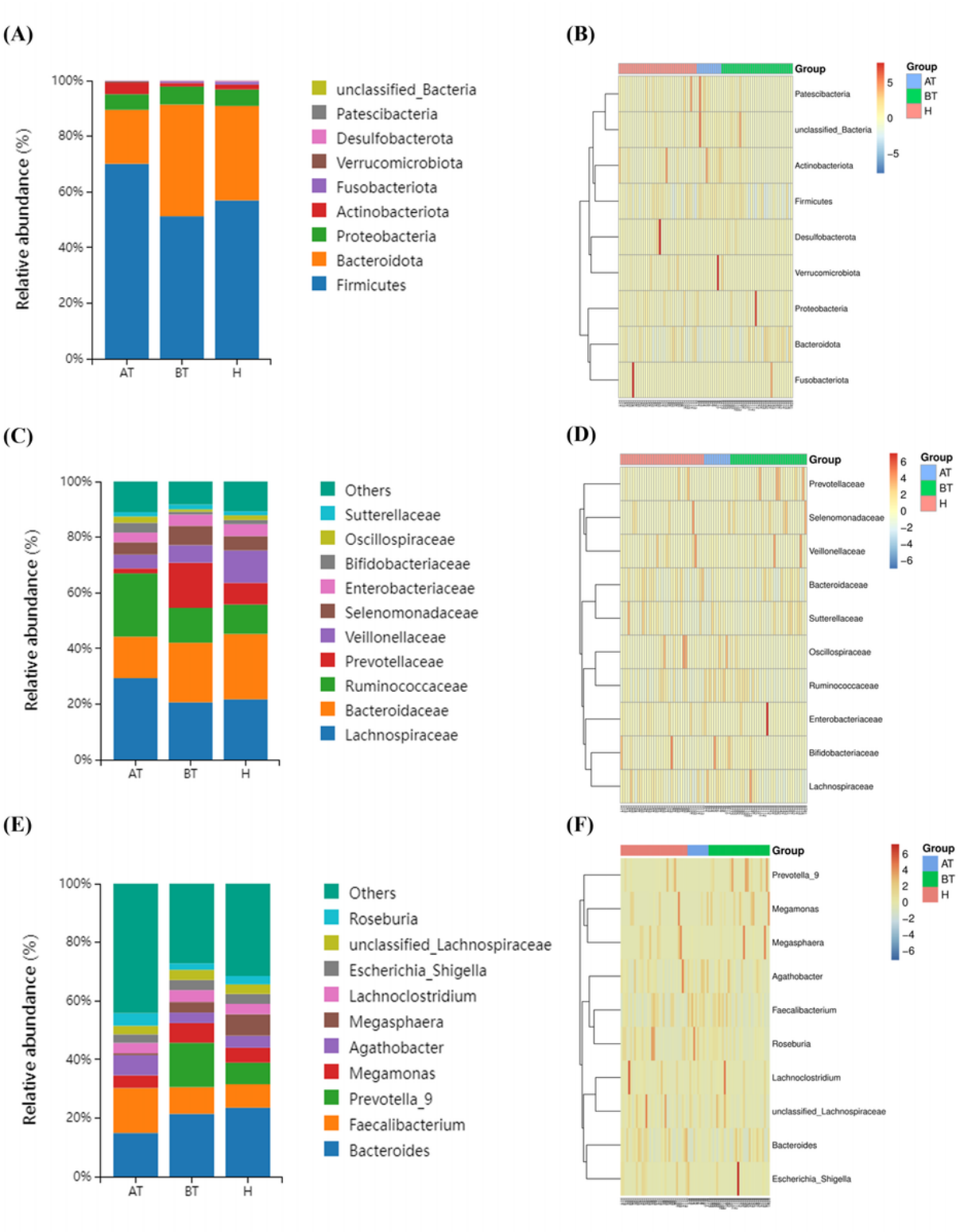

Figure 2

Secukinumab therapy altered microbial community structure at the phylum, family and genus levels. Relative abundance (%) of the intestinal microbiota determined at the phylum (**A, B**), family (**C, D**), and

genus (**E, F**) levels. The columns represent individuals in the AT, BT or H group (**B, D** and **F**). *AT* psoriatic patients after receiving 5-month secukinumab treatment, *BT* psoriatic patients without therapy, *H* healthy people.

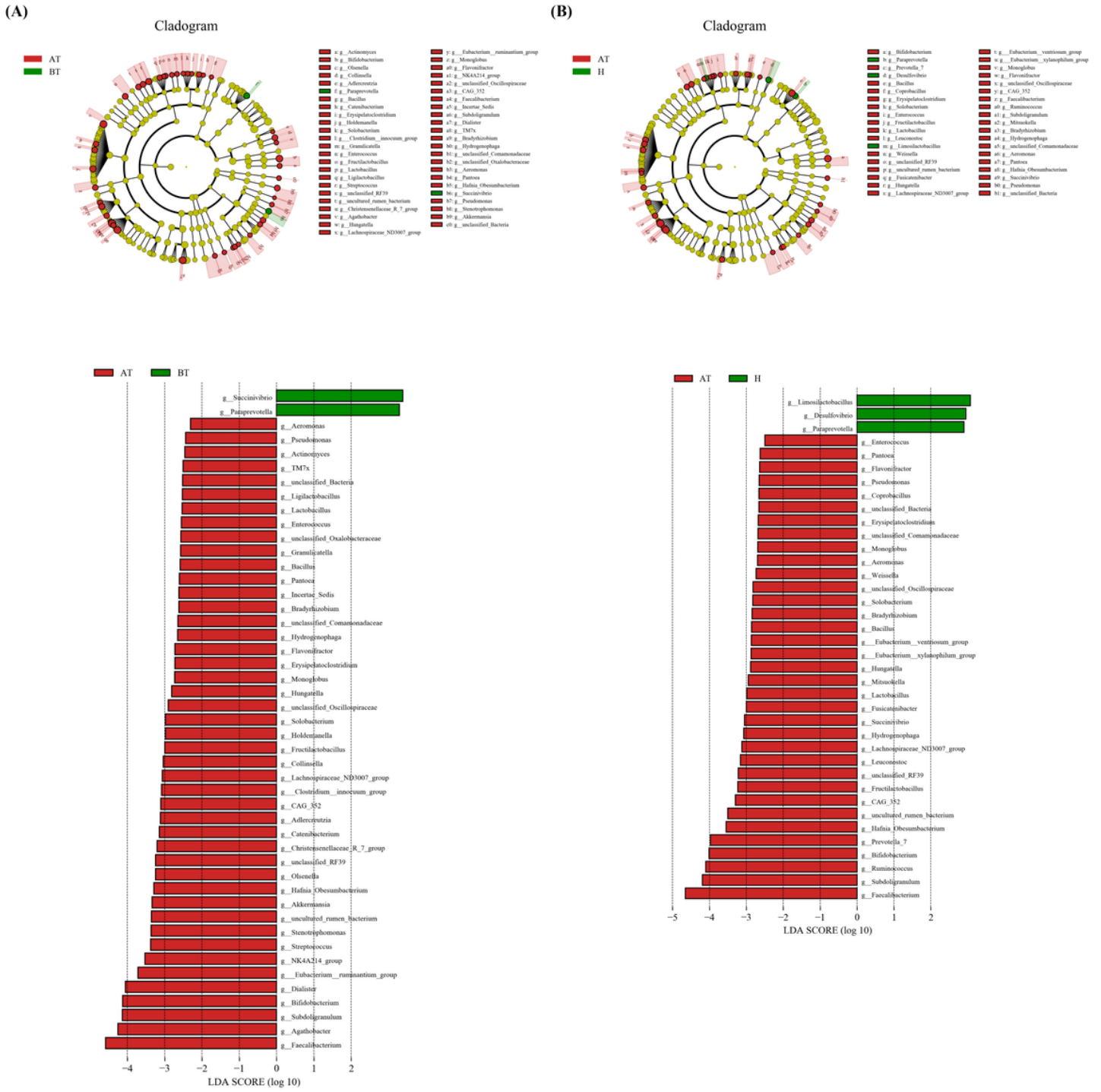

Figure 3

The significant difference of bacterial taxa induced by secukinumab therapy. (**A, B**) Taxonomic cladogram obtained from LEfSe analysis indicates the phylogenetic distribution of the gut microbiota of psoriatic patients after secukinumab therapy and without therapy (**A**), and healthy people (**B**) in genus

level. Histogram of LDA scores to demonstrates the effect size and rank of differentially abundant taxon. (LDA score > 2.0). *AT* psoriatic patients after receiving 5-month secukinumab treatment, *BT* psoriatic patients without therapy, *H* healthy people.

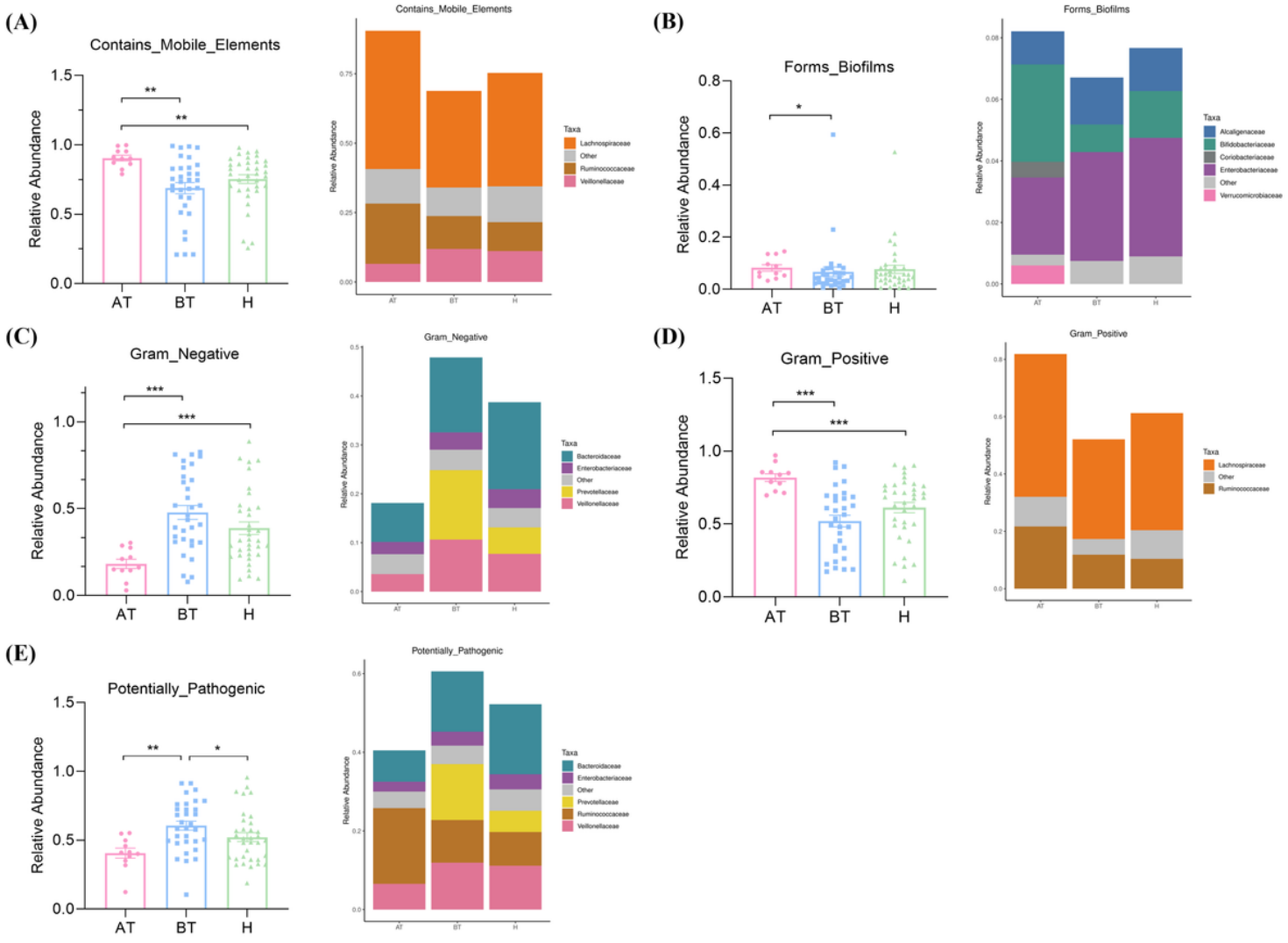

Figure 4

The potential prediction for phenotypic functions of gut microbiota after secukinumab therapy. 5 predicted phenotypic functions by BugBase, including contains mobile elements (**A**), forms biofilms (**B**), gram-negative (**C**), gram-positive (**D**) and potentially pathogenic (**E**), have been found significantly changed after 5-month secukinumab therapy. *AT* psoriatic patients after receiving 5-month secukinumab treatment, *BT* psoriatic patients without therapy, *H* healthy people. $^{*}p < 0.05$ versus AT, $^{**}p < 0.01$, $^{***}p < 0.001$.

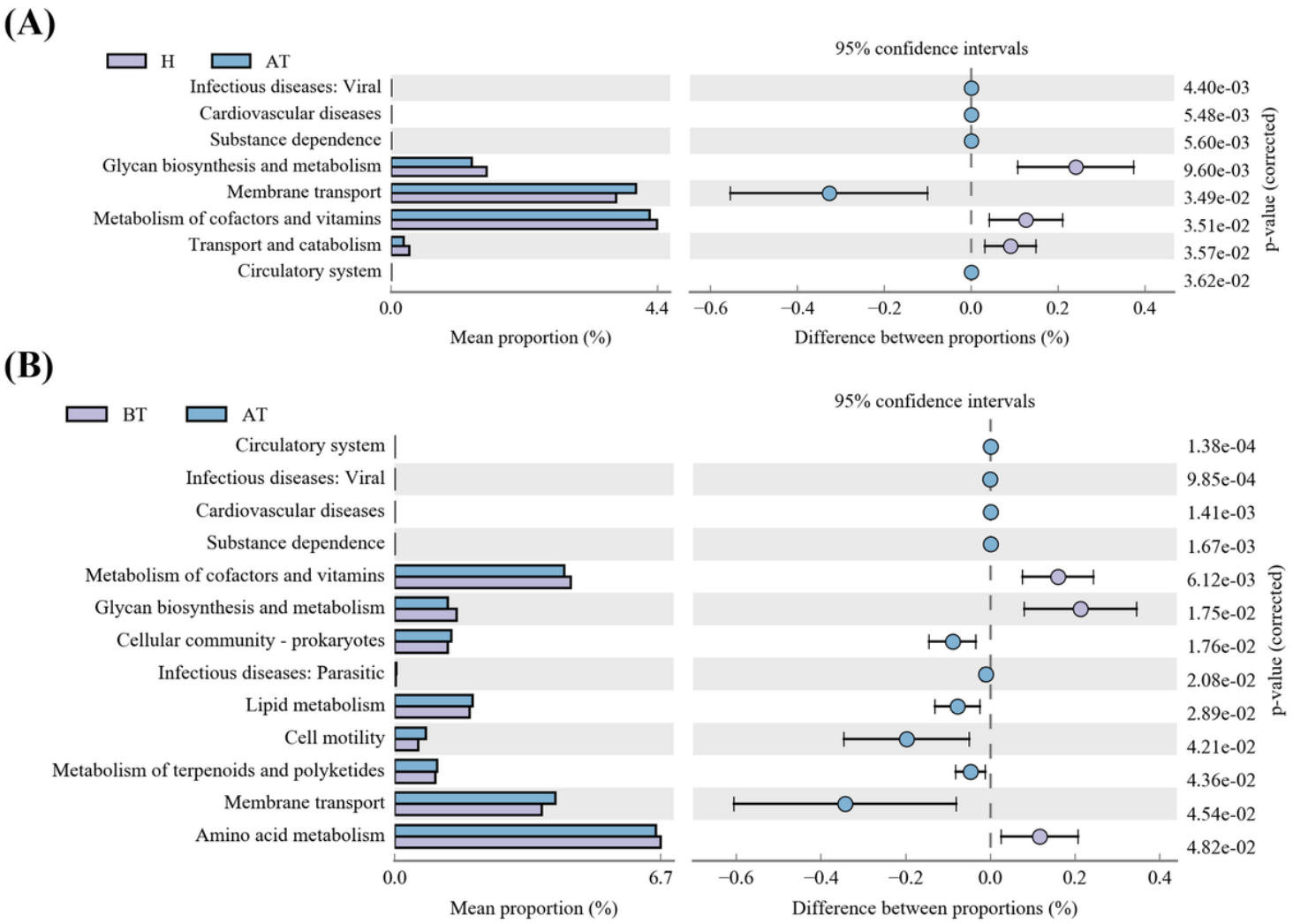

Figure 5

Functional capability analysis based on the mean abundances of KEGG pathways. (**A**) Comparison of KEGG pathways between secukinumab therapy group and healthy control group. (**B**) Functional differences of KEGG pathways between psoriasis with secukinumab therapy and psoriasis without therapy. *AT* psoriatic patients after receiving 5-month secukinumab treatment, *BT* psoriatic patients without therapy, *H* healthy people.

Supplementary Files

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

- Additionalfile1.pdf
- Additionalfile2.xlsx