Disordered intestinal microbes are associated with the activity of Systemic Lupus Erythematosus

Running title: Intestinal microbes in systemic lupus erythematosus

Yao Li[1,2#], Haifang Wang[1#], Xin Li[1#], Haixia Li[1], Qiong Zhang[1], Hongwei Zhou[3], Yan He[3], Pan Li[3], Chen Fu[1], Xiaohe Zhang[1], Yurong Qiu[1,4*], Ji-Liang Li[2,5,6*]

[1] Laboratory Medicine Center, Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong 510515, P.R. China

[2] Institute of Antibody Engineering, School of Laboratory Medicine and Biotechnology, Southern Medical University, Guangzhou 510515, China

[3] Division of Laboratory Medicine, Microbiome Medicine Center, Zhujiang Hospital, Southern Medical University, Guangzhou, Guangdong, 510282, P.R. China

[4] Huayin Medical Laboratory Center Co., Ltd., Guangzhou, Guangdong, 510515, P.R. China

[5] Wenzhou Medical University School of Biomedical Engineering and Eye Hospital, Wenzhou Institute of Biomaterials and Engineering, Wenzhou 325035, China

[6] Institute of Translational and Stratified Medicine, Plymouth University Faculty of Medicine and Dentistry, Plymouth PL6 8BU, UK.

[*]Corresponding author, Yurong Qiu, qyr@smu.edu.cn or Ji-Liang Li, Ji-liang.li@plymouth.ac.uk

[#] These authors contributed equally to this work.

Abstract

Intestinal dysbiosis is implicated in Systemic Lupus Erythematosus (SLE). However, the evidence of gut microbiome changes in SLE is limited, and the association of changed gut microbiome with the activity of SLE, as well as its functional relevance with SLE still remains unknown. Here, we sequenced 16S rRNA amplicon on fecal samples from 40 SLE patients (19 active patients, 21 remissive patients), 20 disease controls (Rheumatoid Arthritis patients), and 22 healthy controls, and investigated the association of functional categories with taxonomic composition by Phylogenetic Investigation of Communities by Reconstruction of Unobserved States (PICRUSt). We demonstrated SLE patients, particularly those active patients, had significant dysbiosis in gut microbiota with reduced bacterial diversity and biased community constitutions. Among the disordered microbiota, the genera *Streptococcus*, *Campylobacter*, *Veillonella*, the species *anginosus* and *dispar*, were positively correlated with lupus activity, while the genus *Bifidobacterium* was negatively associated with disease activity. PICRUSt analysis showed metabolic pathways were different between SLE and healthy controls, and also between active and remissive SLE patients. Moreover, we revealed that a random forest model could distinguish SLE from RA and healthy controls (AUC = 0.792), and another random forest model could well predict the activity of SLE patients (AUC = 0.811). In summary, SLE patients, especially the active patients, show an apparent dysbiosis in gut microbiota and its related metabolic pathways. Among the disordered microflora, 4 genera and 2 species are associated with lupus activity. Furthermore, the random forest models are able to diagnose SLE and predict disease activity.

Keywords: Systemic lupus erythematosus; gut microbiota; disease activity; PICRUSt; Random forest

Introduction

The gut microbe population, known as “gut microbiota” is heterogeneous and complex, and is composed of more than 1000 different bacterial species (1). Intestinal mucosal immunity have clarified the correlation between the gut microbiota and the host immune system (2). Microbial abnormalities, also known as “dysbiosis”, is thought to be correlated with various diseases, including chronic kidney disease, obesity, type 2 diabetes, atherosclerosis and nonalcoholic fatty liver disease (3-6). Systemic Lupus Erythematosus (SLE) is a heterogenic autoimmune disease promoted by a combination of genetic and environmental factors that bring about an intolerance towards self-antigens (7). Although the etiology of SLE remains unclear, hormonal, environmental and genetic factors are thought to be of importance. Recently, dysbiosis of the gut microbial community in the development of SLE has attracted attention.

Multiple evidences has shown a lower *Firmicutes*/*Bacteroidetes* ratio and decreased abundance of some families in *Firmicutes* phylum may be involved in remissive SLE (8-10) However, such alterations are also discovered in Intestinal Mucositis and Crohn’s disease (11). It was reported that the presence of *Lactobacillus spp.* in gut could attenuate kidney inflammation in lupus-prone mice in a sex hormone-dependent manner (12), suggesting the gut microbiome may be a possible therapeutic target for SLE. The association of the gut microbiome with different diseases has been shown to be diverse due

to many factors such as host's age, sex, genotype, diet and geography (13-16). Therefore, alterations of gut microbiome associated with SLE should be variable in SLE patients in Guangdong Province, China compared with other locations.

So far, there are limited studies on SLE and gut microbiota. Only a study observed the gut microbiota in active SLE patients, other studies have just focused on SLE patients in remission (8-10)(17). Whether the gut microbiota is associated with the disease activity still remains unclear. In this study, we recruited both active and remissive SLE patients to investigate the characteristic of intestinal microbes that are associated with disease activity. Since Rheumatoid Arthritis (RA) is another common autoimmune disease, we also included RA patients as the disease control to define the specificity of the SLE-associated gut microbiome. We found that the gut microbiota in SLE patients, especially in active SLE patients, had a distinct dysbiosis in microbiota and its related metabolic pathways. Six disordered genera and two species were revealed to be closely associated with SLE activity. Furthermore, the results suggested the gut microbiota were validated to have strong diagnostic potential for SLE, and even predict the disease activity through random forest analysis.

Materials and Methods

Research participants and sample collection

40 SLE patients, 20 RA patients and 22 healthy controls were consecutively recruited from Nanfang Hospital, Southern Medical University during 2017. All SLE and RA patients fulfill the American

College of Rheumatology (ACR) classification criteria for SLE or RA disease (18-20). All patients with acute intercurrent illnesses or infections and those who used probiotics or antibiotics within 1 month before admission were excluded(6). The gender- and age-matched healthy controls (HC) who had no known history of autoimmune diseases were also recruited from the Health Examination Centre of Nanfang Hospital. All the participants were female. Average age of SLE, RA and HC group was 37.46 ± 14.17, 44.00 ± 6.53, and 37.18 ± 14.67 respectively (P = 0.142).

Based on the systemic lupus erythematosus disease activity index (SLEDAI) (21), all the SLE patients were divided into the active SLE patients (A) (SLEDAI ≥ 8) (n = 19) and remissive SLE patients (R) (SLEDAI < 8) (n = 21). Exception of the age and gender distribution, patients in group A showed many significant differences from that of group R, having more severe symptoms, including anemia, hypocomplementemia, impaired renal functions and increased autoantibodies, all of which are consistent with the clinical characteristics of SLE (Table 1).

For all participants, the fresh fecal samples were frozen at -80 °C immediately after collection. Ethics approval was granted by the Ethics Committee of Nanfang Hospital, and all of the methods used were in accordance with the approved guidelines. Written informed consent was required from all patients and healthy volunteers in the study.

Illumina Miseq sequencing of 16S rRNA gene-based amplicons and data processing

Total DNA was extracted from thawed fecal samples using the LONGSEE STOOL DNA KIT (Longsee

med Bio Medicai., LTD., Guangdong, China) following the manufacturer's instructions. All the individually processed human fecal DNA extractions were amplified by polymerase chain reaction (PCR). The forward primer (5'-ACT CCT ACG GGA GGC AGC AG-3') and reverse primer (5'-GGA CTA CHV GGG TWT CTA AT-3') were used to amplify the 16S rRNA gene V3-V4 variable region from the bacteria by polymerase chain reaction (PCR) as described previously (22). Briefly, amplifications were performed using a step cycling protocol consisting of 98 °C for 30 s, 35 cycles of 98 °C for 10 s, 54 °C for 30 s, and 72 °C for 45 s, ended with the final elongation at 72 °C for 10 min. PCR products were purified using an AxyPrep PCR Cleanup Kit (Axygen, California, USA).

For the sequencing of 16S rRNA gene-based amplicons, the amplicon library was prepared using a TruSeq Nano DNA LT Library Prep Kit (Illumina Inc, CA, USA). The sequencing reaction was conducted using Illumina MiSeq platforms and the data were analyzed by the Quantitative Insights Into Microbial Ecology platform (QIIME, www.qiime.org) using the default parameters (23). The raw sequence data for 16S rRNA gene sequencing data sets was available from the Sequence ReadArchive (SRA) database (http://www.ncbi.nlm.nih.gov/sra) at accession number PRJNA493726.

Before assembly, sequence reads were first filtered to remove low-quality or ambiguous reads, including reads lacking exact matching with the primer, sequences with mismatch ratio sequences higher than 0.05 in the overlap region and raw reads shorter than 100 bp with Trimmomatic v.0.32 software (24). Paired-end clean reads were merged using FLASH (25) according to the relationship of the overlap between the paired-end reads when at least 10 of the reads overlapped the read generated from the

opposite end of the same DNA fragment, the maximum allowable error ratio of an overlap region of 0.2, and the spliced sequences were called raw tags.

High-quality Sequences with a distance-based similarity of 97% or greater were grouped into operational taxonomic units (OTUs) using the Vsearch algorithm. Representative sequence was then extracted from each OTU. Next, the chimeric sequences were detected and removed. To assign taxonomy information to each clustered feature, extracted representative sequences were subjected to similarity search against Greengenes sequence and taxonomy database using RDP classifier algorithm (ucluster approach with default settings) and the classify-sklearn plugin within Qiime software (version 1.9.1). The phylogenetic relationships were determined based on a representative sequence alignment using Fast-Tree (26). Computation of α-diversity metrics and β-diversity metrics were performed on all samples within the feature table with Qiime diversity alpha/beta plugin. Rarefaction curve plots the number of individual's sample versus the number of species, which was done with Qiime diversity alpha-rarefaction plugin. Rank abundance curve portray relative abundance and species diversity within a community by plotting relative abundance of species (y-axis) against their rank in abundance (x-axis), which plotted using QIIME v.1.9.1 software.

Phylogenetic Investigation of Communities by Reconstruction of Unobserved States (PICRUSt) is a bioinformatics software package designed to predict metagenome functional content from marker gene surveys and full genomes. PICRUSt analysis was performed to identify Kyoto Encyclopedia of Genes and Genomes (KEGG) metabolic pathways, and determine functional categories associated with

taxonomic composition (27).

Comparisons of relative abundance of taxa between groups were performed using Linear discriminant analysis Effect Size (LEfSe), a non-parametric Mann-Whitney U test applied to detect features with significant differential abundance with respect to the groups compared, followed by a Linear Discriminant Analysis (LDA) to estimate the effect size of each differentially abundant feature in Linux platform (28).

Statistical analyses

We used the mean (±SD) to express measurement data that obeyed a normal distribution, the median (interquartile range) to express measurement data that obeyed a skewed distribution, and a percentage to express enumeration data. Mann-Whitney U test or Student t test was performed to compare the variables of 2 sample groups. Multiple group comparisons were made by the Kruskal-Wallis test or one-way analysis of variance. False discovery rate (FDR) correction for multiple comparisons was employed, and the statistical power was analyzed via power and sample size calculation in R software (29, 30), then the False Discovery Rate q-value was calculated.

The α-diversity determines the species richness and evenness within bacterial populations. The α-diversity metrics include: Observed species and Chao1 (microbial richness), and Shannon index and Simpson index (microbial diversity) (31). The β-diversity determines the shared diversity between bacterial populations. Different distance metrics reveal distinctive views of community structure.

UniFrac distances measure the shared phylogenetic diversity between communities. A smaller UniFrac distance between two samples indicates a higher similarity among the two microbial communities (32). Principal coordinates analysis (PCoA) was plotted using the package in R software (Version 3.4.4). The Wilcoxon rank sum test was used to determine significance in α-diversity and β-diversity.

We used spearman algorithm to analyze the relationship among microbiota, predicted pathways and SLE activity index. The Random Forest models were trained by "randomForest" package with default parameters in R, then the performance of the model was assessed with a ten-fold cross-validation approach and measured by area under the receiver-operating characteristic (ROC) (33). All tests were performed using GraphPad Prism (v6.0) (GraphPad Software, Inc., CA, USA), SPSS Statistics (V.24.0.0.0) (SPSS Inc., Chicago, USA) or R software (Version 3.4.4).

Results

Characteristics of 16S rRNA sequences.

A total of 82 samples were subjected to 16S rRNA sequencing. These samples were composed of three groups including 22 healthy individuals, 20 RA patients and 40 SLE patients. We obtained 2182143 16S rRNA sequencing reads from stool samples of SLE patients, 976140 reads from RA patients and 1277858 reads from HC, which belong to 714 kinds of operational taxonomic unit (OTUs). The parameters, including Chao1 rarefaction curves, Shannon rarefaction curve, and rank abundance of OTUs, were evaluated to confirm the reliability of the sequencing data (Supplementary Figure S1).

Difference of the gut microbiota in SLE patients from those of controls

The α-diversity between two groups was compared using Chao1, Observed species, Shannon index and Simpson diversity indices. Overall, the α-diversity metrics Chao1 and Observed species were significantly higher in healthy controls than in SLE patients (P = 0.038; P = 0.004, respectively), indicating that the gut microbiome in SLE patients exhibited a lower richness than healthy controls (Figure 1A and B and Supplementary Table S1). However, no difference in Shannon and Simpson index (P = 0.089; P = 0.092, respectively) was observed between SLE patients and healthy individuals, suggesting that the evenness of the gut microbiome of the two groups had no significant difference (Supplementary Table S1). There were no associations between α-diversity and drug treatments, such as Hydroxychloroquine, Glucocorticoid, Cyclophosphamide, and Biological agent (Supplementary Figure S2).

To measure the extent of the similarity of fecal microbial communities, β-diversity was calculated using unifrac distances. Principal coordinate analysis (PCoA) based on weighted and unweighted UniFrac distance matrix were used for visualizing sample relationships, and ADONIS analysis was used to test the homogeneity of dispersion among different groups. Our results suggested that there were no associations between β-diversity and medicine treatments, including Hydroxychloroquine, Glucocorticoid, Cyclophosphamide, and Biological agent (Supplementary Table S2 and Figure S3), however, the unweighted UniFrac distance analysis of β-diversity difference demonstrated that the

structure of microbiota of SLE patients differed from healthy controls (ADONIS analysis, $P < 0.001$, $R^2 = 0.054$) (Figure 1C and Supplementary Table S3). Thus, the microbial diversity was significantly different between SLE group and healthy controls.

We then analyzed the phylum-level profiles of feces between SLE patients and healthy controls. The phylum level profiles for gut microbiota of SLE patients and controls were fairly similar, except for reads from the phyla *Fusobacteria* ($P = 0.027$) and *Tenericutes* ($P = 0.002$) (Figure 1D-F). A lower *Firmicutes* / *Bacteroidetes* (F/B) ratio was reported in the feces of remissive SLE patients compared to healthy controls (34). However, we showed the ratio of F/B the feces of SLE had a decreasing trend but no significant difference compared with HC group (Supplementary Table S4).

To further determine the phylogenetic clustering pattern between these two groups, the logarithm linear discriminant analysis (LDA) was performed (Figure 2). The phylum *Tenericutes*, along with *Mollicutes* and *RF39*, were significantly reduced in the intestinal flora of SLE patients compared with healthy controls. In addition, patients with SLE exhibited a significant decrease in the genus *Faecalibacterium* alongside its species *prausnitzii*, while the taxonomic clade *Cryptophyta* and genus *Roseburia* were reduced in the gut microbiota of SLE group. On the contrary, the taxonomic clade *Bacilli* from the phylum *Firmicutes* showed clustered differences, while *Streptococcaceae* and *Lactobacillaceae* were expanded in the feces of SLE patients compared with healthy controls. Moreover, the genera *Streptococcus* and *Lactobacillus*, along with their species *Streptococcus. anginosus* and *Lactobacillus. mucosae* were enriched in the intestinal flora of SLE group compared with HC group. In

addition, the feces of SLE patients showed an increase in genus *Megasphaera* (significant taxa [$p<0.005$, Kruskal–Wallis test] with LDA score >2 were shown). Taken together, sequence profiling of the gut microbiota revealed an apparent dysbiosis of the gut microbiota in SLE patients, which was characterized by reduced bacterial α-diversity and biased community constitutions. These results demonstrated the gut microbiota of patients with SLE differed from those of healthy controls.

To investigate whether the disordered intestinal microbes were specific to SLE patients, we further compared the intestinal microflora distribution between SLE and RA patients. There were no significant difference in α-diversity (Supplementary Table S1) and β-diversity (Supplementary Table S3 and Figure S4C-D) between two groups. LEfSe analysis showed the different microbiota between SLE group and RA group (Supplementary Figure S4). The taxonomic clade *EB1017*, *Ellin6529*, and *Anaerofilum* were increased in the intestinal flora of RA patients, while the *Lactobacillales* from the *Bacilli*, with its genus *Streptococcus* were enriched in the feces of SLE patients compared with RA patients. In addition, the phylum *Fusobacteria*, along with its taxonomic clade *Fusobacteriia*, *Fusobacteriales*, *Fusobacteriaceae*, and *Fusobacterium* were increased in the feces of SLE patients. The genus *Megasphaera* and *Veillonella*, with its species *Veillonella. dispar,* were also enriched in the feces of SLE group compared with RA group (significant taxa [$p<0.05$, Kruskal–Wallis test] with LDA score >2.5 were shown).

Collectively, these results demonstrated that the gut microbiota of SLE patients differed from healthy individuals, however, there was no significant difference in gut microflora diversities between SLE and RA patients. The genera *Streptococcus* and *Megasphaera* were specifically increased in the

feces of SLE patients compared with healthy controls and RA patients.

Difference of microbiota profiling in active SLE patients from remissive SLE patients.

Given that the gut microbiota was significantly different between SLE patients and healthy controls, we next investigated whether the gut microbiota was associated with disease activity of SLE. Firstly, we compared 16S rRNA sequences of A group (active SLE patients) with R group (remissive SLE patients). The unweighted UniFrac distance analysis of β-diversity difference demonstrated that the structure of the microbiota of A group differed from R group (ADONIS analysis, P =0.047, R^2 = 0.039) (Figure 3A and Supplementary Table S3), while no obvious difference was observed in α-diversity (Supplementary Table S1), suggesting that the community constitutions in A group were distinctly different from R group, but no difference was found in microbial diversity.

As shown in Figure 3, LEfSe analysis further demonstrated that *Actinomycetales* and *Bifidobacteriales* from phylum *Actinobacteria* showed clustered differences, and the genus *Bifidobacterium* was increased in the feces of remissive SLE patients compared with active SLE patients. In addition, the species *Ruminococcus. gnavus* was reduced in the feces of active SLE patients, whereas *Lactobacillales* from the *Bacilli*, along with its genus *Streptococcus* and species *Streptococcus. anginosus*, were enriched in the feces of A group compared with R group. Moreover, the genus *Oribacterium* was increased in the intestinal flora of active SLE patients. Furthermore, active SLE patients exhibited a remarkable enrichment of the taxa *Epsilonproteobacteria* from phylum

Proteobacteria, along with its *Campylobacterales* and *Campylobacter* (significant taxa [$p<0.005$, Kruskal–Wallis test] with LDA score >2 were shown). Finally, the ratio of F/B in remissive SLE patient group had a decreasing trend but no significant difference compared with HC group (Supplementary Table S4). Altogether, these results indicated that the gut microbiota profiling of active SLE patients were markedly different from that of remissive SLE patients.

Aberrant microbiome-associated pathway is correlated with the activity of SLE patients.

Another emphasis of our study was to disclose the functional variation in the SLE gut microbiota community. Therefore, we predicted the microbiota-derived pathways using the PICRUSt algorithm with the KEGG database and compared functional abundances among the SLE, RA, and HC groups. In total, we characterized six different pathway categories between SLE group and HC group (Figure 4). The pathways of Apoptosis and Purine metabolism were significantly increased in SLE patient group compared with HC group (Figure 4A), while four pathways, including Pathways in cancer, Bacterial chemotaxis, Bacterial motility proteins, and Flagellar assembly, were decreased in SLE patients (Figure 4B). In addition, nine different functional pathways were identified between A group and R group (Figure 5). Five were related to Synthesis and degradation of ketone bodies, Apoptosis, Lipid metabolism, Secretion system, and Staphylococcus aureus infection, which were significantly higher in active SLE patients than remissive patients (Figure 5A). Conversely, Alanine aspartate and glutamate

metabolism, Carbohydrate metabolism, Primary bile acid biosynthesis, and Secondary bile acid biosynthesis, were obviously increased in remissive SLE patients compared with active patients (Figure 5B). However, there was no different pathway between SLE and RA group (date not shown).

We further examined correlations among SLE/HC-associated taxa and disordered functional pathway to obtain an overview of how specific taxa act during metabolic dysfunction in patient gut. For SLE patients, we characterized a positive correlation between the enrichment of *Streptococcus* and increased Apoptosis pathway ($r = 0.807$, $P < 0.000$, $FDR < 0.000$) and a negative correlation between *Streptococcus* and Pathways in cancer ($r = -0.550$, $P < 0.000$, $FDR < 0.000$) (Figure 6A). Further analysis also revealed the active SLE patient-enriched genus *Streptococcus* was negatively associated with pathways of Alanine aspartate and glutamate metabolism, Primary and secondary bile acid biosynthesis ($r = -0.680$; $r = -0.437$; $r = -0.434$, $P < 0.01$, $FDR < 0.05$, respectively) (Figure 6B), but positively associated with five increased pathways, including Synthesis and degradation of ketone bodies, Apoptosis, Lipid metabolism, Secretion system, and Staphylococcus aureus infection ($r = 0.574$; $r = 0.829$; $r = 0.406$; $r = 0.486$; $r = 0.903$, $P < 0.01$, $FDR < 0.05$, respectively) (Figure 6C).

Thus, several aberrant microbiome-associated gut metabolic pathways were associated with SLE using PICRUSt analysis. Interestingly, the SLE-enriched genus *Streptococcus* was positively associated with the pathways of Apoptosis, the metabolism of lipid, amino acid and bile acid, Secretion system, and pathogenic bacteria infection.

Association of disordered microbiota and aberrant microbiome-associated pathway with activity of SLE.

SLEDAI, Complement C3, C reactive protein (CRP), Erythrocyte Sedimentation Rate (ESR) and anti-double stranded DNA (anti-dsDNA) were commonly used to indicate the disease activity of SLE patients (21, 35, 36).

At genus and species levels, *Lactobacillus*, *Streptococcus*, *Megasphaera*, *Fusobacterium*, *Veillonella*, *Lactobacillus. mucosa*, *Streptococcus. anginosus*, and *Veillonella. dispar* were increased in the feces of SLE patients compared with healthy controls or RA patients. Meanwhile, *Streptococcus, Oribacterium*, *Campylobacter*, and *Streptococcus. anginosus* were enriched, but *Bifidobacterium* and *Ruminococcus. gnavus* were reduced in the gut microbiota of active SLE patients compared with that of remissive SLE patients. Except *Bifidobacterium*, five changed genera were positively associated with disease activity (Figure 7A-F and Supplementary Table S5). For example, the abundance of *Streptococcus* was positively correlated to SLEDAI ($r = 0.492$, FDR $q = 0.008$), while negatively associated with Complement C3 ($r = -0.502$, FDR $q = 0.008$) (Figure 7A). *Campylobacter* and *Streptococcus. anginosus* also showed a positive correlation with SLEDAI ($r = 0.470$, FDR $q = 0.009$; $r = 0.388$, FDR $q = 0.040$, respectively) (Figure 7). Moreover, the abundance of *Veillonella* and its species *Veillonella. dispar* showed negative correlations with Complement C3 ($r = -0.475$, FDR $q = 0.008$) (Figure 7).

The genus *Streptococcus*, which was specifically associated with the activity of SLE, was related to

eight aberrant microbiome-associated pathways (Figure 6). We further explored whether these eight disordered pathways were also related to the activity of SLE (Supplementary Table S5). Alanine aspartate and glutamate metabolism, Secondary bile acid biosynthesis, and Lipid metabolism were closely associated with SLEDAI ($r = -0.376$; $r = -0.382$; $r = 0.318$, FDR $q < 0.001$, respectively) (Figure 7G-I). As such we hypothesized that the genus *Streptococcus* might play an important role in the disease progression of SLE through these three pathways.

Potentials of gut microbiota for SLE diagnosis or disease activity monitoring

Given that the gut microbiota in SLE patients, especially in active SLE patients, had a distinct dysbiosis in microbiota, we next addressed the potential diagnostic value of the gut microbiota as potential biomarkers for SLE by ROC curve analyses. Due to its non-parametric assumptions, random forest was used to detect linear and nonlinear effects and potential taxon–taxon interactions, to identify taxa that could differentiate SLE subjects from control subjects (healthy controls and RA patients), and to discriminate active SLE patients from remissive patients. We used 10-fold cross-validation approach to evaluate the performance of model, and predictive power was scored in ROC analysis. We first made the mode to differentiate the SLE patients from healthy controls and RA patients based on the genus and species levels. We showed that the area under the curve (AUC) was 0.792 (95% CI: 0.750−0.835) (Supplementary Table S6 and Figure 8A), suggesting that the gut microbiota had the potential to diagnose SLE from healthy and disease controls (RA patients). We observed that in the model, out of the

top 10 genera and species, 8 belonged to the phylum *Firmicutes*, 1 belonged to *Fusobacteria*, and 1 belonged to *Actinobacteria*. Of the 8 genera in the *Firmicutes* phylum, 5 were part of *Clostridia* class, and 3 were *Bacilli* (Supplementary Table S6). Furthermore, among the 10 genera and species, the *mucosa*, *Lactobacillus*, *Megasphaera*, and *Streptococcus* were significantly enriched, while *Faecalibacterium* was decreased in the feces of SLE patients compared with healthy controls. In addition, both *Veillonella* and *Fusobacterium* were increased in the gut microbiota of SLE patients than RA patients (Figure 2; Supplementary Figure S4 and Table S5). Accordingly, most of the genera and species in the model were the disordered genera in the feces of SLE group compared with healthy controls and RA patients.

We further built another model to distinguish active SLE patients from remissive patients based on the genus and species levels. In this model, the AUC was 0.811 (95% CI: 0.754-0.869) (Supplementary Table S7 and Figure 8B), suggesting that the gut microbiota had the potential to monitor the activity of SLE. Anti-dsDNA was reported to be reasonably sensitive and specific in the diagnosis of SLE, and raised titers of anti-dsDNA along with hypocomplementemia were associated with the activity of SLE(37). We showed that the AUC value for combination of Complement C3 and anti-dsDNA was only 0.773 (95% CI: 0.597–0.949) (Supplementary Figure S6). These results indicated that the combination of the gut microbiota might have a better surveillance value for SLE activity than the combination of Complement C3 and anti-dsDNA. Morever, as shown in the model, out of the top 10 genera and species, 5 belonged to the phylum *Firmicutes*, 4 belonged to *Actinobacteria*, and 1 belonged to *Proteobacteria*.

Among the 5 genera in the *Firmicutes* phylum, 3 were from the *Clostridia* class, 1 was *Erysipelotrichi* and 1 was *Bacilli* (Supplementary Table S7). In this case, the *Campylobacter*, *Streptococcus*, and *Oribacterium* were enriched, while the *gnavus* and *Bifidobacterium* were reduced in active SLE patients compared with remissive SLE patients (Figure 3 and Supplementary Table S7). Altogether, a great part of the genera and species in the model were disordered genera in the feces of active SLE patients, suggesting that the disordered intestinal flora might have potential to diagnose SLE, even monitor disease activity.

Discussion

SLE is an autoimmune disease that affects multiple tissues, and causes joint pain, renal disease, muscle pain, fever, poor circulation, inflammation, fatigue, loss of appetite and other symptoms (38). Though the cause of SLE still remains unclear, it is thought to be involved with hormonal, genetic and environmental factors (39). The gut microbiome was believed to be a key factor in influencing predisposition to autoimmunity diseases (40). Recent studies further supported that gut microbiome dysbiosis could act as an important factor in promoting chronic inflammation into autoimmune diseases (2, 41, 42). However, there were only limited works in exploring the potential relationship of gut microbiome with SLE (8-10, 17, 39). In this study, we have provided new evidence about the gut microbiome dysbiosis in female SLE patients by fecal bacteria sequencing. Importantly, we for the first time explored whether the gut disordered microbes were associated with the activity of SLE.

We investigated the profiling of the gut microbiota and showed a distinct dysbiosis of the gut microbiota in SLE patients, which was characterized by reduced bacterial α-diversity and biased community constitutions. Most of the patients in our study were currently on various immunosuppressants and glucocorticoids treatments. Veena Taneja et al. have demonstrated that RA patients using methotrexate (MTX) and hydroxychloroquine exhibited an increase in species richness and diversity (43). However, our results showed no significant relationship between drug treatments and the abundance diversity of gut microbiota in the SLE patients, which might because the most of enrolled patients were treated with steroids or immunosuppressants, while only 4 patients did not use any drugs.

Phyla *Firmicutes* together with *Bacteroidetes* usually account for more than 90% of all phylogenetic species, were involved in host metabolism and immunity (44). In our study, the Phyla *Firmicutes* and *Bacteroidetes* occupied the most abundant microorganism, consistent with the typical human intestinal microbiome structures. It was reported that the *Firmicutes* / *Bacteroidetes* ratio was significantly lower in the feces of SLE patients in remission (8). However, no significant different for our cohort of remissive SLE patients and healthy controls ($P > 0.05$). Also, there was no significant difference in the *Firmicutes* / *Bacteroidetes* ratio between active SLE and healthy controls ($P > 0.05$), consistent with the available data (17). The changes of the genera in SLE patients of our study were only partly consistent with previous studies (8, 10, 17, 45), which might partially due to the sample size and geographical locations of patients. It is well known that cohorts with different patient characteristics, including disease stage, geographical locations, diet and status, might exhibit different gut microbiota

profiling (15, 16, 46-48). Therefore, the alterations of gut microbiome associated with SLE should display differences among different geographical locations and disease status.

In this study, we found that the abundance of pathogenic genus *Streptococcus*, with its species *anginosus*, and genus *Megasphaera* were significantly enriched in the feces of SLE patients compared with healthy controls; genus *Streptococcus* and its species *anginosus* were positively correlated to the activity of SLE. In addition, the genus *Veillonella* and its species *dispar* were significantly increased in the gut microbiota of SLE patients compared with RA patients and had a positive association with the activity of SLE. The association of these disordered genera with the activity of SLE was most striking, and to our knowledge, this is the first study to describe such a significant relationship with SLE. The genera *Streptococcus* and *Megasphaera* were reported to be closely related to the intestinal disturbance of autoimmune disorders. For example, *Streptococcus* and *Megasphaera* were enriched in primary biliary cirrhosis (49) and Pediatric Autoimmune Neuropsychiatric Disorders (50). Also, *Streptococcus* was relatively increased in RA patients (43). It was demonstrated that *S. anginosus* rarely caused infections in healthy individuals, but caused infections in the immunodeficient individuals(51). As reported, genera *Streptococcus* and *Veillonella* had pro-inflammatory effects. For example, the combination of S*treptococci* with *Veillonella* appeared to negate IL-12p70 production, while augment IL-8, IL-6, IL-10, and tumor necrosis factor alpha (TNF-α) response (52).

The SLE patients, especially the active patients, had an increased population of oral bacteria, which is an interesting phenomenon that occurred in the intestinal flora of SLE. However, the gut

microbiome of liver cirrhosis, colorectal cancer, RA, and ACVD patients also showed an increase in the abundance of oral bacteria in gut microbiota (53), and only RA and ACVD have been epidemiologically associated with periodontitis. Interestingly, our results suggested that the abundance of genus *Streptococcus* were enriched in active SLE patients, suggesting that the oral microbiota might be overrepresented in the lower gastrointestinal populations of patients with active SLE. Besides, more severe forms of periodontitis were found in SLE subjects that had higher bacterial loads (54), resulting in an increase in oral bacteria entering the intestine.

Furthermore, our data showed that many beneficial commensal microbes, such as *Roseburia*, *Faecalibacterium* and its species *prausnitzii* were depleted in SLE patients. Meanwhile, the genus *Bifidobacterium* was adversely correlated with activity of SLE. These microbes belongs to the phylofunctional core of the intestinal microbiota (55, 56) , which can produce short chain fatty acids (SCFAs), especially butyrate-acid, to play multiple critical roles in the maintenance of human health, including producing energy components and intestinal epithelial nutrition (57), reducing the severity of inflammation (58), maintaining intestinal barrier functions (59) and enhancing colon motility functions (60).

Moreover, we observed an increased abundance of beneficial commensal genus *Lactobacillus* and its species *Lactobacillus mucosae* in the feces of SLE cohort compared to healthy controls. Supportive of a role for *Lactobacilli* in the pathogenesis of lupus, taxa in this genus were found to be enriched in female NZB/W F1 mice, the model of systemic lupus. In this study, *Lactobacillus spp*. were

associated with more severe disease, whereas they were reduced as disease is controlled with dexamethasone (17). As reported (61) *Lactobacillus. reuteri* increased over time in the feces of mice from both lupus models as their disease progress, in addition, *Lactobacillus spp.* were increased in a longitudinal cohort of SLE patients compared with healthy controls. In this study, the pDC/IFN-promoting properties of *L. reuteri* in the context of a lupus-prone host suggest a paradigm in which a bacterium that is normally considered a probiotic may become harmful under certain genetic or environmental conditions. We also observed that *Lactobacillus* were enriched in feces of SLE patients, suggesting a potential role for these taxa in SLE pathogenesis, which need further research in the future.

Our study has demonstrated that some pro-inflammatory bacteria in genera *Streptococcus*, and *Campylobacter* expanded, while some anti-inflammatory bacteria in genera *Roseburia*, *Faecalibacterium*, and *Bifidobacterium* reduced in the feces of SLE patients, especially the active patients, resulting in the release of inflammatory factors, then aggravating the systemic inflammation level. Some pro-inflammatory pathogens increased accompanied with the intestinal mucosal barrier compromised, which lead to more bacterial LPS transferring into lymph nodes and blood to stimulate the TOLL-like pathway of the host cells, and produce inflammatory cytokine (62). SLE patients generally used massive immunosuppressive agents and glucocorticoids during the active period, which could inhibit the immune system and might cause a large increase in opportunistic pathogens (63, 64). Notwithstanding, it is questionable whether such changes in gut bacterial profile are a cause or

consequence of SLE. However, to posit further on this, is beyond the scope of this study, and we will focus on this in the future research.

In addition, several aberrant microbiome–associated gut metabolic pathways were revealed to be associated with SLE using PICRUSt analysis. We found that SLE patients were enriched in multiple metabolic pathways containing gene functions of Apoptosis, Purine metabolism, and the Apoptosis were positively associated with the genus *Streptococcus* that was highly enriched in SLE patients and especially in active patients. As reported, Apoptosis pathway played an important role in the pathogenesis of SLE (65). Besides, among these altered pathways, the alanine, aspartate and glutamate metabolism, Secondary bile acid biosynthesis, and Lipid metabolism were not only related to the disease activity, but also significantly associated with *Streptococcus*. The alanine, aspartate and glutamate metabolism, which was identified to be increased in remissive SLE patients in our study, had been previously reported to play a pivotal role in resting or activated T cells (66). Lipid metabolism participates in the regulation of many cellular processes such as cell growth, proliferation, differentiation, survival, apoptosis, inflammation, motility, etc (67). In active SLE patients, the dyslipidemia was more prevalent, suggesting that inflammation may be related to lipid metabolism (68). Thus, *Streptococcus* might play an important role in the pathogenesis of SLE through these pathways.

Due to the heterogeneous presentation of SLE patients and their unpredictable disease course, there is a great need for accurate assessment of disease activity. Several immunologic markers including anti-double stranded DNA (dsDNA) antibody and complement are common used in laboratory

monitoring of disease activity, however, these traditional biomarkers are better related to certain clinical manifestations of the disease, especially nephritis, rather than to the activity of the disease itself (69). Currently, disease activity in SLE can be assessed using composite disease activity indices, such as SLEDAI score and British Isles Lupus Assessment Group (BILAG) score (70). However, the composite disease activity indices depend on differential organ involvement and physical assessments (71, 72). Besides, they could be complex for use in routine clinical practice. Thus, there is a great urgent for the identification of new biomarkers that can quantify disease activity (73, 74).

Moreover, due to the existence of a remarkable difference in microbiota between SLE status, the random forest models were built in this study to examine whether microbiota composition could identify their disease status. Of note, a random forests model was identified for diagnosing SLE from healthy controls and RA patients with a AUC value of 0.792. To be mentioned, another random forest predictive model showed to be a suitable model for the prediction of disease activity of SLE with the AUC of 0.811, which was higher than the combination of Complement C3 and anti-dsDNA (AUC=0.773). Accordingly, our results suggested that the gut microbiota might be potential biomarkers for diagnosis of SLE and even monitoring SLE activity in a non-invasive method. However, the sample size enrolled in our study was relatively small, therefore, more samples are needed to evaluate the performance of the disordered genera in the future.

In summary, these disordered bacteria and related metabolic pathways might provide clues in studying of the SLE pathogenesis, and in searching for suitable biomarkers for the diagnosis SLE or

monitoring SLE activity in a non-invasive method. Specific microbial clades might be viable targets for the therapeutic manipulation by dietary interventions, prebiotics, probiotics and specifically tailored antibiotics. Determining the functions of the microbial clades that expand or contract in SLE will contribute to developing effective strategies to target them. However, the key role of microbiota in SLE pathogenesis and prospective mechanistic studies still need to be further investigated.

Conclusions

In this study, we reveal that intestinal dysbiosis and aberrant metabolism pathways are existed in SLE patients, especially in active SLE patients. Notably, there are 4 disordered genera and 2 species that are associated with the clinical disease activity in our patient cohort. Furthermore, there are two kinds of genera-panels can be the indicators for diagnosing or monitoring disease activity of SLE by random forest algorithm. However, we also recognize the limitations of our study. Since the results are deduced by a single-center study with a relatively small sample size, larger and prospective cohort studies will be required to verify and validate this predictive model.

Declarations of interest

None.

Funding information

This study was supported by grants from the Natural Science Foundation of Guangdong Province of China (grant no. 2016A030313525), Guangzhou Science and Technology Program key projects (grant no. 201604040003), and Science and Technology planning project of Guangzhou (grant no. 201607010015). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The authors have no competing financial interests.

Authors contribution statement

Yao Li, Haifang Wang, Xin Li, Ji-Liang Li, and Yurong Qiu were responsible for the overall design and interpretation of the study; Yurong Qiu and Ji-Liang Li conceived and designed the study; Yao Li, Haifang Wang, Xin Li, Qiong Zhang and Chen Fu performed the experiments; Yao Li, Haifang Wang, Xin Li and Xiaohe Zhang contributed to the experimental data collection and analysis; Hongwei Zhou, Yan He and Pan Li contributed to the bioinformatics analysis; Yao Li, Haifang Wang, Xin Li wrote the manuscript. All authors read and approved the final manuscript.

Acknowledgements

We highly appreciated the Bioinformatics Consulting of the team of prof. Hongwei Zhou in Division of Laboratory Medicine, Microbiome Medicine Center, Zhujiang Hospital, Southern Medical University.

We thank Miss Carly Bunston (University of Plymouth Faculty of Medicine and Dentistry, Plymouth, UK) for constructive comments and editing the manuscript.

Reference

1. Lozupone CA, Stombaugh JI, Gordon JI, Jansson JK, Knight R. Diversity, stability and resilience of the human gut microbiota. Nature. 2012;489(7415):220-30.

2. Lynch SV, Pedersen O. The Human Intestinal Microbiome in Health and Disease. N Engl J Med. 2016;375(24):2369-79.

3. Ridaura VK, Faith JJ, Rey FE, Cheng J, Duncan AE, Kau AL, et al. Gut microbiota from twins discordant for obesity modulate metabolism in mice. Science. 2013;341(6150):1241214.

4. Qin J, Li Y, Cai Z, Li S, Zhu J, Zhang F, et al. A metagenome-wide association study of gut microbiota in type 2 diabetes. Nature. 2012;490(7418):55-60.

5. Abu-Shanab A, Quigley EM. The role of the gut microbiota in nonalcoholic fatty liver disease. Nat Rev Gastroenterol Hepatol. 2010;7(12):691-701.

6. Xu KY, Xia GH, Lu JQ, Chen MX, Zhen X, Wang S, et al. Impaired renal function and dysbiosis of gut microbiota contribute to increased trimethylamine-N-oxide in chronic kidney disease patients. Sci Rep. 2017;7(1):1445.

7. Rahman A, Isenberg DA. Systemic lupus erythematosus. N Engl J Med. 2008;358(9):929-39.

8. Hevia A, Milani C, Lopez P, Cuervo A, Arboleya S, Duranti S, et al. Intestinal dysbiosis associated with systemic lupus erythematosus. MBio. 2014;5(5):e01548-14.

9. Rodriguez-Carrio J, Lopez P, Sanchez B, Gonzalez S, Gueimonde M, Margolles A, et al. Intestinal Dysbiosis Is Associated with Altered Short-Chain Fatty Acids and Serum-Free Fatty Acids in Systemic Lupus Erythematosus. Front Immunol. 2017;8.

10. He Z, Shao T, Li H, Xie Z, Wen C. Alterations of the gut microbiome in Chinese patients with systemic lupus erythematosus. Gut Pathog. 2016; 8: 64.

11. Ma F, Zhang Y, Xing J, Song X, Huang L, Weng H, et al. Fecal bacteria from treatment-naive Crohn's disease patients can skew helper T cell responses. Exp Cell Res. 2017;361(1):135-40.

12. Mu Q, Zhang H, Liao X, Lin K, Liu H, Edwards MR, et al. Control of lupus nephritis by changes of gut microbiota. Microbiome. 2017;5(1):73.

13. Yatsunenko T, Rey FE, Manary MJ, Trehan I, Dominguez-Bello MG, Contreras M, et al. Human gut microbiome viewed across age and geography. Nature. 2012;486(7402):222-+.

14. Markle JG, Frank DN, Mortin-Toth S, Robertson CE, Feazel LM, Rolle-Kampczyk U, et al. Sex differences in the gut microbiome drive hormone-dependent regulation of autoimmunity. Science. 2013;339(6123):1084-8.

15. Xu ZJ, Knight R. Dietary effects on human gut microbiome diversity. Brit J Nutr. 2015;113:S1-S5.

16. He Y, Wu W, Zheng HM, Li P, McDonald D, Sheng HF, et al. Regional variation limits applications of healthy gut microbiome reference ranges and disease models. Nat Med. 2018.

17. Luo XM, Edwards MR, Mu Q, Yu Y, Vieson MD, Reilly CM, et al. Gut Microbiota in Human Systemic Lupus Erythematosus and a Mouse Model of Lupus. Appl Environ Microbiol. 2018;84(4).

18. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1982;25(11):1271-7.

19. Petri M, Orbai AM, Alarcon GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum. 2012;64(8):2677-86.

20. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, 3rd, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62(9):2569-81.

21. Romero-Diaz J, Isenberg D, Ramsey-Goldman R. Measures of adult systemic lupus erythematosus: updated version of British Isles Lupus Assessment Group (BILAG 2004), European Consensus Lupus Activity Measurements (ECLAM), Systemic Lupus Activity Measure, Revised (SLAM-R), Systemic Lupus Activity Questionnaire for Population Studies (SLAQ), Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K), and Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI). Arthritis Care Res (Hoboken). 2011;63 Suppl 11:S37-46.

22. Fadrosh DW, Ma B, Gajer P, Sengamalay N, Ott S, Brotman RM, et al. An improved dual-indexing approach for multiplexed 16S rRNA gene sequencing on the Illumina MiSeq platform. Microbiome. 2014;2(1):6.

23. Caporaso JG, Kuczynski J, Stombaugh J, Bittinger K, Bushman FD, Costello EK, et al. QIIME allows analysis of high-throughput community sequencing data. Nat Methods. 2010;7(5):335-6.

24. Bolger AM, Lohse M, Usadel B. Trimmomatic: a flexible trimmer for Illumina sequence data. Bioinformatics. 2014;30(15):2114-20.

25. Magoc T, Salzberg SL. FLASH: fast length adjustment of short reads to improve genome assemblies. Bioinformatics. 2011;27(21):2957-63.

26. Price MN, Dehal PS, Arkin AP. FastTree: computing large minimum evolution trees with profiles instead of a distance matrix. Mol Biol Evol. 2009;26(7):1641-50.

27. Langille MGI, Zaneveld J, Caporaso JG, McDonald D, Knights D, Reyes JA, et al. Predictive functional profiling of microbial communities using 16S rRNA marker gene sequences. Nat Biotechnol. 2013;31(9):814-+.

28. Segata N, Izard J, Waldron L, Gevers D, Miropolsky L, Garrett WS, et al. Metagenomic biomarker discovery and explanation. Genome Biol. 2011;12(6):R60.

29. Sarkar SK. FDR-controlling stepwise procedures and their false negatives rates. J Stat Plan Infer. 2004;125(1-2):119-37.

30. Glickman ME, Rao SR, Schultz MR. False discovery rate control is a recommended alternative to Bonferroni-type adjustments in health studies. J Clin Epidemiol. 2014;67(8):850-7.

31. Qin N, Yang F, Li A, Prifti E, Chen Y, Shao L, et al. Alterations of the human gut microbiome in liver cirrhosis. Nature. 2014;513(7516):59-64.

32. Lozupone C, Knight R. UniFrac: a new phylogenetic method for comparing microbial communities. Appl Environ Microbiol. 2005;71(12):8228-35.

33. Roguet A, Eren AM, Newton RJ, McLellan SL. Fecal source identification using random forest. Microbiome. 2018;6(1):185.

34. Lopez P, Sanchez B, Margolles A, Suarez A. Intestinal dysbiosis in systemic lupus erythematosus: cause or consequence? Curr Opin Rheumatol. 2016;28(5):515-22.

35. Sandhu V, Quan M. SLE and Serum Complement: Causative, Concomitant or Coincidental? Open Rheumatol J. 2017;11:113-22.

36. Stojan G, Fang H, Magder L, Petri M. Erythrocyte sedimentation rate is a predictor of renal and overall SLE disease activity. Lupus. 2013;22(8):827-34.

37. Lloyd W, Schur PH. Immune complexes, complement, and anti-DNA in exacerbations of systemic lupus erythematosus (SLE). Medicine (Baltimore). 1981;60(3):208-17.

38. Furie R, Wang L, Illei G, Drappa J. Systemic Lupus Erythematosus (SLE) Responder Index response is associated with global benefit for patients with SLE. Lupus. 2018;27(6):955-62.

39. Neuman H, Koren O. The gut microbiota: a possible factor influencing systemic lupus erythematosus. Curr Opin Rheumatol. 2017;29(4):374-7.

40. Shamriz O, Mizrahi H, Werbner M, Shoenfeld Y, Avni O, Koren O. Microbiota at the crossroads of autoimmunity. Autoimmun Rev. 2016;15(9):859-69.

41. Proal AD, Albert PJ, Marshall TG. The human microbiome and autoimmunity. Curr Opin Rheumatol. 2013;25(2):234-40.

42. van der Meulen TA, Harmsen HJM, Bootsma H, Spijkervet FKL, Kroese FGM, Vissink A. The microbiome-systemic diseases connection. Oral Dis. 2016;22(8):719-34.

43. Jun Chen1 KW, John M. Davis2. An expansion of rare lineage intestinal microbes characterizes rheumatoid arthritis. 2016.

44. Round JL, Mazmanian SK. The gut microbiota shapes intestinal immune responses during health and disease. Nat Rev Immunol. 2009;9(5):313-23.

45. Katz-Agranov N, Zandman-Goddard G. The microbiome and systemic lupus erythematosus. Immunol Res. 2017;65(2):432-7.

46. Kim MS, Bae JW, Park EJ. Geographic and host-associated variations in bacterial communities on the floret surfaces of field-grown broccoli. Appl Environ Microbiol. 2018.

47. Wang JZ, Du WT, Xu YL, Cheng SZ, Liu ZJ. Gut microbiome-based medical methodologies for early-stage disease prevention. Microb Pathog. 2017;105:122-30.

48. Quigley EMM. Gut microbiome as a clinical tool in gastrointestinal disease management: are we there yet? Nat Rev Gastroenterol Hepatol. 2017;14(5):315-20.

49. Lv LX, Fang DQ, Shi D, Chen DY, Yan R, Zhu YX, et al. Alterations and correlations of the gut microbiome, metabolism and immunity in patients with primary biliary cirrhosis. Environ Microbiol. 2016;18(7):2272-86.

50. Stagi S, Lepri G, Rigante D, Matucci Cerinic M, Falcini F. Cross-Sectional Evaluation of Plasma Vitamin D Levels in a Large Cohort of Italian Patients with Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections. J Child Adolesc Psychopharmacol. 2018;28(2):124-9.

51. Ganju SA, Gautam N, Sharma G. Pyogenic liver abscess associated with oral flora bacterium, Streptococcus anginosus in a patient with underlying tuberculosis. Indian J Pathol Microbiol. 2017;60(4):587-9.

52. van den Bogert B, Meijerink M, Zoetendal EG, Wells JM, Kleerebezem M. Immunomodulatory properties of Streptococcus and Veillonella isolates from the human small intestine microbiota. PLoS One. 2014;9(12):e114277.

53. Wang J, Jia HJ. Metagenome-wide association studies: fine-mining the microbiome. Nat Rev Microbiol. 2016;14(8):508-22.

54. Correa JD, Calderaro DC, Ferreira GA, Mendonca SMS, Fernandes GR, Xiao E, et al. Subgingival microbiota dysbiosis in systemic lupus erythematosus: association with periodontal status. Microbiome. 2017;5.

55. Barcenilla A, Pryde SE, Martin JC, Duncan SH, Stewart CS, Henderson C, et al. Phylogenetic relationships of butyrate-producing bacteria from the human gut. Appl Environ Microbiol. 2000;66(4):1654-61.

56. Tamanai-Shacoori Z, Smida I, Bousarghin L, Loreal O, Meuric V, Fong SB, et al. Roseburia spp.: a marker of health? Future Microbiol. 2017;12:157-70.

57. den Besten G, van Eunen K, Groen AK, Venema K, Reijngoud DJ, Bakker BM. The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. Journal of Lipid Research. 2013;54(9):2325-40.

58. Keku TO, Dulal S, Deveaux A, Jovov B, Han X. The gastrointestinal microbiota and colorectal cancer. Am J Physiol Gastrointest Liver Physiol. 2015;308(5):G351-63.

59. Peng L, Li ZR, Green RS, Holzman IR, Lin J. Butyrate enhances the intestinal barrier by facilitating tight junction assembly via activation of AMP-activated protein kinase in Caco-2 cell monolayers. J Nutr. 2009;139(9):1619-25.

60. Rios-Covian D, Ruas-Madiedo P, Margolles A, Gueimonde M, de los Reyes-Gavilan CG, Salazar N. Intestinal Short Chain Fatty Acids and their Link with Diet and Human Health. Front Microbiol. 2016;7.

61. Daniel F. Zegarra-Ruiz, Asmaa El Beidaq, Alonso J. Iñiguez, Teri M. Greiling, Carina Dehner, Martin A. Kriegel, et al. A Diet-Sensitive Commensal Lactobacillus Strain Mediates TLR7-Dependent Systemic Autoimmunity. Cell Host Microbe. 2018. DOI: https://doi.org/10.1016/j.chom.2018.11.009.

62. Triantafilou M, Triantafilou K. Lipopolysaccharide recognition: CD14, TLRs and the LPS-activation cluster. Trends Immunol. 2002;23(6):301-4.

63. Mok CC, Tse SM, Chan KL, Ho LY. Effect of immunosuppressive therapies on survival of systemic lupus erythematosus: a propensity score analysis of a longitudinal cohort. Lupus. 2018;27(5):722-7.

64. Atisha-Fregoso Y, Lima G, Carrillo-Maravilla E, Posadas-Sanchez R, Perez-Hernandez N, Banos-Pelaez M, et al. C-reactive protein (CRP) polymorphisms and haplotypes are associated with SLE susceptibility and activity but not with serum CRP levels in Mexican population. Clin Rheumatol. 2018;37(7):1817-24.

65. Bouts YM, Wolthuis DF, Dirkx MF, Pieterse E, Simons EM, van Boekel AM, et al. Apoptosis and NET formation in the pathogenesis of SLE. Autoimmunity. 2012;45(8):597-601.

66. Yang Z, Matteson EL, Goronzy JJ, Weyand CM. T-cell metabolism in autoimmune disease. Arthritis Res Ther. 2015;17:29.

67. Huang C, Freter C. Lipid metabolism, apoptosis and cancer therapy. Int J Mol Sci. 2015;16(1):924-49.

68. Szabo MZ, Szodoray P, Kiss E. Dyslipidemia in systemic lupus erythematosus. Immunol Res. 2017;65(2):543-50.

69. Pisetsky DS. Anti-DNA and autoantibodies. Curr Opin Rheumatol. 2000;12(5):364-8.

70. Liang MH, Socher SA, Larson MG, Schur PH. Reliability and validity of six systems for the clinical assessment of disease activity in systemic lupus erythematosus. Arthritis Rheum. 1989;32(9):1107-18.

71. Merrill JT, Erkan D, Buyon JP. Challenges in bringing the bench to bedside in drug development for SLE. Nat Rev Drug Discov. 2004;3(12):1036-46.

72. Petri M. Disease activity assessment in SLE: do we have the right instruments? Ann Rheum Dis. 2007;66:61-4.

73. Suh CH, Kim HA. Cytokines and their receptors as biomarkers of systemic lupus erythematosus. Expert Rev Mol Diagn. 2008;8(2):189-98.

74. Illei GG, Tackey E, Lapteva L, Lipsky PE. Biomarkers in systemic lupus erythematosus: II. Markers of disease activity. Arthritis Rheum. 2004;50(7):2048-65.

Table

Table 1: Characteristics of the active SLE patients and remissive SLE patients.

	A (n = 19)	R (n = 21)	P-value
Age, years	34.05 (13.92)	40.57 (13.63)	0.143
WBC, 10^9/L #	7.40 (5.32-8.53)	6.72 (5.72-8.22)	0.955
RBC, 10^{12}/L #	4.17 (3.49-4.35)	4.33 (4.00-4.58)	0.0389*
HGB, g/L #	106 (95-117.50)	126 (115-133.25)	< 0.001 ***
PLT, 10^9/L#	205 (152.50-308.00)	235.50 (202.25-272.50)	0.558
C3, g/L	0.68 (0.32)	0.93 (0.23)	0.0013**
CRP, mg/L #	1.68 (0.65-4.66)	1.56 (0.57-4.07)	0.765
ESR, mm/h #	21.50 (11-53.50)	19.00 (5.00-60.00)	0.457
Pyuria, n (%)			
- (negative)	6 (31.58)	17 (80.95)	0.002**
+ (positive)	13 (68.42)	4 (19.05)	
Albuminuria , n (%)			
- (negative)	3 (15.79)	15 (71.43)	0.000***
+ (positive)	16 (84.21)	6 (28.57)	
Hematuria , n (%)			
- (negative)	4 (21.05)	19 (90.48)	0.000***
+ (positive)	15 (78.95)	2 (9.52)	
24-UTP, mg/24h #	0.68 (0.22-2.29)	0.17 (0.11-0.46)	0.048*
Anti-dsDNA, UI/ml #	65.64 (16.24–156.66)	20.07 (2.88–62.20)	0.0186*
Lupus nephritis, n (%)	15 (78.95)	9 (42.86)	0.20
SLEDAI#	12 (9.5-14.0)	4 (1.5-6.0)	< 0.001 ***
Medication use			
Hydroxychloroquine	12	10	0.119
Glucocorticoid	17	16	0.527
Cyclophosphamide	3	3	0.574
Biological agent	5	2	0.894

A, the active SLE patients; R, the remissive SLE patients; WBC, white blood cell; RBC, red blood cell; HGB, haemoglobin; PLT, platelet; C3, Complement component 3; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; 24-UTP, 24-hour urine protein; Anti-dsDNA, anti-double stranded DNA; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index. Data represent the mean (standard deviation), and the data $^{\#}$ represents the median (interquartile range). The P values were calculated by Mann-Whitney U test or Chi-square test. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

Figure legend

Figure 1. The different microbial diversity between SLE patient group and healthy controls. A-B. Significantly different richness of α-diversity between the gut microbiota of SLE and HC. C. Principal coordinate analysis illustrating the grouping patterns of SLE and HC group based on the unweighted UniFrac distances. Each closed circle represented a sample. Distances between any pair of samples represented their dissimilarities. D. The average relative abundances of the predominant bacterial taxa at the phylum level in the SLE patients and HC group. E-F. The significantly different phyla in SLE patients compared to healthy controls. HC, healthy controls; SLE, Systemic lupus erythematosus patients.

Figure 2. The differentially abundant taxa between the feces of SLE patients and healthy controls. LEfSe analysis was performed to identify differentially abundant taxa, which are highlighted by the phylogenetic tree in cladogram format (A) and the LDA scores (B). Green color indicates an increase taxa in the feces of SLE compared with HC, while the red color indicates an increase taxa in the feces of HC compared with SLE (significant taxa [$p<0.005$, Kruskal–Wallis test] with LDA score >2 were shown). SLE, Systemic lupus erythematosus patients; HC, healthy controls.

Figure 3. The different microbial diversity between the feces of active SLE patients and remissive SLE patients. A. Principal coordinate analysis illustrating the grouping patterns of the feces of A group and R group based on the unweighted UniFrac distances. Each closed circle represented a sample. Distances between any pair of samples represented their dissimilarities. B. The significantly different phyla in the feces of A group compared with R group. C-D. LEfSe analysis was performed to identify differentially abundant taxa, which are highlighted by by the phylogenetic tree in cladogram format (C) and the LDA scores (D). Significantly discriminative taxa among the active patients (red), remissive patients (blue) and healthy controls (green) were determined using Linear Discriminant Analysis Effect Size (LEfSe) (significant taxa [$p<0.005$, Kruskal–Wallis test] with LDA score >2 were shown). A, the active SLE patients; R, the remissive SLE patients.

Figure 4. The significantly different predicted metabolic pathways between SLE patients and healthy controls. A. Significantly two predicted metabolic pathways were increased in SLE compared with healthy controls. B. Four predicted metabolic pathways were decreased in SLE patient group compared with healthy controls. It was analyzed by Kruskal–Wallis, and the False Discovery Rate (FDR) q-value was then calculated, and q-values <0.1 was considered significant. SLE, Systemic lupus erythematosus patients; HC, healthy controls.

Figure 5. The significantly different predicted metabolic pathways between active SLE patients and remissive SLE patients. A. Significantly five predicted metabolic pathways were increased in active SLE compared with remissive SLE patients. B. Four predicted metabolic pathways were enriched in remissive SLE patients compared with active SLE patients. A, the active SLE patient group; R, the remissive SLE patient group. It was analyzed by Kruskal–Wallis, and the False Discovery Rate (FDR) q-value was then calculated, and q-values <0.1 was considered significant.

Figure 6. The associations between the abundance of genus *Streptococcus* and disordered metabolic pathways. A. The predicted metabolic pathway Apoptosis and Pathways in cancer were correlated with SLE-enriched genus *Streptococcus*. B. The predicted metabolic pathway of Alanine aspartate and glutamate metabolism, Primary bile acid biosynthesis and Secondary bile acid biosynthesis were

negatively associated with active SLE-enriched genus *Streptococcus*. C. Five pathway categories, which were higher in active SLE patients compared to remissive SLE patient group, were positively associated with active SLE-enriched genus *Streptococcus*. They were analyzed by Spearman ranks tests, and the False Discovery Rate (FDR) was calculated for multiple testing. SLE, Systemic lupus erythematosus patients; FDR, the False Discovery Rate.

Figure 7. Associations among disease activity, disordered genera and predicted pathways in the gut microbiota of SLE patients. A-C. Three genera, *Streptococcus*, *Campylobacter*, and *Veillonella*, were positively correlated with lupus activity. D-E. Two species, *Streptococcus. anginosus*, and *Veillonella. dispar*, were positively correlated with lupus activity. F. The genus *Bifidobacterium* was negatively related to lupus activity. G-I. The aberrant microbiome-associated pathways, Alanine aspartate and glutamate metabolism, Secondary bile acid biosynthesis and Lipid metabolism, had a positive association with the activity of SLE patients. It was analyzed by Spearman ranks tests, and the False Discovery Rate (FDR) q-value was then calculated for multiple testing. SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; C3, Complement component 3.

Figure 8. Receiver operating characteristic (ROC) curves demonstrating the performance of the genus and species in participants. A. Prediction model of the gut microbiota to distinguish the SLE patients

among the healthy controls and RA patients based on the genus/species-level relative abundances using random forests. B. Prediction model of the gut microbiota to differentiate the active SLE patients from remissive SLE patients. AUC, Area under the curves of ROC; CI, Confidence Interval; SLE, Systemic lupus erythematosus patients; RA, Rheumatoid Arthritis patients.

Supplemental materials

Table S1: The comparison of α-diversity among different groups.

SLE, Systemic lupus erythematosus patients; HC, healthy controls; RA, Rheumatoid Arthritis patients; A, the active SLE patients; R, the remissive SLE patients. The Wilcoxon rank sum test was used to determine significance in α-diversity. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

Table S2: The comparisons of β-diversity among different medicine treatments in SLE patients.

SLE, Systemic lupus erythematosus patients; Y= treated with specific drug; N= not treated. The ADONIS analysis was used to determine significance in β-diversity. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

Table S3: The comparisons of β-diversity among different groups.

SLE, Systemic lupus erythematosus patients; HC, healthy controls; RA, Rheumatoid Arthritis patients;

A, the active SLE patients; R, the remissive SLE patients. The ADONIS analysis was used to determine significance in β-diversity. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

Table S4: The comparisons of *Firmicutes*/*Bacteroidetes* ratio between different groups.

F/B, *Firmicutes*/*Bacteroidetes* ratio; SLE, Systemic lupus erythematosus patients; HC, healthy controls; RA, Rheumatoid Arthritis patients; A, the active SLE patients; R, the remissive SLE patients. The Wilcoxon rank sum test was used to determine significance in α-diversity. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

Table S5: Association of disordered genera and aberrant microbiome-associated pathways with activity of SLE.

SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; C3, Complement component 3; CRP, C-reactive protein; ESR, Erythrocyte Sedimentation Rate; Anti-dsDNA, anti-double stranded DNA. They were analyzed by Spearman ranks tests, and False discovery rate (FDR) correction for multiple comparisons was employed. The FDR q-value was then calculated (r coefficient and FDR q-value were indicated for each parameter). $^{*}q < 0.05$; $^{**}q < 0.01$; $^{***}q < 0.001$.

.

Table S6: The importance of Genus and species in the random forests model to distinguish the SLE

patients from healthy controls and RA patients.

Table S7: The importance of Genus and species in the random forests model to distinguish the active SLE patients from remissive SLE patients.

Figure S1. Evaluation of sample preparation and sequencing quality. A. Chao1 dilution curve; B. Shannon dilution curve; C. OTU rank abundance.

Figure S2. The associations among α-diversity and Hydroxychloroquine, Glucocorticoid, Cyclophosphamide and Biological agent in SLE patients. SLE, Systemic lupus erythematosus patients; Y= treated with specific drug; N= not treated.

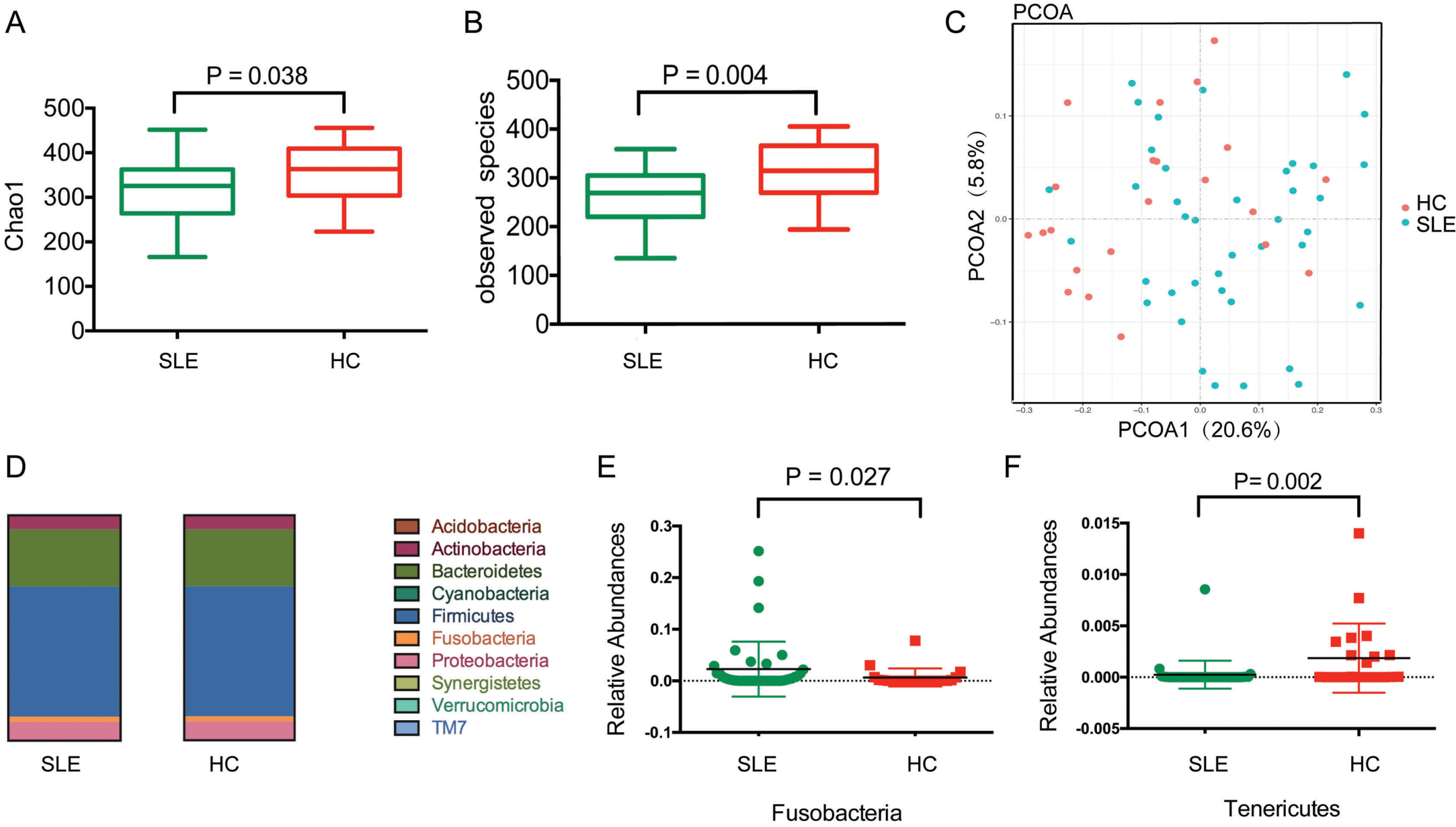
Figure S3. The Principal coordinate analysis (PCoA) of different medicine treatments. A-B. PCoA illustrating the grouping patterns of the Hydroxychloroquine-treated group (red) and Hydroxychloroquine-not treated group (blue) based on the weighted UniFrac distances (A) and unweighted UniFrac distances (B). C-D. PCoA illustrating the grouping patterns of the Glucocorticoid-treated group (red) and Glucocorticoid-not treated group (blue) based on the weighted UniFrac distances (C) and unweighted UniFrac distances (D). E-F. PCoA illustrating the grouping patterns of the Cyclophosphamide-treated group (red) and Cyclophosphamide-not treated group (blue)

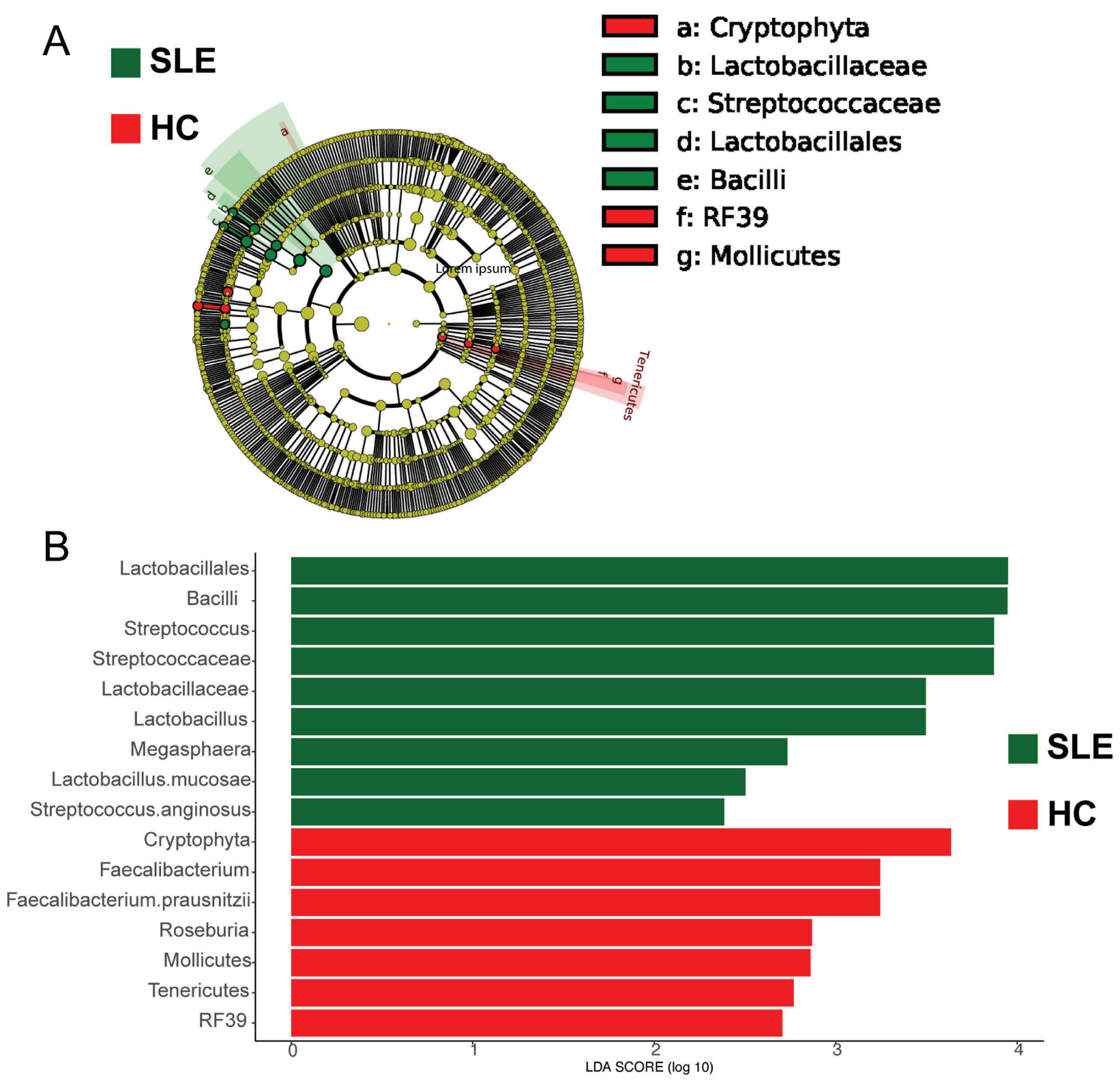
based on the weighted UniFrac distances (E) and unweighted UniFrac distances (F). G-H. PCoA illustrating the grouping patterns of the Biological agent-treated group (red) and Biological agent-not treated group (blue) based on the weighted UniFrac distances (G) and unweighted UniFrac distances (H). SLE, Systemic lupus erythematosus patients; Y= treated with specific drug; N= not treated.

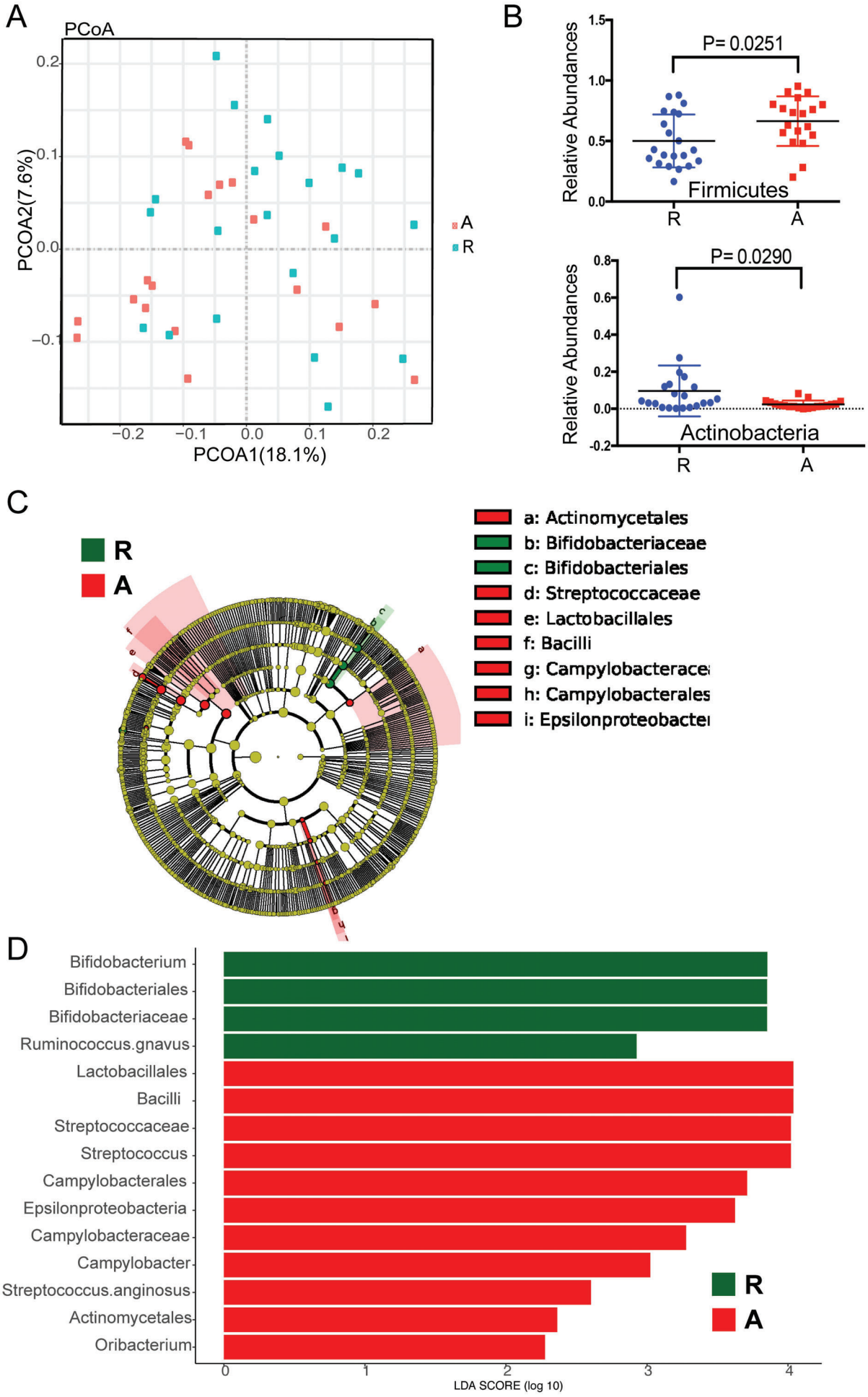
Figure S4. The Principal coordinate analysis (PCoA) of different groups. A-B. PCoA illustrating the grouping patterns of the SLE patients and healthy controls based on the weighted UniFrac distances (A) and unweighted UniFrac distances (B). C-D. PCoA illustrating the grouping patterns of the SLE patients and RA patients based on the weighted UniFrac distances (C) and unweighted UniFrac distances (D). E-F. PCoA illustrating the grouping patterns of the active SLE patients and remissive SLE patients based on the weighted UniFrac distances (E) and unweighted UniFrac distances (F). SLE, Systemic lupus erythematosus patients; HC, the healthy controls; A, the active SLE patients; R, the remissive SLE patients.

Figure S5. The differentially abundant taxa between SLE patient group and RA patient group. LEfSe analysis was performed to identify differentially abundant taxa, which are highlighted on the phylogenetic tree in cladogram format (A) and for which the LDA scores are shown (B). Green color indicates an increase taxa in SLE compared with RA, while the red color indicates an increase taxa in RA compared with SLE. For cladogram format, from the interior to the exterior, each layer represents the phylum, class, order, family, and genus level (significant taxa [$p<0.05$, Kruskal–Wallis test] with LDA score >2.5 were shown). SLE, Systemic lupus erythematosus patients; RA, Rheumatoid Arthritis patients.

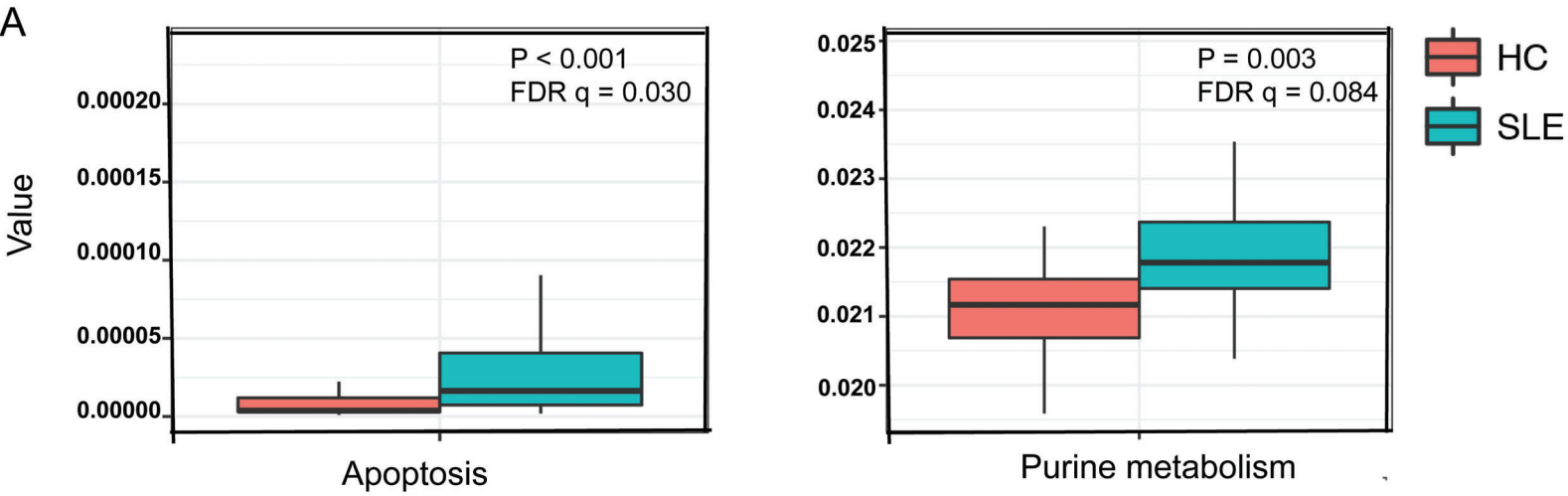
Figure S6. Receiver operating characteristic (ROC) curves demonstrating the performance of the anti-double stranded DNA and complement C3 to monitor the disease activity.


A
P = 0.038
Chao1
500
400
300
200
100
0
SLE
HC
B
P = 0.004
observed species
500
400
300
200
100
0
SLE
HC
C
PCOA
PCOA2 (5.8%)
PCOA1 (20.6%)
HC
SLE
D
SLE
HC
Acidobacteria
Actinobacteria
Bacteroidetes
Cyanobacteria
Firmicutes
Fusobacteria
Proteobacteria
Synergistetes
Verrucomicrobia
TM7
E
P = 0.027
Relative Abundances
0.3
0.2
0.1
0.0
-0.1
SLE
HC
Fusobacteria
F
P= 0.002
Relative Abundances
0.015
0.010
0.005
0.000
-0.005
SLE
HC
Tenericutes

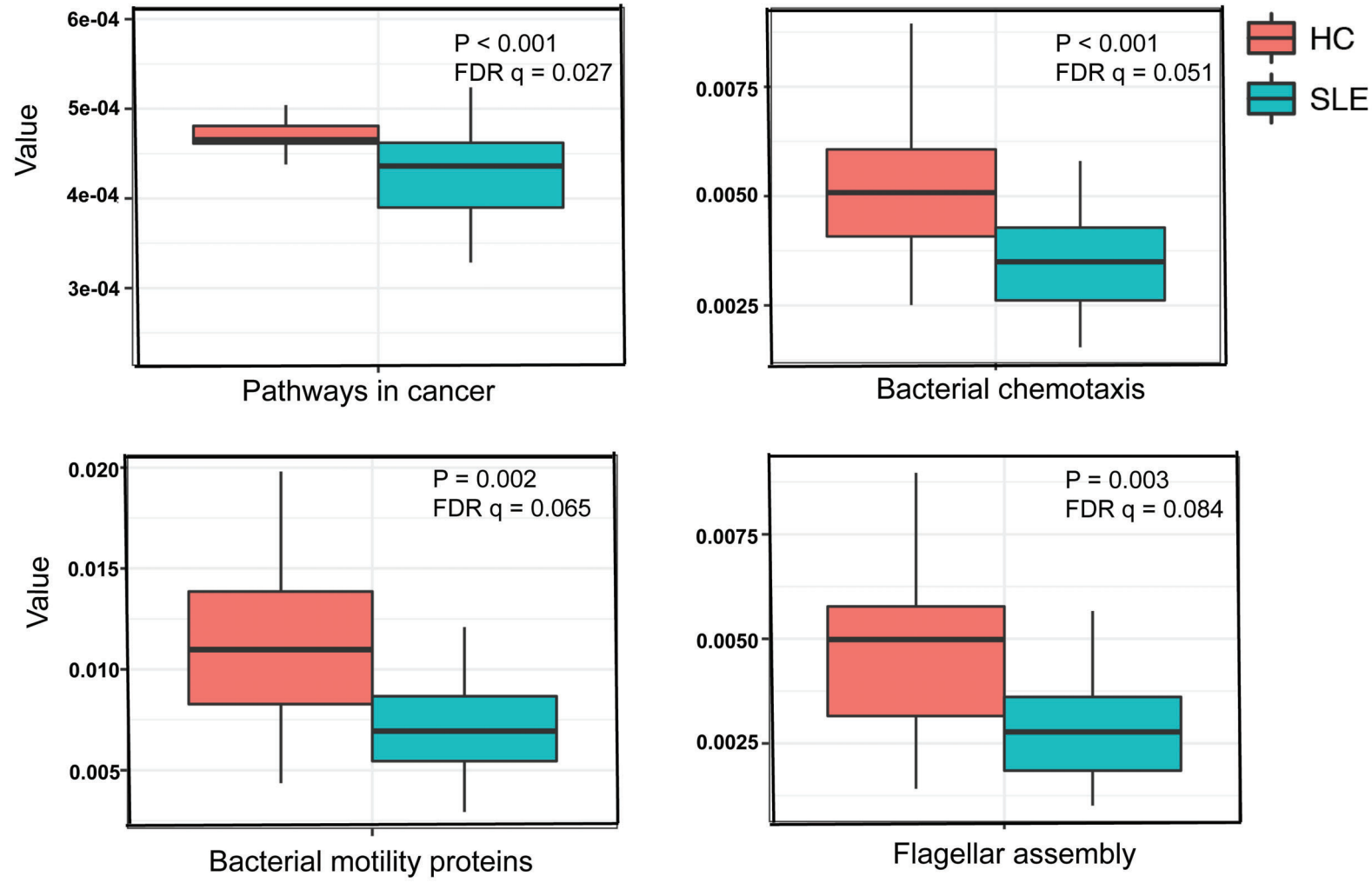

A
SLE
HC
a: Cryptophyta
b: Lactobacillaceae
c: Streptococcaceae
d: Lactobacillales
e: Bacilli
f: RF39
g: Mollicutes
Lorem ipsum
Tenericutes
B
Lactobacillales
Bacilli
Streptococcus
Streptococcaceae
Lactobacillaceae
Lactobacillus
Megasphaera
Lactobacillus.mucosae
Streptococcus.anginosus
Cryptophyta
Faecalibacterium
Faecalibacterium.prausnitzii
Roseburia
Mollicutes
Tenericutes
RF39
SLE
HC
0
1
2
3
4
LDA SCORE (log 10)

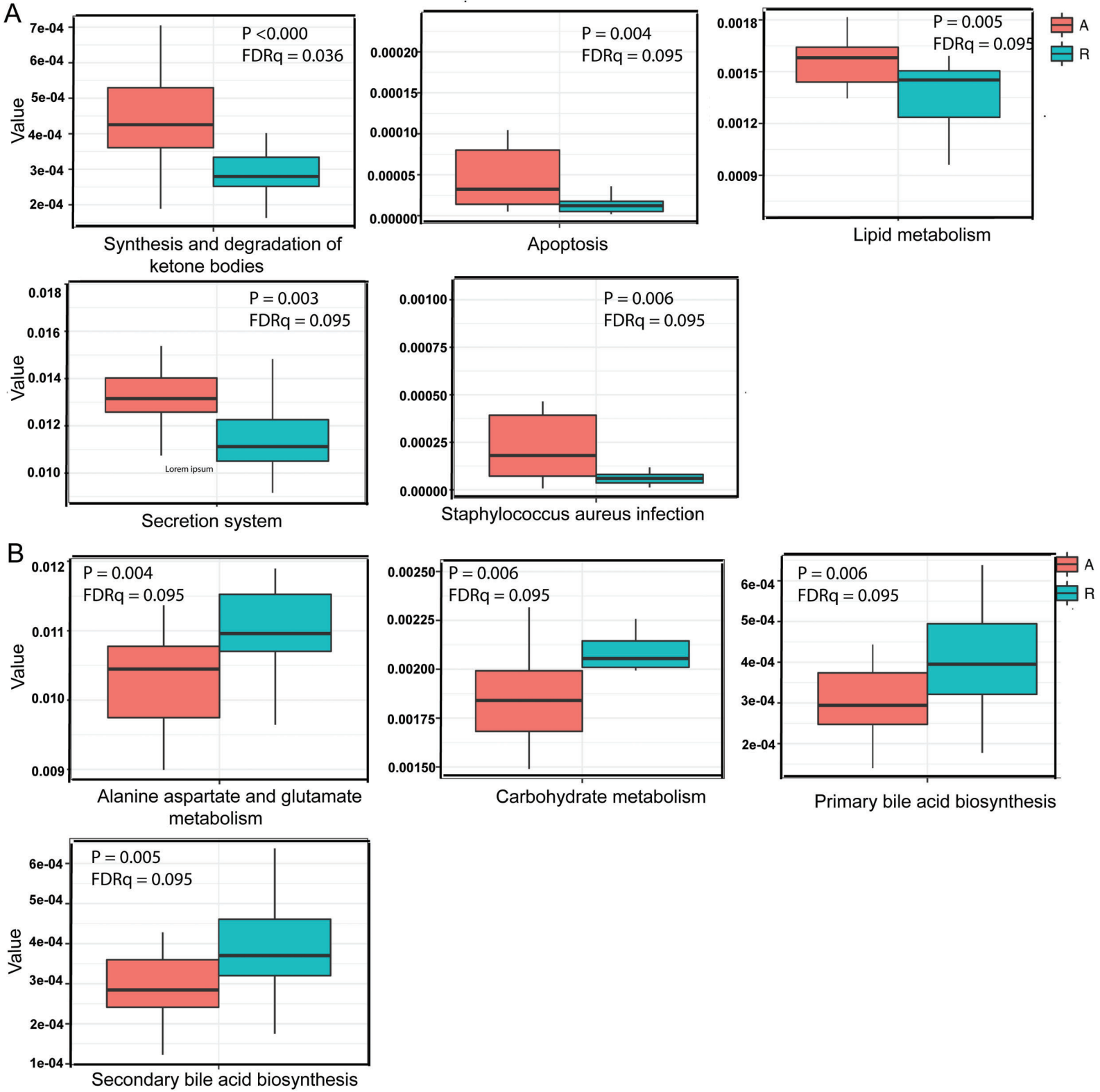

A
PCoA
PCOA2(7.6%)
PCOA1(18.1%)
A
R
B
Relative Abundances
P= 0.0251
Firmicutes
R
A
P= 0.0290
Actinobacteria
C
R
A
a: Actinomycetales
b: Bifidobacteriaceae
c: Bifidobacteriales
d: Streptococcaceae
e: Lactobacillales
f: Bacilli
g: Campylobacterace
h: Campylobacterales
i: Epsilonproteobacte
D
Bifidobacterium
Bifidobacteriales
Bifidobacteriaceae
Ruminococcus.gnavus
Lactobacillales
Bacilli
Streptococcaceae
Streptococcus
Campylobacterales
Epsilonproteobacteria
Campylobacteraceae
Campylobacter
Streptococcus.anginosus
Actinomycetales
Oribacterium
R
A
LDA SCORE (log 10)

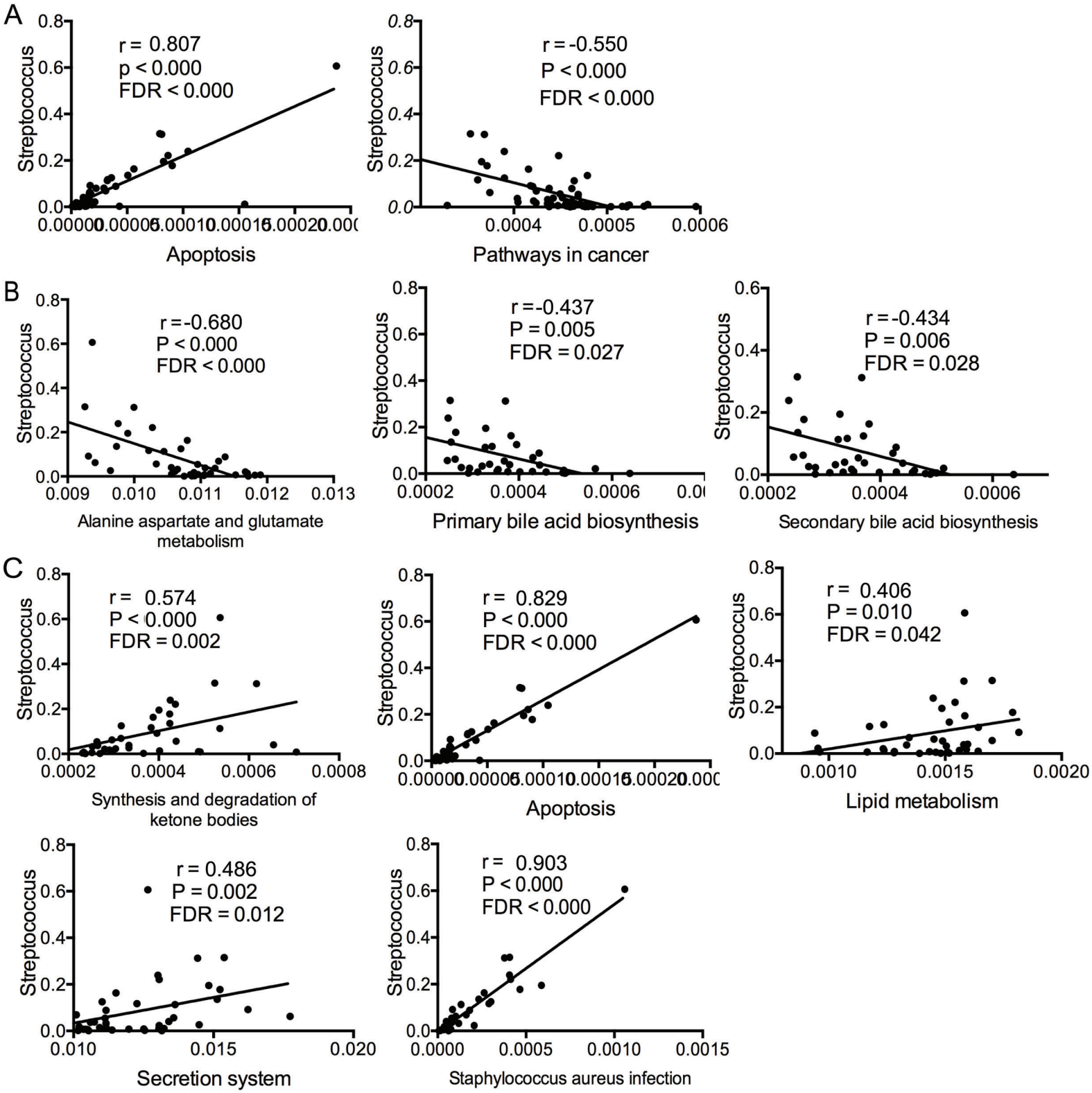
A

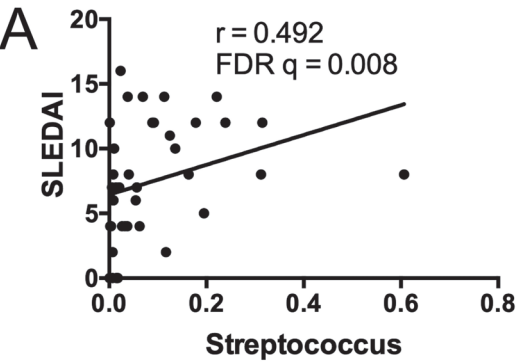

Value
0.00020
0.00015
0.00010
0.00005
0.00000
P < 0.001
FDR q = 0.030
Apoptosis
0.025
0.024
0.023
0.022
0.021
0.020
P = 0.003
FDR q = 0.084
Purine metabolism
HC
SLE

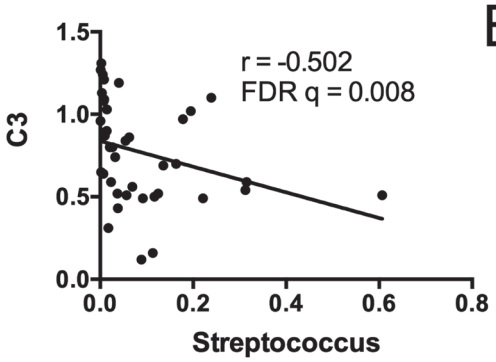
B

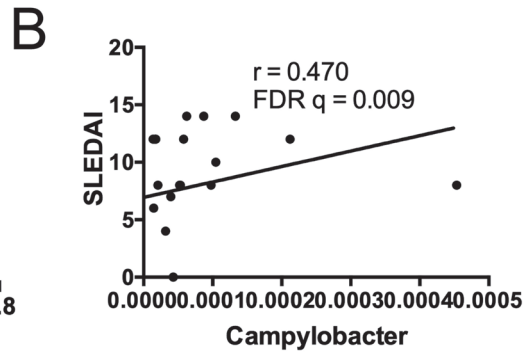

Value
6e-04
5e-04
4e-04
3e-04
P < 0.001
FDR q = 0.027
Pathways in cancer
0.0075
0.0050
0.0025
P < 0.001
FDR q = 0.051
Bacterial chemotaxis
HC
SLE
0.020
0.015
0.010
0.005
P = 0.002
FDR q = 0.065
Bacterial motility proteins
0.0075
0.0050
0.0025
P = 0.003
FDR q = 0.084
Flagellar assembly

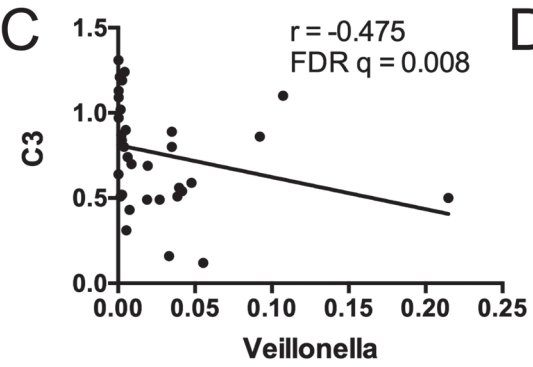

A
Value
P <0.000
FDRq = 0.036
Synthesis and degradation of ketone bodies
P = 0.004
FDRq = 0.095
Apoptosis
P = 0.005
FDRq = 0.095
A
R
Lipid metabolism
P = 0.003
FDRq = 0.095
Lorem ipsum
Secretion system
P = 0.006
FDRq = 0.095
Staphylococcus aureus infection
B
P = 0.004
FDRq = 0.095
Alanine aspartate and glutamate metabolism
P = 0.006
FDRq = 0.095
Carbohydrate metabolism
P = 0.006
FDRq = 0.095
Primary bile acid biosynthesis
P = 0.005
FDRq = 0.095
Secondary bile acid biosynthesis

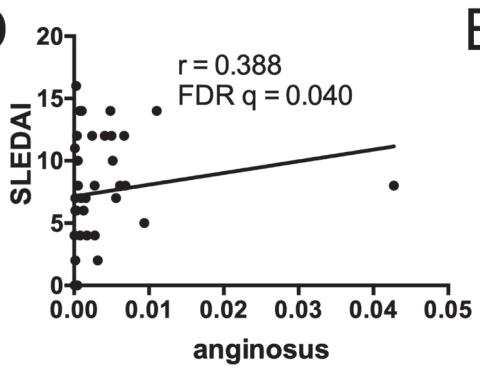

A
Streptococcus
r = 0.807
p < 0.000
FDR < 0.000
Apoptosis
r = -0.550
P < 0.000
FDR < 0.000
Pathways in cancer
B
r = -0.680
P < 0.000
FDR < 0.000
Alanine aspartate and glutamate metabolism
r = -0.437
P = 0.005
FDR = 0.027
Primary bile acid biosynthesis
r = -0.434
P = 0.006
FDR = 0.028
Secondary bile acid biosynthesis
C
r = 0.574
P < 0.000
FDR = 0.002
Synthesis and degradation of ketone bodies
r = 0.829
P < 0.000
FDR < 0.000
Apoptosis
r = 0.406
P = 0.010
FDR = 0.042
Lipid metabolism
r = 0.486
P = 0.002
FDR = 0.012
Secretion system
r = 0.903
P < 0.000
FDR < 0.000
Staphylococcus aureus infection

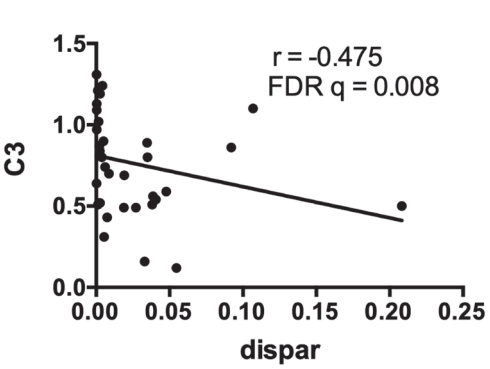

A
r = 0.492
FDR q = 0.008
SLEDAI
Streptococcus

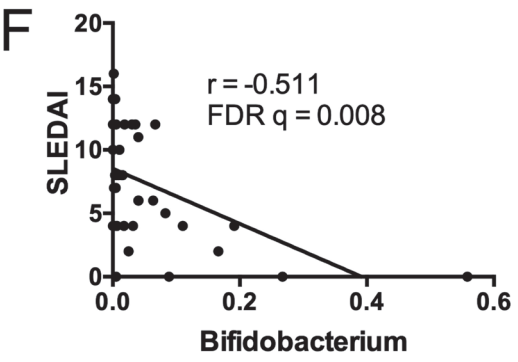

r = -0.502
FDR q = 0.008
C3
Streptococcus

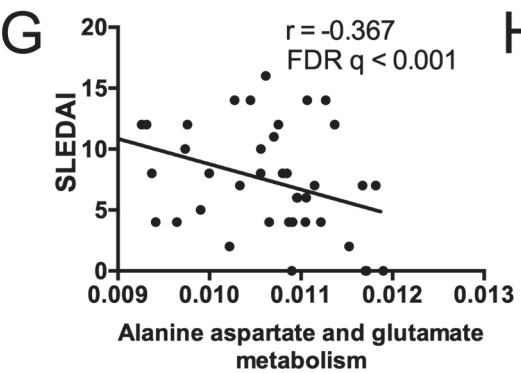

B
r = 0.470
FDR q = 0.009
SLEDAI
Campylobacter

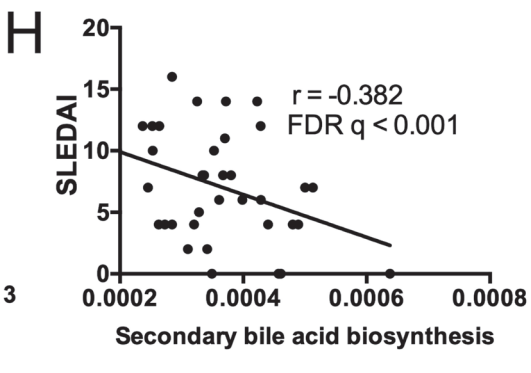

C
r = -0.475
FDR q = 0.008
C3
Veillonella

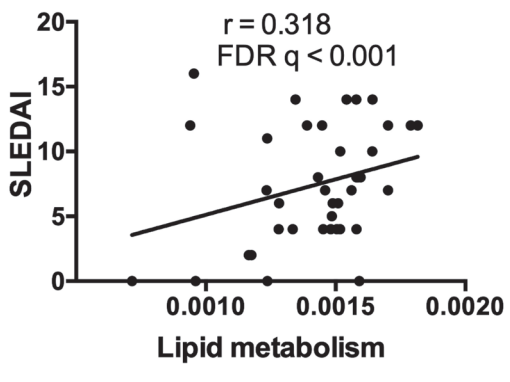

D
r = 0.388
FDR q = 0.040
SLEDAI
anginosus

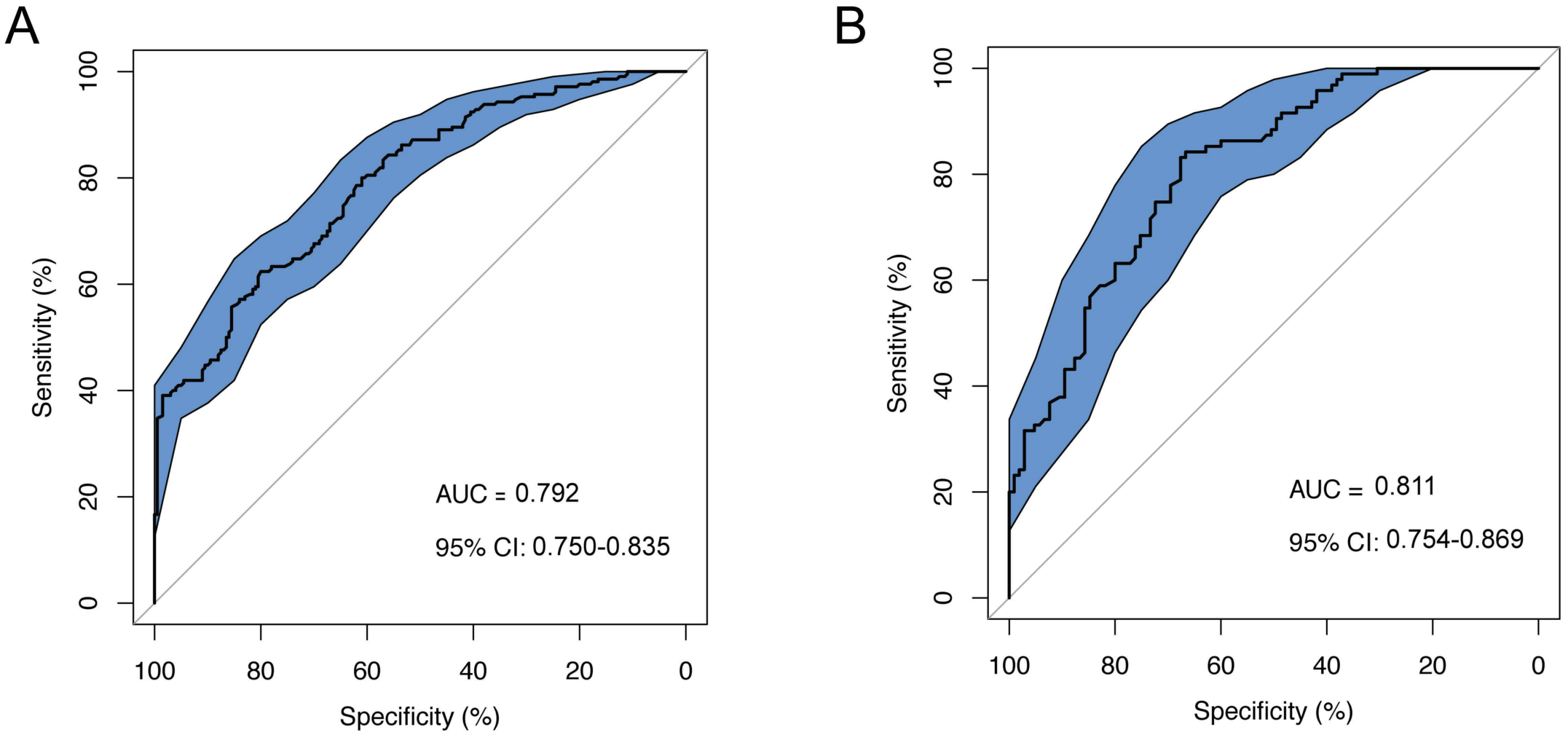

E
r = -0.475
FDR q = 0.008
C3
dispar


F
r = -0.511
FDR q = 0.008
SLEDAI
Bifidobacterium

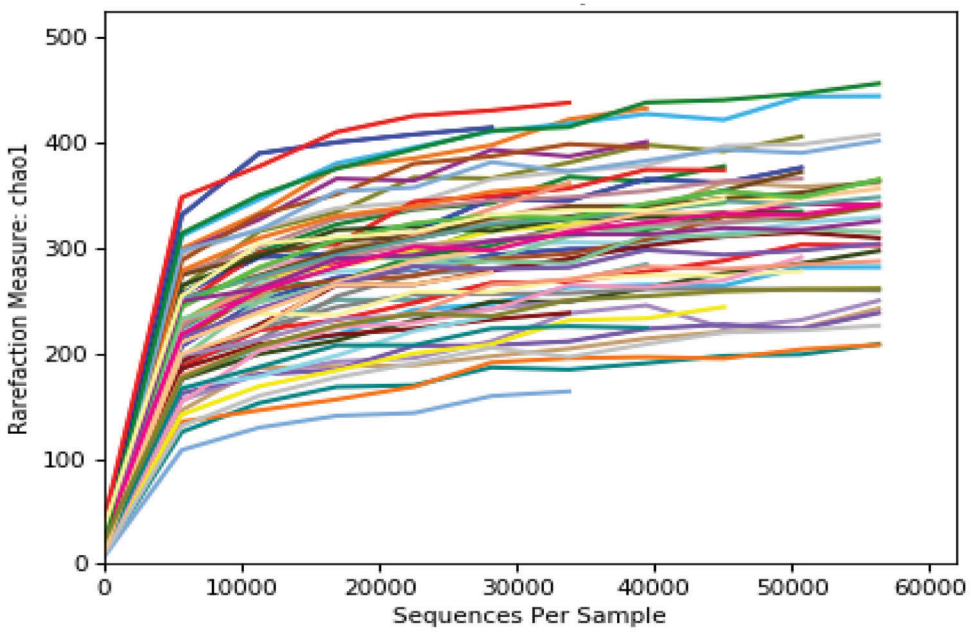

G
r = -0.367
FDR q < 0.001
SLEDAI
Alanine aspartate and glutamate metabolism


H
r = -0.382
FDR q < 0.001
SLEDAI
Secondary bile acid biosynthesis

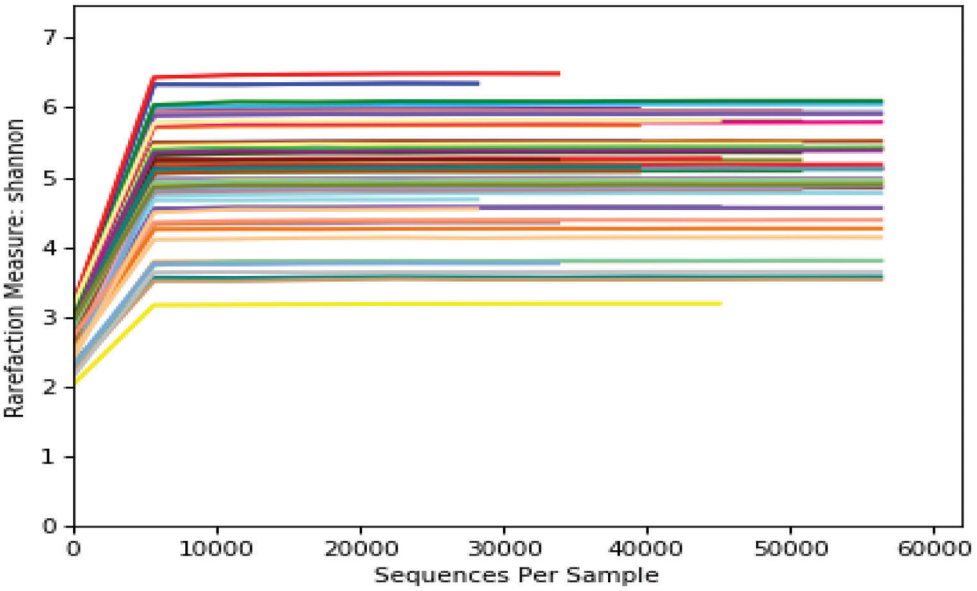

I
r = 0.318
FDR q < 0.001
SLEDAI
Lipid metabolism


A
Sensitivity (%)
100
80
60
40
20
0
AUC = 0.792
95% CI: 0.750-0.835
100
80
60
40
20
0
Specificity (%)
B
Sensitivity (%)
100
80
60
40
20
0
AUC = 0.811
95% CI: 0.754-0.869
100
80
60
40
20
0
Specificity (%)

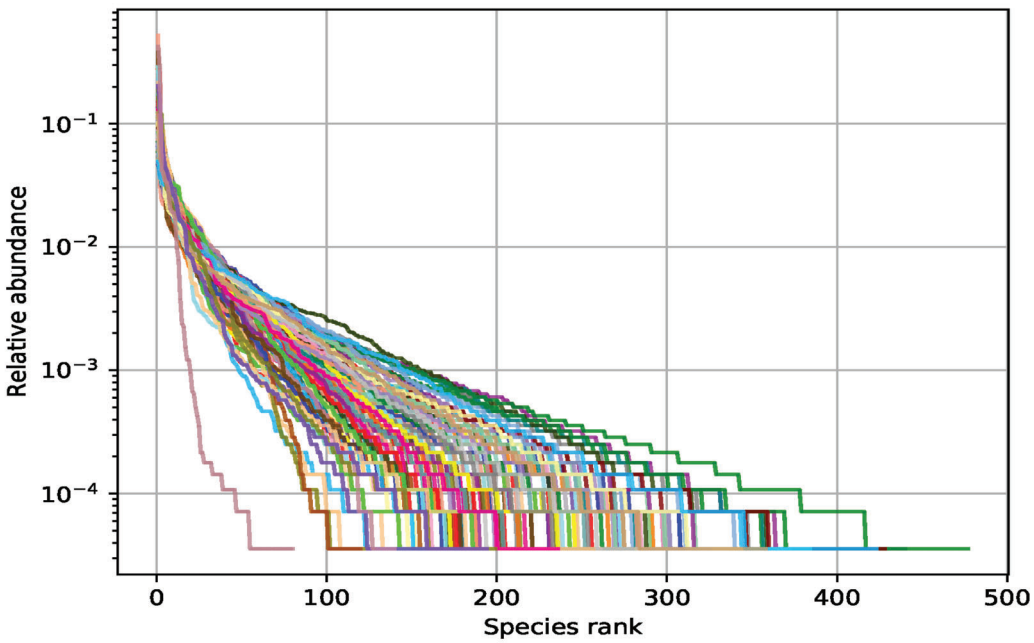
A

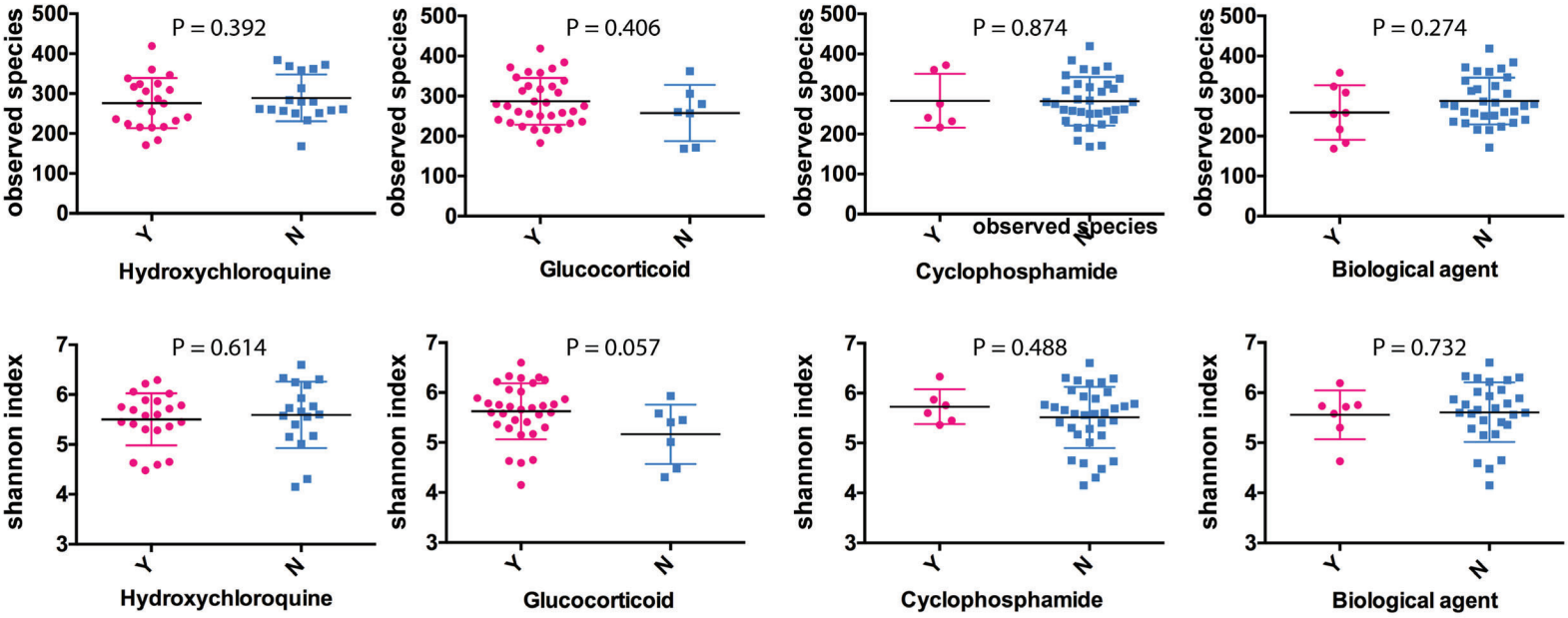

Rarefaction Measure: chao1
Sequences Per Sample
0
100
200
300
400
500
0
10000
20000
30000
40000
50000
60000

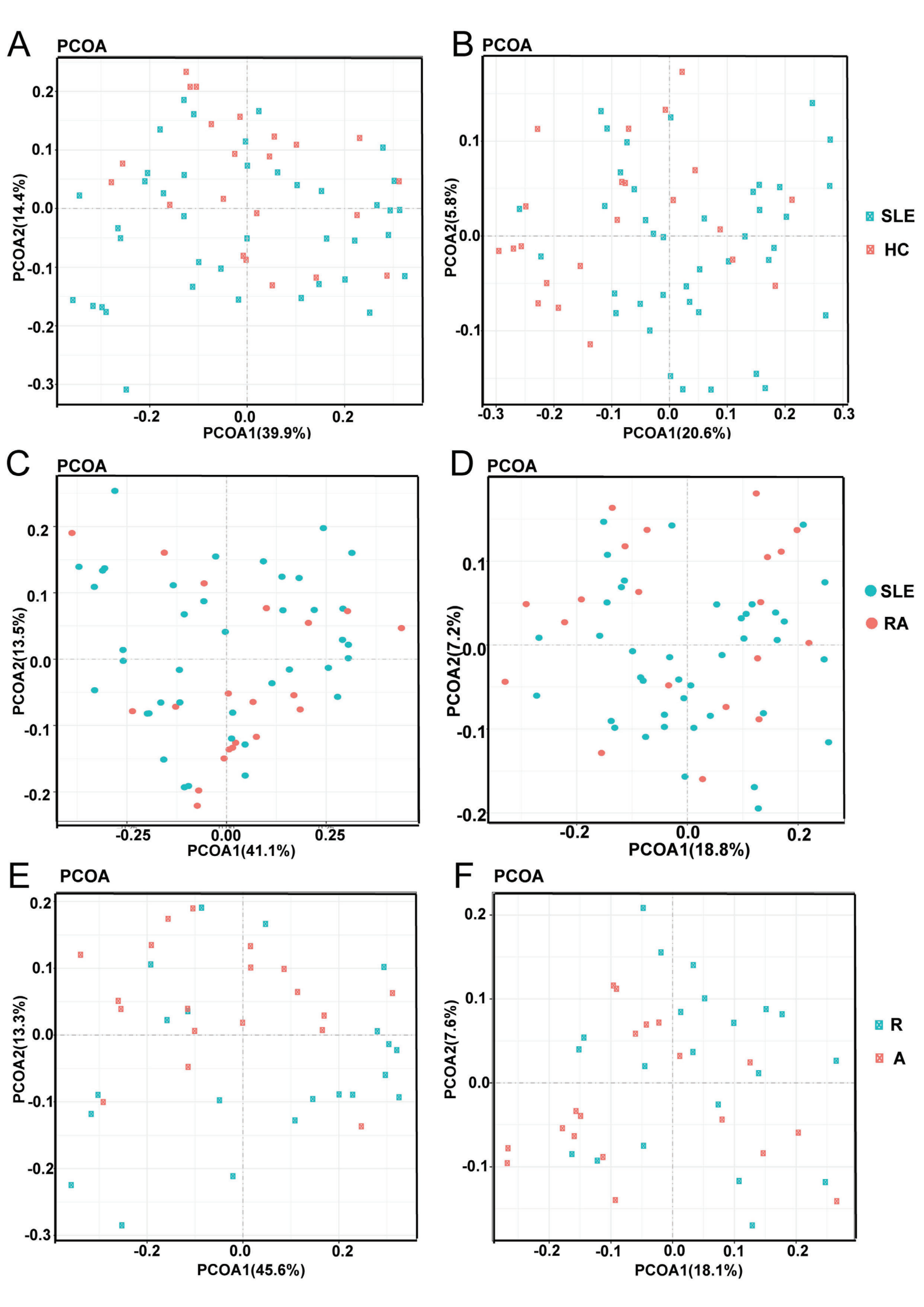
B

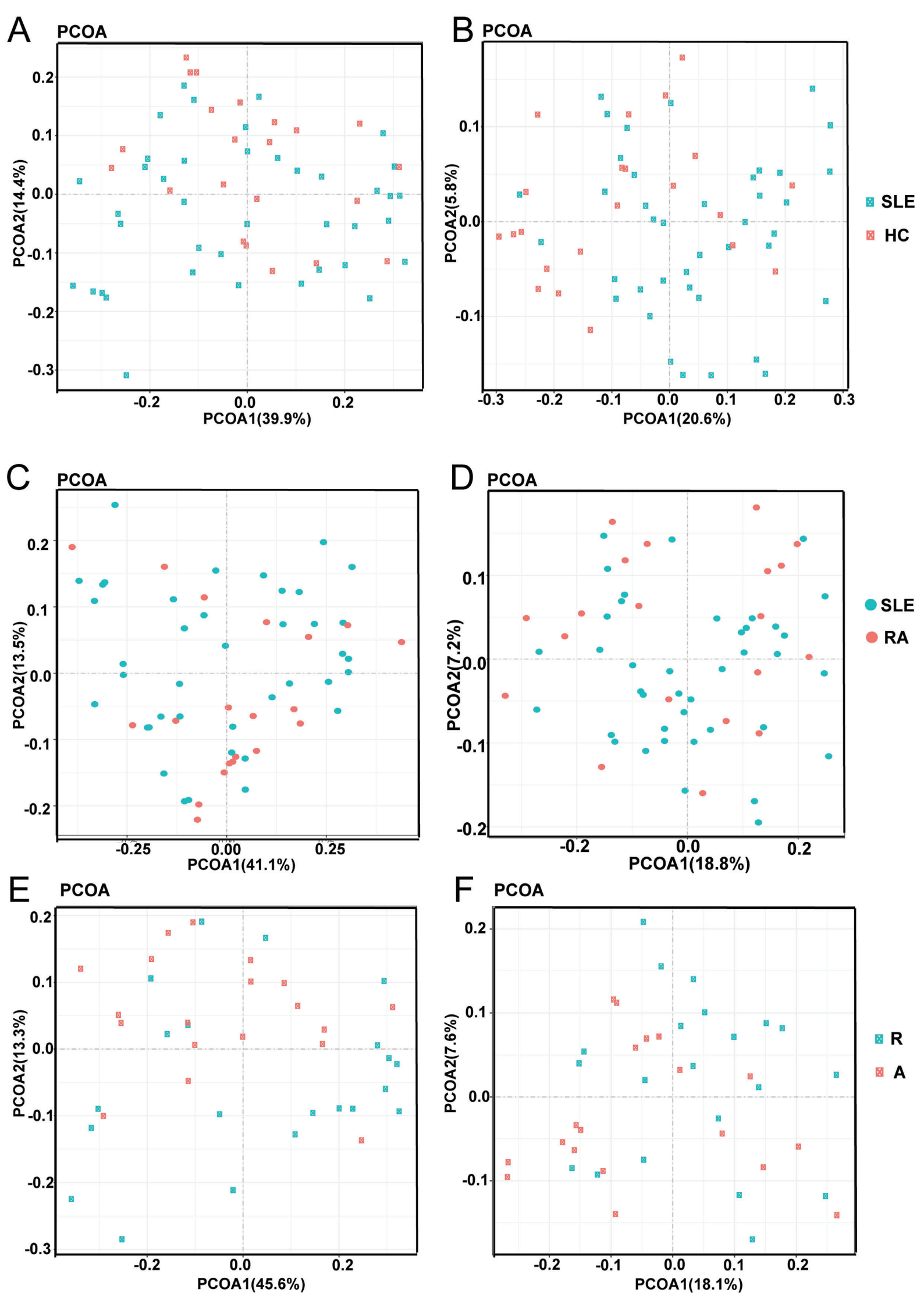

Rarefaction Measure: shannon
Sequences Per Sample
0
1
2
3
4
5
6
7
0
10000
20000
30000
40000
50000
60000

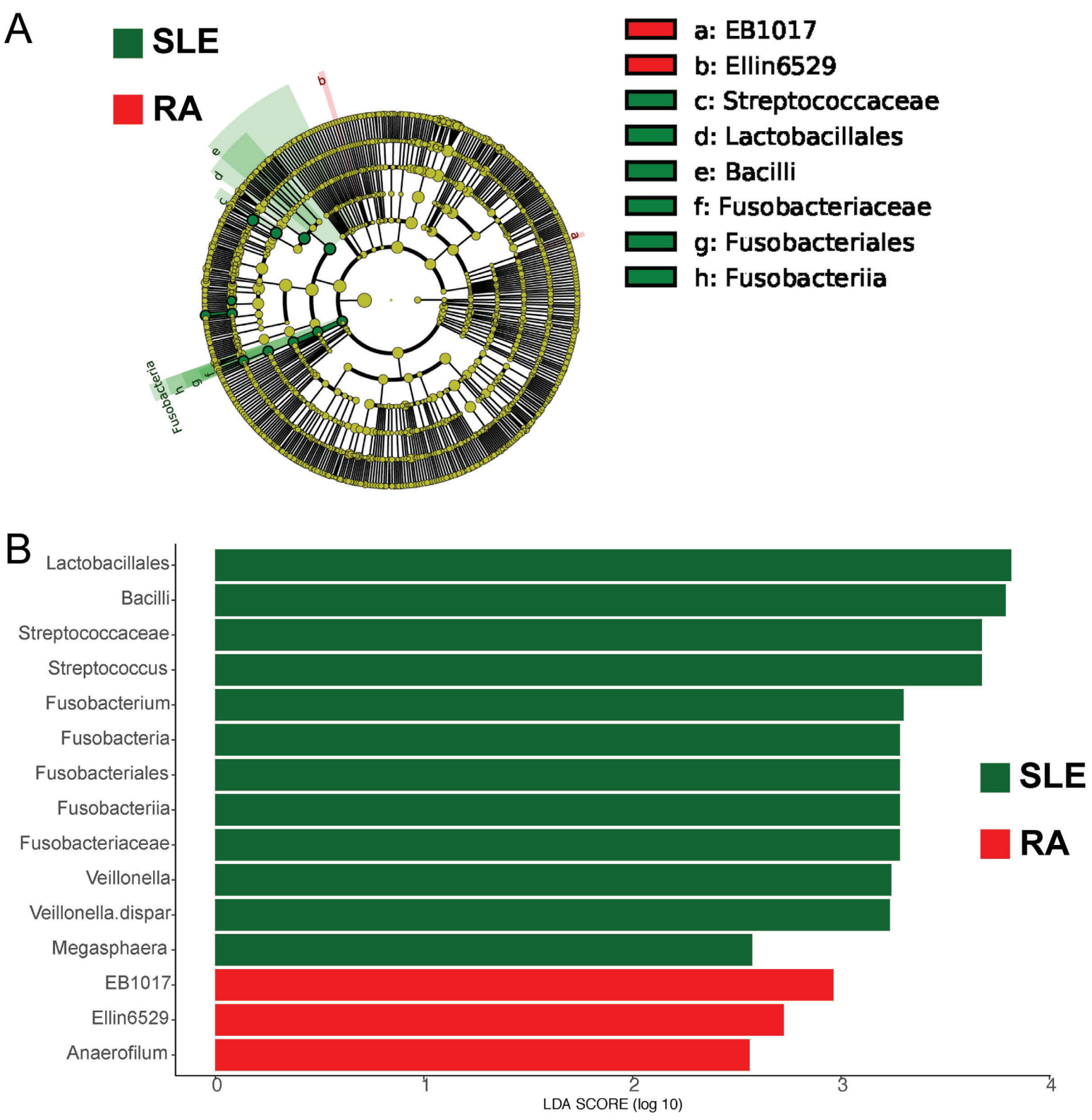
C


Relative abundance
Species rank
10^{-1}
10^{-2}
10^{-3}
10^{-4}
0
100
200
300
400
500


observed species
P = 0.392
Y
N
Hydroxychloroquine
observed species
P = 0.406
Y
N
Glucocorticoid
observed species
P = 0.874
Y
N
Cyclophosphamide
observed species
P = 0.274
Y
N
Biological agent
shannon index
P = 0.614
Y
N
Hydroxychloroquine
shannon index
P = 0.057
Y
N
Glucocorticoid
shannon index
P = 0.488
Y
N
Cyclophosphamide
shannon index
P = 0.732
Y
N
Biological agent


A
PCOA
PCOA2(14.4%)
PCOA1(39.9%)
B
PCOA
PCOA2(5.8%)
PCOA1(20.6%)
SLE
HC
C
PCOA
PCOA2(13.5%)
PCOA1(41.1%)
D
PCOA
PCOA2(7.2%)
PCOA1(18.8%)
SLE
RA
E
PCOA
PCOA2(13.3%)
PCOA1(45.6%)
F
PCOA
PCOA2(7.6%)
PCOA1(18.1%)
R
A


A
PCOA
PCOA2(14.4%)
PCOA1(39.9%)
B
PCOA
PCOA2(5.8%)
PCOA1(20.6%)
SLE
HC
C
PCOA
PCOA2(13.5%)
PCOA1(41.1%)
D
PCOA
PCOA2(7.2%)
PCOA1(18.8%)
SLE
RA
E
PCOA
PCOA2(13.3%)
PCOA1(45.6%)
F
PCOA
PCOA2(7.6%)
PCOA1(18.1%)
R
A


A
SLE
RA
a: EB1017
b: Ellin6529
c: Streptococcaceae
d: Lactobacillales
e: Bacilli
f: Fusobacteriaceae
g: Fusobacteriales
h: Fusobacteriia
B
Lactobacillales
Bacilli
Streptococcaceae
Streptococcus
Fusobacterium
Fusobacteria
Fusobacteriales
Fusobacteriia
Fusobacteriaceae
Veillonella
Veillonella.dispar
Megasphaera
EB1017
Ellin6529
Anaerofilum
0
1
2
3
4
LDA SCORE (log 10)
SLE
RA

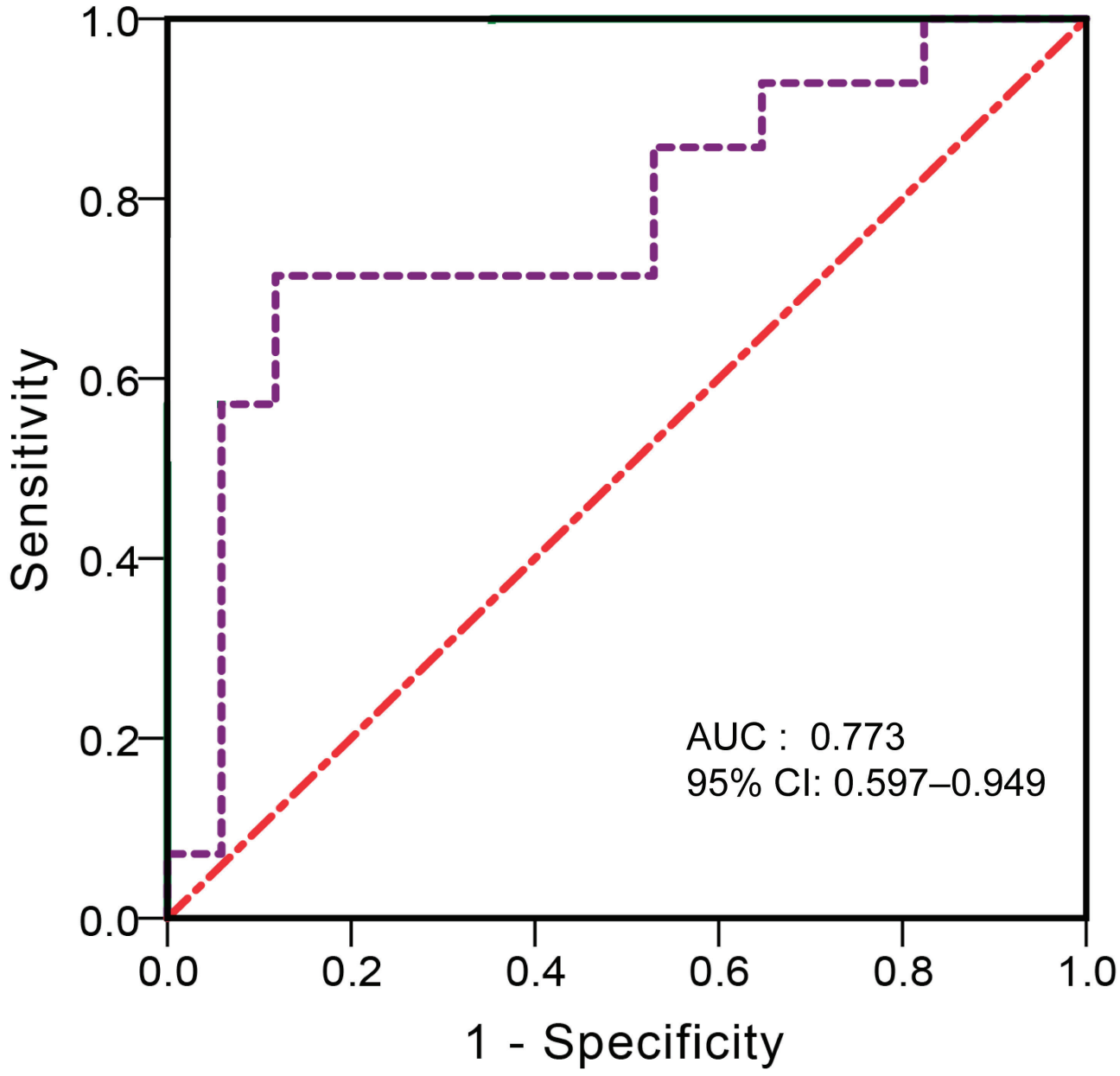

1.0
0.8
0.6
0.4
0.2
0.0
Sensitivity
0.0
0.2
0.4
0.6
0.8
1.0
1 - Specificity
AUC : 0.773
95% CI: 0.597–0.949

Table S1: The comparison of α-diversity among different groups.

	SLE	HC	P-value
Chao1	325.7	363.4	0.038*
Observed species	269	314.5	0.004**
Shannon index	5.043	5.202	0.089
Simpson index	0.931	0.948	0.092
	SLE	RA	P-value
Chao1	325.7	288.5	0.326
Observed species	269	216	0.324
Shannon index	5.043	4.643	0.493
Simpson index	0.931	0.920	0.629
	A	R	P-value
Chao1	351.7	303.1	0.123
Observed species	300	251	0.092
Shannon index	5.244	4.871	0.359
Simpson index	0.931	0.924	0.663

SLE, Systemic lupus erythematosus patients; HC, healthy controls; RA, Rheumatoid Arthritis patients; A, the active SLE patients; R, the remissive SLE patients. The Wilcoxon rank sum test was used to determine significance in α-diversity. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

Table S2: The comparison of β-diversity among different medicine treatments in SLE patients.

Group		F. Modle	R2	P-value
Hydroxychloroquine VS no Hydroxychloroquine	weighted UniFrac	1.55	0.039	0.143
	Unweighted UniFrac	1.081	0.028	0.317
Glucocorticoid VS no Hydroxychloroquine	weighted UniFrac	0.657	0.017	0.647
	Unweighted UniFrac	1.3	0.033	0.129
Cyclophosphamide VS no Cyclophosphamide	weighted UniFrac	1.315	0.033	0.208
	Unweighted UniFrac	0.695	0.018	0.908
Biological agent VS no Biological agent	weighted UniFrac	0.155	0.004	0.996
	Unweighted UniFrac	0.857	0.022	0.672

SLE, Systemic lupus erythematosus patients. The ADONIS analysis was used to determine significance in β-diversity.

Table S3: The comparison of β-diversity among different groups.

Group		F. Modle	R^2	P-value
SLE - HC	Unweighted UniFrac	3.406	0.054	0.000^{***}
	Weighted UniFrac	1.705	0.028	0.132
SLE - RA	Unweighted UniFrac	1.271	0.021	0.143
	Weighted UniFrac	0.993	0.017	0.399
A -R	Unweighted UniFrac	1.549	0.039	0.047^{*}
	Weighted UniFrac	2.532	0.062	0.037^{*}

SLE, Systemic lupus erythematosus patients; HC, healthy controls; RA, Rheumatoid Arthritis patients; A, the active SLE patients; R, the remissive SLE patients. The ADONIS analysis was used to determine significance in β-diversity. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

Table S4: The comparison of *Firmicutes*/*Bacteroidetes* ratio (F/B) between different groups.

F/B	SLE	HC	P-value
	2.471	2.661	0.666
	A	HC	P-value
	3.907	2.661	0.549
	R	HC	P-value
	1.341	2.661	0.200

F/B, *Firmicutes*/*Bacteroidetes* ratio; SLE, Systemic lupus erythematosus patients; HC, healthy controls; RA, Rheumatoid Arthritis patients; A, the active SLE patients; R, the remissive SLE patients. The Wilcoxon rank sum test was used to determine significance.

Table S5: Association of disordered genera and aberrant microbiome-associated pathway with activity of SLE.

Genus and species levels	CRP		SLEDAI		ESR		C3		dsDNA	
	r	FDR q-value	r	FDR q-value	r	FDR q-value	r	FDR q-value	r	FDR q-value
Lactobacillus	0.089	0.676	0.054	0.810	0.397	0.056	-0.039	0.893	-0.127	0.725
Streptococcus	0.098	0.676	0.492	0.008**	0.370	0.056	-0.502	0.008**	-0.118	0.725
Megasphaera	-0.150	0.676	0.166	0.409	0.052	0.796	-0.123	0.674	0.079	0.838
Fusobacterium	-0.148	0.676	0.076	0.770	-0.042	0.796	0.305	0.168	0.059	0.860
Veillonella	0.088	0.676	0.223	0.250	0.078	0.760	-0.475	0.008**	-0.115	0.725
Oribacterium	0.325	0.492	0.282	0.186	0.102	0.760	-0.137	0.674	0.022	0.893
Campylobacter	0.038	0.818	0.470	0.009**	0.423	0.056	-0.201	0.427	-0.114	0.725
Bifidobacterium	0.121	0.676	-0.511	0.008**	-0.217	0.358	0.009	0.954	-0.038	0.889
mucosae	0.099	0.676	0.001	0.994	0.370	0.056	0.038	0.893	-0.228	0.725
anginosus	0.104	0.676	0.388	0.040*	0.244	0.311	-0.253	0.275	-0.130	0.725
dispar	0.081	0.676	0.237	0.242	0.082	0.760	-0.473	0.008**	-0.122	0.725
gnavus	0.106	0.676	-0.257	0.218	-0.130	0.726	-0.087	0.792	0.117	0.725

Pathway	CRP		SLEDAI		ESR		C3		dsDNA	
	r	FDR q-value	r	FDR q-value	r	FDR q-value	r	FDR q-value	r	FDR q-value
Synthesis and degradation of ketone bodies	-0.003	0.968	0.464	0.655	0.329	0.635	-0.096	0.010*	-0.137	0.670
Alanine aspartate and glutamate metabolism	-0.234	0.511	-0.367	0.000***	-0.253	0.000***	0.195	0.154	0.126	0.670
Apoptosis	0.037	0.724	0.451	0.655	0.414	0.635	-0.236	0.601	-0.117	0.328
Lipid metabolism	-0.076	0.724	0.318	0.001**	0.243	0.001**	-0.175	0.639	0.108	0.818
Primary bile acid	-0.172	0.850	-0.371	0.655	-0.196	0.635	0.137	0.927	0.144	0.670

biosynthesis										
Secondary bile acid biosynthesis	-0.196	0.511	-0.382	0.000***	-0.186	0.000***	0.125	0.269	0.131	0.670
Secretion system	0.034	0.450	0.375	0.012*	0.295	0.014*	0.040	0.089	-0.153	0.670
Staphylococcus aureus infection	0.179	0.724	0.420	0.232	0.360	0.225	-0.462	0.002**	-0.187	0.670

SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; C3, Complement component 3; CRP, C-reactive protein; ESR, Erythrocyte Sedimentation Rate; Anti-dsDNA, anti-double stranded DNA. They were analyzed by Spearman ranks tests; False discovery rate (FDR) correction for multiple comparisons was employed; the False Discovery Rate q-value was then calculated (r coefficient and FDR q-value were indicated for each parameter). $^{*}q < 0.05$; $^{**}q < 0.01$; $^{***}q < 0.001$.

.

Table S6: The importance of genus and species in the random forests model to distinguish the SLE patients from healthy controls and RA patients.

Genus and species levels	HC and RA (importance)	SLE (importance)	Model	Field
Bacteria.Firmicutes.Bacilli.Lactobacillales.Lactobacillaceae.Lactobacillus.mucosae	100	100	rf	group
NA	NA	NA	rf	group
Bacteria.Firmicutes.Bacilli.Lactobacillales.Lactobacillaceae.Lactobacillus	88.85409372	88.85409372	rf	group
NA.1	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Veillonellaceae.Acidaminococcus	88.68289399	88.68289399	rf	group
NA.2	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Ruminococcaceae.Faecalibacterium	86.97736331	86.97736331	rf	group
NA.3	NA	NA	rf	group
Bacteria.Fusobacteria.Fusobacteriia.Fusobacteriales.Fusobacteriaceae.Fusobacterium	84.8349689	84.8349689	rf	group
NA.4	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Lachnospiraceae.[Ruminococcus].gnavus	71.90878315	71.90878315	rf	group
NA.5	NA	NA	rf	group
Bacteria.Actinobacteria.Actinobacteria.Bifidobacteriales.Bifidobacteriaceae.Scardovia	68.46093202	68.46093202	rf	group
NA.6	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Veillonellaceae.Megasphaera	68.05296209	68.05296209	rf	group
NA.7	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Veillonellaceae.Veillonella	67.60858273	67.60858273	rf	group
NA.8	NA	NA	rf	group
Bacteria.Firmicutes.Bacilli.Lactobacillales.Streptococcaceae.Streptococcus	65.97768935	65.97768935	rf	group
NA.9	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Ruminococcaceae.Oscillospira	64.0312026	64.0312026	rf	group
NA.10	NA	NA	rf	group

Bacteria.Actinobacteria.Coriobacteriia.Coriobacteriales.Coriobacteriaceae.Atopobium	63.99564483	63.99564483	rf	group
NA.11	NA	NA	rf	group
Bacteria.Actinobacteria.Actinobacteria.Bifidobacteriales.Bifidobacteriaceae.Bifidobacterium.adolescentis	59.45545463	59.45545463	rf	group
NA.12	NA	NA	rf	group
Bacteria.Firmicutes.Bacilli.Lactobacillales.Streptococcaceae.Streptococcus.anginosus	57.46571436	57.46571436	rf	group
NA.13	NA	NA	rf	group
Bacteria.Proteobacteria.Gammaproteobacteria.Alteromonadales.Shewanellaceae.Shewanella	57.22999146	57.22999146	rf	group
NA.14	NA	NA	rf	group
Bacteria.Proteobacteria.Gammaproteobacteria.Vibrionales.Vibrionaceae.Vibrio	57.17790843	57.17790843	rf	group
NA.15	NA	NA	rf	group
Bacteria.Firmicutes.Bacilli.Lactobacillales.Lactobacillaceae.Lactobacillus.ruminis	56.0413187	56.0413187	rf	group
NA.16	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Lachnospiraceae.Epulopiscium	55.22378743	55.22378743	rf	group
NA.17	NA	NA	rf	group
Bacteria.Proteobacteria.Gammaproteobacteria.Pasteurellales.Pasteurellaceae.Aggregatibacter	52.88839954	52.88839954	rf	group
NA.18	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.[Mogibacteriaceae].Mogibacterium	52.54622762	52.54622762	rf	group
NA.19	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Lachnospiraceae.Coprococcus	52.25074908	52.25074908	rf	group
NA.20	NA	NA	rf	group
Bacteria.Firmicutes.Bacilli.Lactobacillales.Leuconostocaceae.Leuconostoc	50.3798187	50.3798187	rf	group
NA.21	NA	NA	rf	group
Bacteria.Actinobacteria.Actinobacteria.Bifidobacteriales.Bifidobacteriaceae.Bifidobacterium.longum	49.80819378	49.80819378	rf	group
NA.22	NA	NA	rf	group
Bacteria.Proteobacteria.Gammaproteobacteria.Pasteurellales.Pasteurellaceae.Haemophilus.parainfluenzae	49.58079343	49.58079343	rf	group

NA.23	NA	NA	rf	group
Bacteria.Bacteroidetes.Bacteroidia.Bacteroidales.Bacteroidaceae.Bacteroides.coprophilus	47.65558031	47.65558031	rf	group
NA.24	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.[Tissierellaceae].Anaerococcus	46.82957796	46.82957796	rf	group
NA.25	NA	NA	rf	group
Bacteria.Firmicutes.Bacilli.Lactobacillales.Streptococcaceae.Lactococcus.garvieae	45.52283009	45.52283009	rf	group
NA.26	NA	NA	rf	group
Bacteria.Firmicutes.Bacilli.Lactobacillales.Enterococcaceae.Enterococcus.cecorum	44.32467961	44.32467961	rf	group
NA.27	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Veillonellaceae.Phascolarctobacterium	43.74564786	43.74564786	rf	group
NA.28	NA	NA	rf	group
Bacteria.Actinobacteria.Actinobacteria.Actinomycetales.Micrococcaceae.Arthrobacter	42.44845749	42.44845749	rf	group
NA.29	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Lachnospiraceae.Moryella	42.42318053	42.42318053	rf	group
NA.30	NA	NA	rf	group
Bacteria.Proteobacteria.Gammaproteobacteria.Vibrionales.Vibrionaceae.Photobacterium	42.26698874	42.26698874	rf	group
NA.31	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Veillonellaceae.Veillonella.parvula	41.89619119	41.89619119	rf	group
NA.32	NA	NA	rf	group
Bacteria.Actinobacteria.Actinobacteria.Actinomycetales.Corynebacteriaceae.Corynebacterium	40.86771112	40.86771112	rf	group
NA.33	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Lachnospiraceae.Lachnospira	40.79412299	40.79412299	rf	group
NA.34	NA	NA	rf	group
Bacteria.Actinobacteria.Actinobacteria.Bifidobacteriales.Bifidobacteriaceae.Bifidobacterium	40.21416926	40.21416926	rf	group
NA.35	NA	NA	rf	group
Bacteria.Actinobacteria.Coriobacteriia.Coriobacteriales.Coriobact	39.8194	39.819	rf	group

eriaceae.Collinsella	3692	43692		
NA.36	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Veillonellaceae.Megamonas	39.81183832	39.81183832	rf	group
NA.37	NA	NA	rf	group
Bacteria.Actinobacteria.Actinobacteria.Actinomycetales.Micrococcaceae.Rothia.mucilaginosa	39.23986869	39.23986869	rf	group
NA.38	NA	NA	rf	group
Bacteria.Firmicutes.Bacilli.Lactobacillales.Carnobacteriaceae.Granulicatella	38.9446691	38.9446691	rf	group
NA.39	NA	NA	rf	group
Bacteria.Proteobacteria.Gammaproteobacteria.Pasteurellales.Pasteurellaceae.Aggregatibacter.pneumotropica	38.75869962	38.75869962	rf	group
NA.40	NA	NA	rf	group
Bacteria.Firmicutes.Erysipelotrichi.Erysipelotrichales.Erysipelotrichaceae.[Eubacterium]	38.49916132	38.49916132	rf	group
NA.41	NA	NA	rf	group
Bacteria.Proteobacteria.Gammaproteobacteria.Enterobacteriales.Enterobacteriaceae.Enterobacter	38.41667038	38.41667038	rf	group
NA.42	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Lachnospiraceae.Coprococcus.eutactus	38.40812124	38.40812124	rf	group
NA.43	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Veillonellaceae.Pectinatus	38.0030853	38.0030853	rf	group
NA.44	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Ruminococcaceae.Ruminococcus	37.58584095	37.58584095	rf	group
NA.45	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Lachnospiraceae.[Ruminococcus]	37.37462973	37.37462973	rf	group
NA.46	NA	NA	rf	group
Bacteria.Firmicutes.Bacilli.Bacillales.Staphylococcaceae.Staphylococcus.sciuri	37.33989497	37.33989497	rf	group
NA.47	NA	NA	rf	group
Bacteria.Actinobacteria.Actinobacteria.Bifidobacteriales.Bifidobacteriaceae.Bifidobacterium.pseudolongum	37.07949274	37.07949274	rf	group
NA.48	NA	NA	rf	group

Bacteria.Proteobacteria.Gammaproteobacteria.Pseudomonadales.Moraxellaceae.Acinetobacter.rhizosphaerae	36.63366509	36.63366509	rf	group
NA.49	NA	NA	rf	group
Bacteria.Bacteroidetes.Bacteroidia.Bacteroidales.[Odoribacteraceae].Butyricimonas	36.0353703	36.0353703	rf	group
NA.50	NA	NA	rf	group
Bacteria.Firmicutes.Bacilli.Lactobacillales.Streptococcaceae.Streptococcus.sobrinus	36.00237768	36.00237768	rf	group
NA.51	NA	NA	rf	group
Bacteria.Actinobacteria.Actinobacteria.Actinomycetales.Micrococcaceae.Rothia.dentocariosa	35.88981106	35.88981106	rf	group
NA.52	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Lachnospiraceae.Lachnobacterium	35.55457379	35.55457379	rf	group
NA.53	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Clostridiaceae.Clostridium.neonatale	35.28042355	35.28042355	rf	group
NA.54	NA	NA	rf	group
Bacteria.Firmicutes.Bacilli.Lactobacillales.Lactobacillaceae.Lactobacillus.zeae	35.25260325	35.25260325	rf	group
NA.55	NA	NA	rf	group
Bacteria.Proteobacteria.Gammaproteobacteria.Pasteurellales.Pasteurellaceae.Aggregatibacter.segnis	34.9841941	34.9841941	rf	group
NA.56	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Veillonellaceae.Dialister	34.83681098	34.83681098	rf	group
NA.57	NA	NA	rf	group
Bacteria.Proteobacteria.Deltaproteobacteria.Desulfovibrionales.Desulfovibrionaceae.Bilophila	34.39921159	34.39921159	rf	group
NA.58	NA	NA	rf	group
Bacteria.Firmicutes.Erysipelotrichi.Erysipelotrichales.Erysipelotrichaceae.Catenibacterium	34.31245602	34.31245602	rf	group
NA.59	NA	NA	rf	group
Bacteria.Bacteroidetes.Bacteroidia.Bacteroidales.Porphyromonadaceae.Parabacteroides.distasonis	33.83134522	33.8313 34522	rf	group
NA.60	NA	NA	rf	group
Bacteria.Proteobacteria.Gammaproteobacteria.Enterobacteriales.Enterobacteriaceae.Proteus	33.74981453	33.74981453	rf	group

NA.61	NA	NA	rf	group
Bacteria.Proteobacteria.Gammaproteobacteria.Enterobacteriales.Enterobacteriaceae.Morganella.morganii	33.25013725	33.25013725	rf	group
NA.62	NA	NA	rf	group
Bacteria.Firmicutes.Bacilli.Lactobacillales.Aerococcaceae.Abiotrophia	33.05906176	33.05906176	rf	group
NA.63	NA	NA	rf	group
Bacteria.Actinobacteria.Actinobacteria.Actinomycetales.Corynebacteriaceae.Corynebacterium.variabile	33.01262432	33.01262432	rf	group
NA.64	NA	NA	rf	group
Bacteria.Bacteroidetes.Bacteroidia.Bacteroidales.Prevotellaceae.Prevotella.copri	32.80675676	32.80675676	rf	group
NA.65	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.[Tissierellaceae].Parvimonas	32.25837793	32.25837793	rf	group
NA.66	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Lachnospiraceae.Roseburia.faecis	31.60298925	31.60298925	rf	group
NA.67	NA	NA	rf	group
Bacteria.Firmicutes.Erysipelotrichi.Erysipelotrichales.Erysipelotrichaceae.[Eubacterium].cylindroides	31.51728508	31.51728508	rf	group
NA.68	NA	NA	rf	group
Bacteria.Proteobacteria.Gammaproteobacteria.Enterobacteriales.Enterobacteriaceae.Serratia	31.4975089	31.4975089	rf	group
NA.69	NA	NA	rf	group
Bacteria.Proteobacteria.Betaproteobacteria.Burkholderiales.Alcaligenaceae.Sutterella	30.73488424	30.73488424	rf	group
NA.70	NA	NA	rf	group
Bacteria.Proteobacteria.Betaproteobacteria.Burkholderiales.Burkholderiaceae.Lautropia	30.14684743	30.14684743	rf	group
NA.71	NA	NA	rf	group
Bacteria.Proteobacteria.Betaproteobacteria.Burkholderiales.Oxalobacteraceae.Oxalobacter.formigenes	30.04022971	30.04022971	rf	group
NA.72	NA	NA	rf	group
Bacteria.Actinobacteria.Coriobacteriia.Coriobacteriales.Coriobacteriaceae.Adlercreutzia	29.73669898	29.73669898	rf	group
NA.73	NA	NA	rf	group
Bacteria.Bacteroidetes.Bacteroidia.Bacteroidales.Porphyromonad	29.4897	29.489	rf	group

aceae.Porphyromonas	9366	79366		
NA.74	NA	NA	rf	group
Bacteria.Verrucomicrobia.Verrucomicrobiae.Verrucomicrobiales.Verrucomicrobiaceae.Akkermansia.muciniphila	29.43843701	29.43843701	rf	group
NA.75	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Clostridiaceae.Clostridium	29.39924741	29.39924741	rf	group
NA.76	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.[Tissierellaceae].Peptoniphilus	29.30587477	29.30587477	rf	group
NA.77	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Clostridiaceae.SMB53	29.29678578	29.29678578	rf	group
NA.78	NA	NA	rf	group
Bacteria.Firmicutes.Bacilli.Turicibacterales.Turicibacteraceae.Turicibacter	29.06865286	29.06865286	rf	group
NA.79	NA	NA	rf	group
Bacteria.Bacteroidetes.Bacteroidia.Bacteroidales.[Paraprevotellaceae].Paraprevotella	29.0013282	29.0013282	rf	group
NA.80	NA	NA	rf	group
Bacteria.Proteobacteria.Betaproteobacteria.Burkholderiales.Comamonadaceae.Comamonas	28.60421255	28.60421255	rf	group
NA.81	NA	NA	rf	group
Bacteria.Firmicutes.Erysipelotrichi.Erysipelotrichales.Erysipelotrichaceae.Coprobacillus	28.44111353	28.44111353	rf	group
NA.82	NA	NA	rf	group
Bacteria.Bacteroidetes.Bacteroidia.Bacteroidales.Bacteroidaceae.Bacteroides.acidifaciens	28.30507096	28.30507096	rf	group
NA.83	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Peptostreptococcaceae.Peptostreptococcus	27.83946022	27.83946022	rf	group
NA.84	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Lachnospiraceae.Roseburia	26.9286069	26.9286069	rf	group
NA.85	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Lachnospiraceae.Oribacterium	26.87897591	26.87897591	rf	group
NA.86	NA	NA	rf	group

Bacteria.Firmicutes.Clostridia.Clostridiales.Veillonellaceae.Megamonas.hypermegale	26.68164863	26.68164863	rf	group
NA.87	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Lachnospiraceae.[Ruminococcus].torques	26.64962874	26.6496 2874	rf	group
NA.88	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Clostridiaceae.Clostridium.perfringens	26.28168591	26.2816 8591	rf	group
NA.89	NA	NA	rf	group
Bacteria.Bacteroidetes.Bacteroidia.Bacteroidales.Bacteroidaceae.Bacteroides.caccae	26.00655196	26.0065 5196	rf	group
NA.90	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Eubacteriaceae.Pseudoramibacter_Eubacterium	26.00646297	26.0064 6297	rf	group
NA.91	NA	NA	rf	group
Bacteria.Actinobacteria.Coriobacteriia.Coriobacteriales.Coriobacteriaceae.Eggerthella.lenta	25.91425774	25.9142 5774	rf	group
NA.92	NA	NA	rf	group
Bacteria.Firmicutes.Erysipelotrichi.Erysipelotrichales.Erysipelotrichaceae.Bulleidia	25.79082525	25.7908 2525	rf	group
NA.93	NA	NA	rf	group
Bacteria.Bacteroidetes.Bacteroidia.Bacteroidales.Bacteroidaceae.Bacteroides.uniformis	25.76792493	25.7679 2493	rf	group
NA.94	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Lachnospiraceae.Anaerostipes	25.30478209	25.3047 8209	rf	group
NA.95	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Lachnospiraceae.Blautia	25.23880196	25.2388 0196	rf	group
NA.96	NA	NA	rf	group
Bacteria.Proteobacteria.Gammaproteobacteria.Pseudomonadales.Pseudomonadaceae.Pseudomonas	25.16469872	25.1646 9872	rf	group
NA.97	NA	NA	rf	group
Bacteria.Bacteroidetes.Bacteroidia.Bacteroidales.Bacteroidaceae.Bacteroides	24.84664938	24.8466 4938	rf	group
NA.98	NA	NA	rf	group
Bacteria.Actinobacteria.Actinobacteria.Actinomycetales.Corynebacteriaceae.Corynebacterium.durum	24.83633268	24.8363 3268	rf	group

NA.99	NA	NA	rf	group
Bacteria.Actinobacteria.Coriobacteriia.Coriobacteriales.Coriobacteriaceae.Collinsella.aerofaciens	24.64074462	24.64074462	rf	group
NA.100	NA	NA	rf	group
Bacteria.Proteobacteria.Deltaproteobacteria.Desulfovibrionales.Desulfovibrionaceae.Desulfovibrio	24.38252099	24.38252099	rf	group
NA.101	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Christensenellaceae.Christensenella	24.13263095	24.13263095	rf	group
NA.102	NA	NA	rf	group
Bacteria.Proteobacteria.Epsilonproteobacteria.Campylobacterales.Campylobacteraceae.Campylobacter	24.1198909	24.1198909	rf	group
NA.103	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.[Tissierellaceae].WAL_1855D	23.81380153	23.81380153	rf	group
NA.104	NA	NA	rf	group
Bacteria.Firmicutes.Erysipelotrichi.Erysipelotrichales.Erysipelotrichaceae.Holdemania	23.65007397	23.65007397	rf	group
NA.105	NA	NA	rf	group
Bacteria.Firmicutes.Erysipelotrichi.Erysipelotrichales.Erysipelotrichaceae.cc_115	23.52060571	23.52060571	rf	group
NA.106	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.[Tissierellaceae].Finegoldia	23.21877036	23.21877036	rf	group
NA.107	NA	NA	rf	group
Bacteria.Actinobacteria.Actinobacteria.Actinomycetales.Micrococcaceae.Rothia.aeria	22.46201986	22.46201986	rf	group
NA.108	NA	NA	rf	group
Bacteria.Firmicutes.Erysipelotrichi.Erysipelotrichales.Erysipelotrichaceae.[Eubacterium].dolichum	22.45830272	22.45830272	rf	group
NA.109	NA	NA	rf	group
Bacteria.Bacteroidetes.Bacteroidia.Bacteroidales.Bacteroidaceae.Bacteroides.fragilis	22.12062078	22.12062078	rf	group
NA.110	NA	NA	rf	group
Bacteria.Bacteroidetes.Bacteroidia.Bacteroidales.Bacteroidaceae.Bacteroides.ovatus	22.00843585	22.00843585	rf	group
NA.111	NA	NA	rf	group
Bacteria.Actinobacteria.Actinobacteria.Actinomycetales.Actinom	21.8661	21.866	rf	group

ycetaceae.Actinomyces	1256	11256		
NA.112	NA	NA	rf	group
Bacteria.Synergistetes.Synergistia.Synergistales.Dethiosulfovibrionaceae.Pyramidobacter.piscolens	21.53403295	21.53403295	rf	group
NA.113	NA	NA	rf	group
Bacteria.Actinobacteria.Actinobacteria.Actinomycetales.Propionibacteriaceae.Propionibacterium.acnes	21.25019523	21.25019523	rf	group
NA.114	NA	NA	rf	group
Bacteria.Bacteroidetes.Bacteroidia.Bacteroidales.Prevotellaceae.Prevotella.stercorea	20.79841373	20.79841373	rf	group
NA.115	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Lachnospiraceae.Dorea.formicigenerans	19.96870781	19.96870781	rf	group
NA.116	NA	NA	rf	group
Bacteria.Fusobacteria.Fusobacteriia.Fusobacteriales.Fusobacteriaceae.Cetobacterium	19.69570239	19.69570239	rf	group
NA.117	NA	NA	rf	group
Bacteria.Proteobacteria.Gammaproteobacteria.Enterobacteriales.Enterobacteriaceae.Citrobacter	18.40984322	18.40984322	rf	group
NA.118	NA	NA	rf	group
Bacteria.Proteobacteria.Betaproteobacteria.Neisseriales.Neisseriaceae.Neisseria	18.39872368	18.39872368	rf	group
NA.119	NA	NA	rf	group
Bacteria.Bacteroidetes.Bacteroidia.Bacteroidales.[Odoribacteraceae].Odoribacter	18.3464621	18.34644621	rf	group
NA.120	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Dehalobacteriaceae.Dehalobacterium	18.27854652	18.27854652	rf	group
NA.121	NA	NA	rf	group
Bacteria.Proteobacteria.Gammaproteobacteria.Enterobacteriales.Enterobacteriaceae.Klebsiella	18.25734312	18.25734312	rf	group
NA.122	NA	NA	rf	group
Bacteria.Actinobacteria.Coriobacteriia.Coriobacteriales.Coriobacteriaceae.Slackia	18.24343874	18.24343874	rf	group
NA.123	NA	NA	rf	group
Bacteria.Bacteroidetes.Bacteroidia.Bacteroidales.[Paraprevotellaceae].CF231	17.72801522	17.72801522	rf	group
NA.124	NA	NA	rf	group

Bacteria.Actinobacteria.Coriobacteriia.Coriobacteriales.Coriobacteriaceae.Collinsella.stercoris	17.36284412	17.36284412	rf	group
NA.125	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Veillonellaceae.Selenomonas	16.70418065	16.70418065	rf	group
NA.126	NA	NA	rf	group
Bacteria.Actinobacteria.Actinobacteria.Bifidobacteriales.Bifidobacteriaceae.Bombiscardovia	16.63243517	16.63243517	rf	group
NA.127	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Peptococcaceae.Peptococcus	16.52592837	16.52592837	rf	group
NA.128	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Lachnospiraceae.Blautia.producta	15.10781489	15.10781489	rf	group
NA.129	NA	NA	rf	group
Bacteria.Bacteroidetes.Bacteroidia.Bacteroidales.Bacteroidaceae.Bacteroides.eggerthii	14.75118964	14.75118964	rf	group
NA.130	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Lachnospiraceae.Dorea	14.24703583	14.24703583	rf	group
NA.131	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Ruminococcaceae.Anaerotruncus	13.33263207	13.33263207	rf	group
NA.132	NA	NA	rf	group
Bacteria.Bacteroidetes.Bacteroidia.Bacteroidales.Bacteroidaceae.Bacteroides.barnesiae	12.95960718	12.95960718	rf	group
NA.133	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Ruminococcaceae.Ruminococcus.bromii	12.51076103	12.51076103	rf	group
NA.134	NA	NA	rf	group
Bacteria.Firmicutes.Erysipelotrichi.Erysipelotrichales.Erysipelotrichaceae.Clostridium	11.837976	11.837976	rf	group
NA.135	NA	NA	rf	group
Bacteria.Proteobacteria.Gammaproteobacteria.Enterobacteriales.Enterobacteriaceae.Erwinia	11.76211028	11.76211028	rf	group
NA.136	NA	NA	rf	group
Bacteria.Proteobacteria.Alphaproteobacteria.Rhizobiales.Rhizobiaceae.Rhizobium.leguminosarum	11.44238598	11.44238598	rf	group

NA.137	NA	NA	rf	group
Bacteria.Proteobacteria.Alphaproteobacteria.Rhodobacterales.Rhodobacteraceae.Paracoccus	10.96709042	10.96709042	rf	group
NA.138	NA	NA	rf	group
Bacteria.Firmicutes.Bacilli.Bacillales.Bacillaceae.Bacillus	10.94995981	10.94995981	rf	group
NA.139	NA	NA	rf	group
Bacteria.Proteobacteria.Gammaproteobacteria.Pasteurellales.Pasteurellaceae.Actinobacillus.parahaemolyticus	5.848371674	5.848371674	rf	group
NA.140	NA	NA	rf	group
Bacteria.Bacteroidetes.Bacteroidia.Bacteroidales.Porphyromonadaceae.Parabacteroides.gordonii	0	0	rf	group
NA.141	NA	NA	rf	group

SLE, Systemic lupus erythematosus patients; HC, the healthy controls; RA, Rheumatoid Arthritis patients.

Table S7: The importance of genus and species in the random forests model to distinguish the active SLE patients from remissive SLE patients.

The species and genus in the model	A	R	Model	Field
Bacteria.Proteobacteria.Epsilonproteobacteria.Campylobacterales.Campylobacteraceae.Campylobacter	100	100	rf	group
NA	NA	NA	rf	group
Bacteria.Actinobacteria.Coriobacteriia.Coriobacteriales.Coriobacteriaceae.Eggerthella.lenta	73.52938197	73.52938197	rf	group
NA.1	NA	NA	rf	group
Bacteria.Firmicutes.Bacilli.Lactobacillales.Streptococcaceae.Streptococcus	67.68391813	67.68391813	rf	group
NA.2	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Lachnospiraceae.[Ruminococcus].gnavus	63.1348269	63.1348269	rf	group
NA.3	NA	NA	rf	group
Bacteria.Actinobacteria.Actinobacteria.Bifidobacteriales.Bifidobacteriaceae.Bifidobacterium	60.08269062	60.08269062	rf	group
NA.4	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Lachnospiraceae.[Ruminococcus]	57.01375484	57.01375484	rf	group
NA.5	NA	NA	rf	group
Bacteria.Actinobacteria.Actinobacteria.Bifidobacteriales.Bifidobacteriaceae.Bifidobacterium.longum	55.72173618	55.72173618	rf	group
NA.6	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Lachnospiraceae.Oribacterium	52.49955531	52.49955531	rf	group
NA.7	NA	NA	rf	group
Bacteria.Firmicutes.Erysipelotrichi.Erysipelotrichales.Erysipelotrichaceae.[Eubacterium].dolichum	51.54641774	51.54641774	rf	group
NA.8	NA	NA	rf	gro

				up
Bacteria.Actinobacteria.Actinobacteria.Actinomycetales.Micrococcaceae.Rothia.aeria	51.03511293	51.03511293	rf	group
NA.9	NA	NA	rf	group
Bacteria.Actinobacteria.Actinobacteria.Actinomycetales.Micrococcaceae.Rothia.mucilaginosa	49.30034397	49.30034397	rf	group
NA.10	NA	NA	rf	group
Bacteria.Bacteroidetes.Bacteroidia.Bacteroidales.Bacteroidaceae.Bacteroides.barnesiae	48.41822378	48.41822378	rf	group
NA.11	NA	NA	rf	group
Bacteria.Bacteroidetes.Bacteroidia.Bacteroidales.Prevotellaceae.Prevotella.copri	46.43251718	46.43251718	rf	group
NA.12	NA	NA	rf	group
Bacteria.Bacteroidetes.Bacteroidia.Bacteroidales.Bacteroidaceae.Bacteroides.ovatus	43.1757673	43.1757673	rf	group
NA.13	NA	NA	rf	group
Bacteria.Bacteroidetes.Bacteroidia.Bacteroidales.Porphyromonadaceae.Parabacteroides.gordonii	40.1985663	40.1985663	rf	group
NA.14	NA	NA	rf	group
Bacteria.Bacteroidetes.Bacteroidia.Bacteroidales.Porphyromonadaceae.Parabacteroides.distasonis	38.72852832	38.72852832	rf	group
NA.15	NA	NA	rf	group
Bacteria.Proteobacteria.Betaproteobacteria.Neisseriales.Neisseriaceae.Neisseria.subflava	38.45308799	38.45308799	rf	group
NA.16	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Lachnospiraceae.Coprococcus.eutactus	38.06077828	38.06077828	rf	group
NA.17	NA	NA	rf	group
Bacteria.Firmicutes.Bacilli.Lactobacillales.Carnobacteriaceae.Granulicatella	36.843671	36.843671	rf	group

NA.18	NA	NA	rf	group
Bacteria.Firmicutes.Bacilli.Lactobacillales.Aerococcaceae.Facklamia	35.79144165	35.79144165	rf	group
NA.19	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Veillonellaceae.Dialister	35.6690292	35.6690292	rf	group
NA.20	NA	NA	rf	group
Bacteria.Proteobacteria.Betaproteobacteria.Neisseriales.Neisseriaceae.Neisseria	35.19798498	35.19798498	rf	group
NA.21	NA	NA	rf	group
Bacteria.Proteobacteria.Gammaproteobacteria.Enterobacteriales.Enterobacteriaceae.Citrobacter	34.49674505	34.49674505	rf	group
NA.22	NA	NA	rf	group
Bacteria.Actinobacteria.Actinobacteria.Actinomycetales.Actinomycetaceae.Actinomyces	34.46613425	34.46613425	rf	group
NA.23	NA	NA	rf	group
Bacteria.Bacteroidetes.Bacteroidia.Bacteroidales.[Odoribacteraceae].Butyricimonas	34.32334571	34.32334571	rf	group
NA.24	NA	NA	rf	group
Bacteria.Bacteroidetes.Bacteroidia.Bacteroidales.Bacteroidaceae.Bacteroides.coprophilus	34.32328296	34.32328296	rf	group
NA.25	NA	NA	rf	group
Bacteria.Firmicutes.Erysipelotrichi.Erysipelotrichales.Erysipelotrichaceae.Clostridium	34.2798772	34.2798772	rf	group
NA.26	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Lachnospiraceae.Lachnobacterium	33.48050449	33.48050449	rf	group
NA.27	NA	NA	rf	group
Bacteria.Proteobacteria.Betaproteobacteria.Burkholderiales.Comam	33.117	33.117	rf	gro

onadaceae.Comamonas	8873	8873		up
NA.28	NA	NA	rf	gro up
Bacteria.Firmicutes.Clostridia.Clostridiales.[Mogibacteriaceae].Mogibacterium	32.701 68673	32.701 68673	rf	gro up
NA.29	NA	NA	rf	gro up
Bacteria.Proteobacteria.Betaproteobacteria.Burkholderiales.Comamonadaceae.Acidovorax	31.636 28904	31.636 28904	rf	gro up
NA.30	NA	NA	rf	gro up
Bacteria.Firmicutes.Bacilli.Lactobacillales.Lactobacillaceae.Lactobacillus.ruminis	31.381 70548	31.381 70548	rf	gro up
NA.31	NA	NA	rf	gro up
Bacteria.Firmicutes.Clostridia.Clostridiales.Veillonellaceae.Veillonella.parvula	31.235 66388	31.235 66388	rf	gro up
NA.32	NA	NA	rf	gro up
Bacteria.Firmicutes.Bacilli.Lactobacillales.Streptococcaceae.Streptococcus.luteciae	30.932 3495	30.932 3495	rf	gro up
NA.33	NA	NA	rf	gro up
Bacteria.Bacteroidetes.Bacteroidia.Bacteroidales.[Paraprevotellaceae].CF231	30.560 69782	30.560 69782	rf	gro up
NA.34	NA	NA	rf	gro up
Bacteria.Firmicutes.Clostridia.Clostridiales.Lachnospiraceae.Lachnospira	30.338 19745	30.338 19745	rf	gro up
NA.35	NA	NA	rf	gro up
Bacteria.Actinobacteria.Actinobacteria.Actinomycetales.Corynebacteriaceae.Corynebacterium	29.941 54974	29.941 54974	rf	gro up
NA.36	NA	NA	rf	gro up
Bacteria.Proteobacteria.Betaproteobacteria.Burkholderiales.Alcaligenaceae.Sutterella	29.842 49298	29.842 49298	rf	gro up
NA.37	NA	NA	rf	gro up

Bacteria.Firmicutes.Bacilli.Lactobacillales.Lactobacillaceae.Lactobacillus.zeae	29.63442159	29.63442159	rf	group
NA.38	NA	NA	rf	group
Bacteria.Actinobacteria.Coriobacteriia.Coriobacteriales.Coriobacteriaceae.Collinsella.stercoris	29.02275774	29.02275774	rf	group
NA.39	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.[Tissierellaceae].Parvimonas	28.88739082	28.88739082	rf	group
NA.40	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Eubacteriaceae.Anaerofustis	28.80523234	28.80523234	rf	group
NA.41	NA	NA	rf	group
Bacteria.Bacteroidetes.Bacteroidia.Bacteroidales.Bacteroidaceae.Bacteroides.plebeius	28.7925053	28.7925053	rf	group
NA.42	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Lachnospiraceae.Anaerostipes	28.78858746	28.78858746	rf	group
NA.43	NA	NA	rf	group
Bacteria.Bacteroidetes.Bacteroidia.Bacteroidales.Prevotellaceae.Prevotella.stercorea	28.39272239	28.39272239	rf	group
NA.44	NA	NA	rf	group
Bacteria.Actinobacteria.Actinobacteria.Bifidobacteriales.Bifidobacteriaceae.Bifidobacterium.adolescentis	28.12693767	28.12693767	rf	group
NA.45	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Ruminococcaceae.Faecalibacterium	28.1115794	28.1115794	rf	group
NA.46	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Lachnospiraceae.Roseburia.faecis	27.78399522	27.78399522	rf	group
NA.47	NA	NA	rf	gro

				up
Bacteria.Firmicutes.Clostridia.Clostridiales.Clostridiaceae.SMB53	27.18079088	27.18079088	rf	group
NA.48	NA	NA	rf	group
Bacteria.Proteobacteria.Alphaproteobacteria.Rhizobiales.Bradyrhizobiaceae.Bradyrhizobium	26.8327741	26.8327741	rf	group
Bacteria.Proteobacteria.Gammaproteobacteria.Enterobacteriales.Enterobacteriaceae.Enterobacter	26.8327741	26.8327741	rf	group
NA.49	NA	NA	rf	group
NA.50	NA	NA	rf	group
Bacteria.Bacteroidetes.Bacteroidia.Bacteroidales.Bacteroidaceae.Bacteroides	26.6521353	26.6521353	rf	group
NA.51	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Lachnospiraceae.Blautia	26.4731981	26.4731981	rf	group
NA.52	NA	NA	rf	group
Bacteria.Proteobacteria.Alphaproteobacteria.Sphingomonadales.Sphingomonadaceae.Sphingomonas	25.60083609	25.60083609	rf	group
NA.53	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Lachnospiraceae.Blautia.producta	25.58321546	25.58321546	rf	group
NA.54	NA	NA	rf	group
Bacteria.Proteobacteria.Gammaproteobacteria.Pasteurellales.Pasteurellaceae.Aggregatibacter.segnis	25.38520542	25.38520542	rf	group
NA.55	NA	NA	rf	group
Bacteria.Actinobacteria.Actinobacteria.Actinomycetales.Propionibacteriaceae.Propionibacterium.acnes	25.27807469	25.27807469	rf	group
NA.56	NA	NA	rf	group
Bacteria.Proteobacteria.Gammaproteobacteria.Enterobacteriales.Enterobacteriaceae.Erwinia	25.21796039	25.21796039	rf	group

NA.57	NA	NA	rf	group
Bacteria.Firmicutes.Erysipelotrichi.Erysipelotrichales.Erysipelotrichaceae.Allobaculum	25.01462599	25.01462599	rf	group
NA.58	NA	NA	rf	group
Bacteria.Proteobacteria.Betaproteobacteria.Burkholderiales.Comamonadaceae.Delftia	24.86247222	24.86247222	rf	group
NA.59	NA	NA	rf	group
Bacteria.Firmicutes.Bacilli.Lactobacillales.Enterococcaceae.Enterococcus	24.45321906	24.45321906	rf	group
NA.60	NA	NA	rf	group
Bacteria.Fusobacteria.Fusobacteriia.Fusobacteriales.Fusobacteriaceae.Fusobacterium	24.33328104	24.33328104	rf	group
NA.61	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Christensenellaceae.Christensenella	24.23742137	24.23742137	rf	group
NA.62	NA	NA	rf	group
Bacteria.Proteobacteria.Deltaproteobacteria.Desulfovibrionales.Desulfovibrionaceae.Desulfovibrio	24.04906378	24.04906378	rf	group
NA.63	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Peptococcaceae.Peptococcus	23.58404599	23.58404599	rf	group
NA.64	NA	NA	rf	group
Bacteria.Firmicutes.Bacilli.Lactobacillales.Lactobacillaceae.Lactobacillus	23.46152666	23.46152666	rf	group
NA.65	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Lachnospiraceae.Dorea.formicigenerans	23.10278563	23.10278563	rf	group
NA.66	NA	NA	rf	group
Bacteria.Proteobacteria.Gammaproteobacteria.Cardiobacteriales.Car	22.832	22.832	rf	gro

diobacteriaceae.Cardiobacterium	39661	39661		up
NA.67	NA	NA	rf	group
Bacteria.Bacteroidetes.Bacteroidia.Bacteroidales.Porphyromonadaceae.Porphyromonas	22.74859324	22.74859324	rf	group
NA.68	NA	NA	rf	group
Bacteria.Actinobacteria.Coriobacteriia.Coriobacteriales.Coriobacteriaceae.Slackia	22.606795	22.606795	rf	group
NA.69	NA	NA	rf	group
Bacteria.Firmicutes.Erysipelotrichi.Erysipelotrichales.Erysipelotrichaceae.Coprobacillus	22.47422131	22.47422131	rf	group
NA.70	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Ruminococcaceae.Oscillospira	22.22288802	22.22288802	rf	group
NA.71	NA	NA	rf	group
Bacteria.Bacteroidetes.Bacteroidia.Bacteroidales.[Odoribacteraceae].Odoribacter	22.16867135	22.16867135	rf	group
NA.72	NA	NA	rf	group
Bacteria.Actinobacteria.Actinobacteria.Actinomycetales.Corynebacteriaceae.Corynebacterium.durum	21.98346407	21.98346407	rf	group
NA.73	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Clostridiaceae.Clostridium.neonatale	21.98240515	21.98240515	rf	group
NA.74	NA	NA	rf	group
Bacteria.Bacteroidetes.Bacteroidia.Bacteroidales.Bacteroidaceae.Bacteroides.eggerthii	21.79162676	21.79162676	rf	group
NA.75	NA	NA	rf	group
Archaea.Euryarchaeota.Methanobacteria.Methanobacteriales.Methanobacteriaceae.Methanobrevibacter	21.52966662	21.52966662	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.[Tissierellaceae].Finegoldia	21.52966662	21.52966662	rf	group

NA.76	NA	NA	rf	group
NA.77	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Dehalobacteriaceae.Dehalobacterium	21.08632381	21.08632381	rf	group
NA.78	NA	NA	rf	group
Bacteria.Actinobacteria.Coriobacteriia.Coriobacteriales.Coriobacteriaceae.Atopobium	21.07700539	21.07700539	rf	group
NA.79	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.[Tissierellaceae].Peptoniphilus	21.05192188	21.05192188	rf	group
NA.80	NA	NA	rf	group
Bacteria.Proteobacteria.Gammaproteobacteria.Pseudomonadales.Moraxellaceae.Enhydrobacter	20.80661893	20.80661893	rf	group
NA.81	NA	NA	rf	group
Bacteria.Bacteroidetes.Bacteroidia.Bacteroidales.Bacteroidaceae.Bacteroides.caccae	20.670882	20.670882	rf	group
NA.82	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Veillonellaceae.Acidaminococcus	20.65532082	20.65532082	rf	group
NA.83	NA	NA	rf	group
Bacteria.Firmicutes.Bacilli.Lactobacillales.Streptococcaceae.Lactococcus.garvieae	19.64370853	19.64370853	rf	group
NA.84	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Lachnospiraceae.Dorea	19.55429461	19.55429461	rf	group
NA.85	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Peptostreptococcaceae.Peptostreptococcus	19.49068014	19.49068014	rf	group
NA.86	NA	NA	rf	gro

				up
Bacteria.Firmicutes.Bacilli.Lactobacillales.Aerococcaceae.Abiotrophia	19.44962163	19.44962163	rf	group
NA.87	NA	NA	rf	group
Bacteria.Proteobacteria.Gammaproteobacteria.Pasteurellales.Pasteurellaceae.Actinobacillus.parahaemolyticus	19.2373219	19.2373219	rf	group
NA.88	NA	NA	rf	group
Bacteria.Firmicutes.Bacilli.Bacillales.Staphylococcaceae.Staphylococcus	19.18529474	19.18529474	rf	group
NA.89	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Veillonellaceae.Phascolarctobacterium	18.8964304	18.8964304	rf	group
NA.90	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Ruminococcaceae.Anaerotruncus	18.83332406	18.83332406	rf	group
NA.91	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Veillonellaceae.Veillonella	18.2533258	18.2533258	rf	group
NA.92	NA	NA	rf	group
Bacteria.Proteobacteria.Gammaproteobacteria.Pseudomonadales.Moraxellaceae.Acinetobacter	17.8564516	17.8564516	rf	group
NA.93	NA	NA	rf	group
Bacteria.Proteobacteria.Gammaproteobacteria.Vibrionales.Vibrionaceae.Vibrio	17.66261202	17.66261202	rf	group
NA.94	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Ruminococcaceae.Ruminococcus	17.60051784	17.60051784	rf	group
NA.95	NA	NA	rf	group
Bacteria.Proteobacteria.Gammaproteobacteria.Pasteurellales.Pasteurellaceae.Aggregatibacter	17.39505105	17.39505105	rf	group

NA.96	NA	NA	rf	group
Bacteria.Synergistetes.Synergistia.Synergistales.Dethiosulfovibrionaceae.Pyramidobacter.piscolens	17.29599524	17.29599524	rf	group
NA.97	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Eubacteriaceae.Pseudoramibacter_Eubacterium	17.22992569	17.22992569	rf	group
NA.98	NA	NA	rf	group
Bacteria.Proteobacteria.Gammaproteobacteria.Enterobacteriales.Enterobacteriaceae.Morganella.morganii	16.80609917	16.80609917	rf	group
NA.99	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Clostridiaceae.Clostridium.perfringens	16.80147762	16.80147762	rf	group
NA.100	NA	NA	rf	group
Bacteria.Bacteroidetes.Bacteroidia.Bacteroidales.Rikenellaceae.AF12	16.47167993	16.47167993	rf	group
NA.101	NA	NA	rf	group
Bacteria.Actinobacteria.Coriobacteriia.Coriobacteriales.Coriobacteriaceae.Adlercreutzia	16.45371933	16.45371933	rf	group
NA.102	NA	NA	rf	group
Bacteria.Firmicutes.Erysipelotrichi.Erysipelotrichales.Erysipelotrichaceae.Holdemania	16.35676276	16.35676276	rf	group
NA.103	NA	NA	rf	group
Bacteria.Actinobacteria.Actinobacteria.Actinomycetales.Micrococcaceae.Rothia.dentocariosa	16.22655915	16.22655915	rf	group
NA.104	NA	NA	rf	group
Bacteria.Proteobacteria.Gammaproteobacteria.Pasteurellales.Pasteurellaceae.Haemophilus	16.20760864	16.20760864	rf	group
NA.105	NA	NA	rf	group
Bacteria.Actinobacteria.Coriobacteriia.Coriobacteriales.Coriobacteri	15.439	15.439	rf	gro

aceae.Collinsella.aerofaciens	21086	21086		up
NA.106	NA	NA	rf	group
Bacteria.Tenericutes.Mollicutes.Mycoplasmatales.Mycoplasmataceae.Mycoplasma	14.99899739	14.99899739	rf	group
NA.107	NA	NA	rf	group
Bacteria.Proteobacteria.Gammaproteobacteria.Alteromonadales.Shewanellaceae.Shewanella.algae	14.9120434	14.9120434	rf	group
NA.108	NA	NA	rf	group
Bacteria.Bacteroidetes.Bacteroidia.Bacteroidales.[Paraprevotellaceae].[Prevotella].tannerae	14.85849941	14.85849941	rf	group
NA.109	NA	NA	rf	group
Bacteria.Proteobacteria.Alphaproteobacteria.Rhizobiales.Methylobacteriaceae.Methylobacterium.organophilum	14.54146299	14.54146299	rf	group
NA.110	NA	NA	rf	group
Bacteria.Bacteroidetes.Bacteroidia.Bacteroidales.[Paraprevotellaceae].Paraprevotella	14.41788858	14.41788858	rf	group
NA.111	NA	NA	rf	group
Bacteria.Proteobacteria.Gammaproteobacteria.Enterobacteriales.Enterobacteriaceae.Serratia	13.76013394	13.76013394	rf	group
NA.112	NA	NA	rf	group
Bacteria.Actinobacteria.Actinobacteria.Bifidobacteriales.Bifidobacteriaceae.Scardovia	13.37207402	13.37207402	rf	group
NA.113	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Clostridiaceae.Clostridium	13.19604709	13.19604709	rf	group
NA.114	NA	NA	rf	group
Bacteria.Bacteroidetes.Flavobacteriia.Flavobacteriales.Flavobacteriaceae.Flavobacterium	13.02577145	13.02577145	rf	group
NA.115	NA	NA	rf	group

Bacteria.Actinobacteria.Actinobacteria.Actinomycetales.Nocardiaceae.Rhodococcus	12.41173113	12.41173113	rf	group
NA.116	NA	NA	rf	group
Bacteria.Proteobacteria.Alphaproteobacteria.Sphingomonadales.Sphingomonadaceae.Sphingobium	12.41163161	12.41163161	rf	group
NA.117	NA	NA	rf	group
Bacteria.Bacteroidetes.Bacteroidia.Bacteroidales.Bacteroidaceae.Bacteroides.fragilis	12.13445195	12.13445195	rf	group
NA.118	NA	NA	rf	group
Bacteria.Proteobacteria.Gammaproteobacteria.Vibrionales.Vibrionaceae.Vibrio.rumoiensis	12.07604882	12.07604882	rf	group
NA.119	NA	NA	rf	group
Bacteria.Firmicutes.Bacilli.Lactobacillales.Streptococcaceae.Streptococcus.sobrinus	12.01289651	12.01289651	rf	group
NA.120	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Veillonellaceae.Megamonas	11.86828997	11.86828997	rf	group
NA.121	NA	NA	rf	group
Bacteria.Bacteroidetes.Bacteroidia.Bacteroidales.Bacteroidaceae.Bacteroides.uniformis	11.0323025	11.0323025	rf	group
NA.122	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Ruminococcaceae.Ruminococcus.bromii	10.92345167	10.92345167	rf	group
NA.123	NA	NA	rf	group
Bacteria.Firmicutes.Bacilli.Bacillales.Staphylococcaceae.Staphylococcus.sciuri	10.51656122	10.51656122	rf	group
NA.124	NA	NA	rf	group
Bacteria.Proteobacteria.Gammaproteobacteria.Pseudomonadales.Pseudomonadaceae.Pseudomonas	10.25818194	10.25818194	rf	group
NA.125	NA	NA	rf	gro

				up
Bacteria.Bacteroidetes.[Saprospirae].[Saprospirales].Chitinophagaceae.Sediminibacterium	10.13792439	10.13792439	rf	group
NA.126	NA	NA	rf	group
Bacteria.Firmicutes.Erysipelotrichi.Erysipelotrichales.Erysipelotrichaceae.Bulleidia	9.659189488	9.659189488	rf	group
NA.127	NA	NA	rf	group
Bacteria.Actinobacteria.Actinobacteria.Actinomycetales.Pseudonocardiaceae.Saccharopolyspora	9.471662675	9.471662675	rf	group
NA.128	NA	NA	rf	group
Bacteria.Actinobacteria.Actinobacteria.Bifidobacteriales.Bifidobacteriaceae.Bombiscardovia	9.289609429	9.289609429	rf	group
NA.129	NA	NA	rf	group
Bacteria.Proteobacteria.Gammaproteobacteria.Xanthomonadales.Xanthomonadaceae.Stenotrophomonas	9.262601412	9.262601412	rf	group
NA.130	NA	NA	rf	group
Bacteria.Verrucomicrobia.Verrucomicrobiae.Verrucomicrobiales.Verrucomicrobiaceae.Akkermansia.muciniphila	9.125189649	9.125189649	rf	group
NA.131	NA	NA	rf	group
Bacteria.Proteobacteria.Betaproteobacteria.Burkholderiales.Burkholderiaceae.Burkholderia	9.036412749	9.036412749	rf	group
NA.132	NA	NA	rf	group
Bacteria.Proteobacteria.Gammaproteobacteria.Vibrionales.Vibrionaceae.Photobacterium	8.915601809	8.915601809	rf	group
NA.133	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Lachnospiraceae.Moryella	8.745221 91	8.745221 91	rf	group
NA.134	NA	NA	rf	group
Bacteria.Proteobacteria.Betaproteobacteria.Burkholderiales.Oxalobacteraceae.Oxalobacter.formigenes	8.686573361	8.686573361	rf	group

NA.135	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Veillonellaceae.Megasphaera	8.676194629	8.676194629	rf	group
NA.136	NA	NA	rf	group
Bacteria.Proteobacteria.Deltaproteobacteria.Desulfovibrionales.Desulfovibrionaceae.Bilophila	8.550960344	8.550960344	rf	group
NA.137	NA	NA	rf	group
Bacteria.Firmicutes.Bacilli.Lactobacillales.Lactobacillaceae.Lactobacillus.mucosae	8.444865919	8.444865919	rf	group
NA.138	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Veillonellaceae.Selenomonas	8.332826301	8.332826301	rf	group
NA.139	NA	NA	rf	group
Bacteria.Actinobacteria.Actinobacteria.Actinomycetales.Micrococcaceae.Micrococcus	7.746441536	7.746441536	rf	group
NA.140	NA	NA	rf	group
Bacteria.Firmicutes.Clostridia.Clostridiales.Lachnospiraceae.Coprococcus	7.635127255	7.635127255	rf	group
NA.141	NA	NA	rf	group
Bacteria.Proteobacteria.Gammaproteobacteria.Enterobacteriales.Enterobacteriaceae.Klebsiella	7.376770496	7.376770496	rf	group

A, the active SLE patients; R, the remissive SLE patients.